The Virology of Demyelinating Diseases

Richard T. Johnson, MD

Infectious agents have been postulated as causes of multiple sclerosis for over a century. The possible role of a virus or viruses is supported by data that (1) a childhood exposure is involved and "viral" infections may precipitate exacerbations of disease, (2) experimental infections in animals and natural infections in humans can cause diseases with long incubation periods, remitting and relapsing courses, and demyelination, and (3) patients with multiple sclerosis have abnormal immune responses to viruses. The pathogenesis of three human demyelinating diseases of known viral etiology is discussed. In progressive multifocal leukoencephalopathy, a papovavirus selectively infects oligodendrocytes and causes focal areas of demyelination. In postmeasles encephalomyelitis, the virus is lymphotrophic and disrupts immune regulation that can result in an autoimmune perivenular demyelinating illness without evidence of infection of the central nervous system. In human immunodeficiency virus-encephalopathy and myelopathy virus is present in macrophages and microglia and the myelin abnormalities apparently are caused by soluble factors such as viral proteins, cytokines, or neurotoxins. These findings may have implications on how, when, and where to seek viruses in multiple sclerosis.

Johnson RT. The virology of demyelinating diseases. Ann Neurol 1994;36:S54–S60

In 1868 Jean Martin Charcot described the clinical features of the first human demyelinating disease, multiple sclerosis, and postulated that the disease resulted from exposure to dampness or from injuries or emotional stress. Over the next two decades Koch and Pasteur blazed the new era of microbiology; therefore, it was a natural sign of the times that in 1884 Pierre Marie, one of Charcot's students and a successor to his chair in neurology at the University of Paris, postulated an infectious etiology for multiple sclerosis. Because a rabies vaccine had just been introduced by Pasteur, Marie believed a vaccine for multiple sclerosis would soon be produced [1].

Speculation of a viral etiology of multiple sclerosis has recurred during the past century. This speculation has been given credence by three areas of investigation. First, epidemiologic studies have indicated a childhood exposure factor (possibly an infectious agent) in the genesis of multiple sclerosis [2, 3] and also have suggested that infections may precipitate acute exacerbation in established disease [4, 5]. Second, studies in a wide variety of animal models (Table 1) and human diseases have shown that viruses can cause diseases with prolonged incubation periods, with remitting and relapsing courses, and with myelin destruction mediated by a variety of mechanisms. Third, studies of patients with multiple sclerosis consistently have shown higher levels of antibody against measles virus in serum and cerebrospinal fluid (CSF) than in controls and in some studies antibodies have been elevated to other viral agents as well (Table 2).

Subsequent to the description of multiple sclerosis three human demyelinating diseases have been defined in which viral causes are known. In each, the causative virus is from a different family and in each the pathogenesis of demyelination appears to be different.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) was originally described by Astrom and collaborators [21] in 1958 as a rare complication of leukemia and lymphoma. It was subsequently seen in a variety of immunodeficiency states caused by other diseases and medical therapy. Over the last decade, the disease has increased greatly in frequency as a complication of the acquired immunodeficiency syndrome (AIDS).

Clinically, against the background of immune deficiency, multifocal neurological signs develop and follow an ingravescent course usually ending in death in less than 6 months. Very rare cases have stabilized or recovered [22, 23]. The CSF is usually normal. Neuropathology shows demyelinated foci, particularly in the subcortical white matter. Within these foci the oligodendrocytes are gone and astrocytes are enlarged, misshapen, and often multinucleated. Surrounding the foci many of the oligodendroglia are enlarged and contain intranuclear inclusions. The neurons and many of their axons coursing through the demyelinated areas appear normal.

Despite the paucity of inflammation, Richardson [24] postulated that this disease might be a viral infection of the brain in an immunocompromised host. In

From the Departments of Neurology, Molecular Biology and Genetics, and Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, MD

Address correspondence to Dr Johnson, Department of Neurology, Meyer 6-113, The Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287.

Table 1. Animal Models of Acute and Chronic Viral Demyelinating Diseases

Papovavirus	SV_{40} in macaque monkeys [6]
Paramyxovirus	Canine distemper virus [7]
Coronavirus	JHM strain mouse hepatitis virus [8]
Picornavirus	Theiler's virus in mice [9] Encephalomyocarditis virus in mice [10]
Togavirus	Semliki Forest virus in mice [11] Ross River virus in mice [12]
Rhabdovirus	Chandipura [13]
Lentivirus	Visna virus in sheep Caprine arthritis-encephalitis virus [14]

Table 2. Higher Anti-Viral Antibodies in Multiple Sclerosis Patients Than in Controls

Serum	CSF
Measles	Measles
Parainfluenza 3	Parainfluenza 1, 2, 3
Influenza C	Influenza A, B
Varicella	Varicella
Herpes simplex	Herpes simplex
Rubella	Rubella
Epstein-Barr	Epstein-Barr
	Mumps
	Respiratory syncytial
	Coronaviruses
	Adenoviruses
HTLV-I (gag)	HTLV-I (gag)
HTLV-II	
	Simian virus 5

Data are from [15–20].

CSF = cerebrospinal fluid; HTLV = human T-cell lymphotropic virus.

1964 ZuRhein and Chou [25] examined inclusions ultrastructurally and found pseudocrystalline assays of viruslike particles characteristic of papovaviruses, a seemingly bizarre observation considering that the only human papovavirus known at that time was the virus of warts. Armed with the knowledge of the type of virus to seek, methods were developed and a previously unknown papovavirus called JC was found to be the etiologic agent [26–28]. This virus is ubiquitous, usually causes infection of the human populations during childhood, and is not associated with disease. The development of human fetal glial cultures was necessary to make its recovery possible.

The bizarre forms and mitoses in astrocytes are described in the original study as being "ordinarily met with only in neoplastic processes" [21]. Indeed, many of these astrocytes contain viral DNA and express tumor antigen (T antigen), while relatively smaller numbers express viral antigen or contain virions [29]. This suggests a semipermissive infection of astrocytes. In contrast the pathogenesis of demyelination in PML appears straightforward; selective productive and lytic infection of oligodendrocytes causes demyelination and neurons are not susceptible, hence there is preservation of the axons. This selective vulnerability of the cells maintaining the myelin provides a mechanism many of us naively thought might explain all human demyelinating diseases [30]. Other disease mechanisms have not proved as straightforward.

Postinfectious Encephalomyelitis

Postinfectious encephalomyelitis (aka acute disseminated encephalomyelitis, postexanthematous encephalomyelitis, and perivenular leukoencephalitis) is a perivenular demyelinating disease that occurs as an unusual complication of a variety of viral infections. It was most common following measles and vaccination with vaccinia virus [31, 32]. The clinical and pathological disease was defined in clinical–pathological reports in the 1920s and was differentiated from typical acute encephalomyelitis with cortical inflammation and neuronophagia. This syndrome characteristically follows a febrile illness and is characterized by perivenular demyelination. Postmeasles encephalomyelitis, the commonest form that still occurs, will be discussed.

Postinfectious encephalomyelitis complicates clinical measles in approximately 1 per 1,000 cases. It is less frequent in children under 2 years of age. Following uncomplicated measles in otherwise healthy children, the disease typically comes on 4 to 5 days after the rash. The rash coincides with the onset of the immune response and the clearance of virus. After the rash abates and the child is returning to activities outside the house, there is a sudden recurrence of fever, decrease in consciousness, often seizures, and multifocal neurological signs. The disease has an abrupt onset, often reaching its nadir within the first 24 hours. Mortality is approximately 20%, and sequelae persist in the majority of survivors. The electroencephalogram is slow but nonspecific, and the CSF usually shows a mild elevation of protein and some mononuclear cells, but in about one-third of the patients the CSF is entirely normal. Neuropathologic examination shows diffuse perivenular infiltration of mononuclear cells with demyelination. Inflammation of the meninges is limited or absent. Histologically the lesions resemble those that were subsequently induced experimentally by injection of animals with myelin proteins with adjuvant, that is, experimental autoimmune encephalomyelitis. Indeed, the pattern of myelin loss in the lesions is the same as that seen in the experimental autoimmune disease [33].

Because the encephalomyelitis develops after the acute exanthem and because of the unusual pathological changes, it was postulated that this was not the

direct virus invasion of the nervous system but some toxic reaction. Subsequent to the discovery of experimental autoimmune encephalomyelitis in animals in the 1930s it has been assumed that this disease represented an autoimmune response induced by viral infection.

Historically, approximately one-third of the cases of encephalitis were thought to be of this form, but with the elimination of vaccination to prevent smallpox and the widespread use of measles vaccine, few cases are seen in North America. Cases continue in much of the world where measles continues partially or totally unabated. Indeed, measles remains one of the three major killing infectious diseases worldwide, causing about 1.5 million childhood deaths per year [34]. The majority of these deaths are not due to encephalomyelitis, however, but to opportunistic infections that complicate the decreased immune responses seen for several weeks following the measles rash. Thus, in contrast to PML, measles virus appears to induce the immune deficiency, and opportunistic infections lead to death. This immunodeficiency was first observed in 1908 by von Pirquet [35] who found that children converted their tuberculin reactions at the time of rash and over subsequent weeks. Indeed, this was the first documented virus-induced acquired immunodeficiency syndrome.

A paradox is evident. The majority of measles deaths are due to immunodeficiency and opportunistic infections, whereas in 1 per 1,000 patients encephalomyelitis develops, which is thought to have an autoimmune mechanism. In studies of patients with uncomplicated measles, measles with pneumonia, and encephalomyelitis, the degree of nonresponsiveness of lymphocytes to mitogens is equal [36]. In all three groups similar leukopenia develops with maintenance of the normal T4/T8 ratios [37]. All lose their cutaneous tuberculin reactions; those with infectious complications remain negative for a longer period of time [38]. It is clear, however, that these findings do not represent simple immunosuppression. There is activation of lymphoid cells and spontaneous proliferation of lymphocytes (T4, T8, and B cells) (Table 3). Rather than immunosuppression, measles virus produces an activation of lymphocytes and macrophages stimulating immunoresponsive cells such as those responsive to myelin basic protein; proliferation of culture lymphocytes in the presence of myelin basic protein was found in 15% of the cases of measles without neurological findings and in 47% of those who developed encephalomyelitis [46].

Evidence suggests that measles virus may not directly invade the nervous system. Virus has only rarely been isolated from the central nervous system and our isolation attempts have failed. In studies of CSF we found no intrathecal synthesis of antibody in postmeasles encephalomyelitis to suggest antigenic stimulation within the nervous system [46], and interferon levels were not elevated in CSF as they are in the serum during the prodrome of measles or in CSF of herpes encephalitis [44, 47]. On the other hand, neopterin, a product released by activated macrophages is elevated in CSF of measles encephalomyelitis patients [48]. Immunocytochemistry and in situ hybridization for viral proteins and viral RNA, in brains of patients dying with encephalomyelitis, have been consistently negative [49]. In acute fatal measles, antigen can be demonstrated in macrophages, lymphoid organs, skin, systemic vascular endothelium, and epithelial cells of lung, gut, bile duct, and bladder, but no measles antigen was found in cerebrovascular endothelial cells or neural cells [49, 50]. Thus, this demyelinating disease does not appear to be caused by selective vulnerability of any cells of the nervous system but by infection of the lymphoid organs, leading to the activation of lymphocytes including, in some patients, lymphocytes that are reactive against myelin basic protein and possibly other myelin constituents. These activated cells may then selectively home to the central nervous system, causing an autoimmune encephalitis after the virus has been cleared from lymphoid organs.

Table 3. Altered Lymphocyte Function with Measles Virus Infection

Normal responses
Antibody responses to NP, F, and HA proteins [39]
Depressed responses
Tuberculin skin test [38]
Lymphoproliferative responses to mitogens [36]
Lymphopenia (with normal T4/T8 ratio) [37]
Evidence of activation
Spontaneous proliferation of T4, T8, and B lymphocytes [40, 41]
Spontaneous suppressor cell activity [36]
Elevated plasma IgE levels [42]
Elevated C-reactive proteins [43]
Increased lymphocyte activation markers (T10, II-2 receptor) [37]
Elevated levels of soluble IL-2 and CD8 [40]
Elevated plasma levels of interferon-γ and neopterin and CSF levels of neopterin but not interferon in encephalitis [44]
Increased monocyte activation (increased II-1β) [45]
Lymphoproliferative response to myelin basic protein (15% uncomplicated; 47% encephalomyelitis) [46]

IL-2 = interleukin-2; CSF = cerebrospinal fluid.

Human Immunodeficiency Virus Encephalopathy and Myelopathy

The acquired immunodeficiency syndrome was identified in the summer of 1981 with the unusual appearance of Kaposi's sarcoma and pneumocystis pneumonia in otherwise healthy, gay young men [51, 52]. Initial neurological interest focused solely on opportunistic infections of the central nervous system, but in

1985 it became evident that there was direct infection of the nervous system that might lead to neurological diseases. In 1985, multiple laboratories isolated human immunodeficiency virus (HIV) from brain tissue, CSF, and peripheral nerve of patients with neurological disease [53, 54]. HIV DNA and RNA were localized in brain tissue [55], and intrathecal synthesis of antibody against HIV was documented [56]. A further important finding the same year was the establishment that HIV was a lentivirus, not an oncornavirus as previously suspected, and therefore, belonged to a family of viruses all of which produce chronic encephalopathies [57].

Subsequently, a variety of diseases of the central and peripheral nervous system and muscle have been described as complications of HIV infection [58, 59]. These occur at varying times. An acute meningitis or an acute demyelinating polyneuritis may occur at the time of seroconversion; HIV encephalopathy and myelopathy usually evolve years later with full-blown AIDS. These different syndromes show very varied pathological changes, and in all probability have different mechanisms of pathogenesis. In several syndromes, demyelination is a prominent feature both early in disease, when a neuropathy resembling Guillain-Barré syndrome is usually seen, and accompanying AIDS, when unusual myelin changes are seen in the encephalopathy and myelopathy.

AIDS dementia and myelopathy usually evolve insidiously afer the patient has developed an AIDS-defining illness. Dementia is the AIDS-defining disease in about 3% of the patients, is evident in 15 to 20% of ambulatory AIDS patients [58], and may develop in more than 50% by the time of death [60]. AIDS dementia is a so-called subcortical dementia with apathy, memory loss, and withdrawal, and with few features of cortical dementia such as behavioral problems and disorders of language and perception.

Signs of a myelopathy are evident in approximately 20% of patients by the time of death. This often accompanies the encephalopathy but can occur independently. Patients develop weakness, spasticity of the legs, and prominent loss of posterior column function [61].

Three distinctive white matter lesions are found in patients with encephalopathy and myelopathy [62]. The pathological finding that correlates best with dementia is diffuse myelin pallor, which is characterized by hyperintensity of T2-weighted images in the deep white matter with magnetic resonance imaging and by reduced intensity of staining with Luxol fast blue. Immunocytochemical staining for myelin proteins does not show decrease staining intensities in areas of myelin pallor, and light and electron microscopic studies fail to show demyelinated axons or active demyelination [63]. These imaging and staining changes appear to be due to alterations in the blood–brain barrier. The second type of white matter lesions consists of small perivenular areas of demyelination that are found randomly through white matter; they bear a remarkable resemblance to the lesions described above in post-infectious encephalomyelitis. Whether these lesions evolve at the time of lymphocyte activation and autoimmune diseases early during HIV infections or whether they develop through some other mechanism is unknown, because there is no clinical correlate for these lesions. The third abnormality is vacuolar myelin damage found in hemispheric white matter, fiber tracts, and most strikingly in spinal cord primarily in the white matter tracts of the posterior and lateral columns. It is most prominent in the thoracic cord. The vacuoles may be very asymmetrical, few perivascular inflammatory cells or microglial nodules are found, and multinuclear cells are rare. Ultrastructurally, vacuolization represents intralaminar edema; the vacuoles are not intracytoplasmic. Macrophages are seen within these intralaminar gaps. Both demyelination and remyelination are found by electron microscopy [64].

The pathogenesis of these myelin changes associated with HIV infection are unknown. Virus is usually detectable by immunocytochemical staining for HIV antigens and consistently present by polymerase chain reactions in the brains of demented patients. Localization of virus is limited largely, if not exclusively, to cells of macrophage origin, i.e., microglia, macrophages, and perivascular macrophages. Limited defective infection of astrocytes may occur, but there is no convincing evidence of infection of neurons or oligodendrocytes despite the pathological changes in these cells or their membranes. The alterations in myelin membranes and neurons are thought to be mediated by secretory products of infected macrophages and microglia. Virus proteins, cytokines and neurotoxins have all been implicated either directly or via indirect effects on astrocytes or oligodendrocytes [65, 66].

In visna, another lentivirus infection, infected monocytes when they differentiate into tissue macrophages express surface viral proteins that, in turn, induce neighboring lymphocytes to release a lymphokine that induces class II antigen expression on endothelial and possibly glial cells [67]. Marked inflammation ensues. A similar cytokine-mediated disease has been postulated in HIV infection, and the correlation of tumor necrosis factor-α levels to the dementia and myelopathy [68, 69] would be consistent with such a speculation.

Conclusion

More than a century has past since Pierre Marie postulated an infectious agent in multiple sclerosis, and a number of virus isolations have been reported, but none have been convincingly linked to the disease (Table 4). Even those who hold to the idea of a viral etiology are undecided whether it may be many viruses

Table 4. Viruses Recovered from Multiple Sclerosis Patients[a]

Virus	Isolation Method	Year
Rabies virus	Encephalitis in mice inoculated with brain or blood	1946 [70] 1964 [71]
Herpes simplex virus	Cytopathic changes in cell culture inoculated with homogenate of brain	1964 [72]
Scrapie agent	Scrapie developed in sheep 16–21 mo after inoculation with brain	1965 [73]
Multiple sclerosis–associated agent	Decrease in polymorphonuclear cells in mice inoculated with MS tissue	1972 [74]
Parainfluenza virus 1	Cell cultures of brain tissue of 2 patients fused with other cells, and virus recovered	1972 [75]
Measles virus	Cytopathic changes in monkey kidney cells inoculated with homogenate of brain biopsy	1972 [76]
Simian virus 5	Syncytia formed in MRC5 cell cultures inoculated with patients' bone marrow cells	1978 [77]
Chimpanzee cytomegalovirus	Neonatal chimpanzee inoculated with brain cells of patient who developed paralysis 3 years later	1979 [78]
Coronavirus	Fresh unfrozen brains inoculated into mice and grown in culture yielded virus	1980 [79]
SMON-like virus	Cytopathic changes on MRC5 inoculated with CSF	1982 [80]
Tick-borne encephalitis flavivirus	Blood from 2 patients inoculated i.c. into mice	1982 [81]
HTLV-I	RNA identified in T-cells of CSF	1986 [82]
LM7 (retrovirus)	Found in leptomeningeal cell line from CSF	1989 [83]
HSV-I	Isolated from CSF during first attack	1989 [84]

[a]Modified from [85].

MS = multiple sclerosis; SMON = subacute myelo-optico-neuropathy; CSF = cerebrospinal fluid; i.c. = intracerebrally; HTLV = human lymphotrophic virus; HSV = herpes simplex virus.

or only one, whether a childhood viral infection is important for laying the ground work of the disease, the so-called common exposure factor, or whether one or many viruses may precipitate exacerbations.

What have we learned from other demyelinating diseases? We have learned that viruses can produce disease with long incubation periods, remitting and relapsing courses, and the loss of myelin with relative sparing of axons. In the case of progressive multifocal leukoencephalopathy, the most straightforward mechanism of demyelination proved operative, i.e., selective infection destroys oligodendrocytes. The identification of the infectious agent, however, required two steps. First, electron microscopic studies were necessary to know what kind of viruses to look for, and second, laboratory methods had to be developed to recover a new and previously unknown papovavirus. In postmeasles encephalomyelitis and in HIV infections, no infection of oligodendrocytes has been found to explain virus-induced demyelination. In postmeasles encephalomyelitis the etiologic agent has been identified only by the very characteristic manifestation of the systemic disease. At the time encephalitis develops, usually no intrathecal antibody synthesis is found and the virus is not recovered from the central nervous system. Indeed, our studies suggest that virus may have never been in the central nervous system. In this disease an indirect mechanism may be operative, and if an analogous mechanism occurred in multiple sclerosis virus would need to be sought in lymphoid tissues prior to the clinical manifestations of the demyelinating disease. Demyelination of the central nervous system in AIDS shows unique morphological changes in a new disease, due to a new virus. The virus is present in the central nervous system, but it is present in the "wrong" cells; a correlation between the amount of virus and the amount of disease is lacking, making it hard to fulfill even the most liberal modifications of Koch's postulates [86]. The obvious mediators of demyelination appear to be virally infected macrophages or microglia and current work focuses on the possible role of their soluble products in disruption of myelin sheaths.

In these studies the knowledge of what virus to look for, and when and where and how to search, is evident. That the virus has not been identified consistently in multiple sclerosis is certainly not evidence against the role of a virus. "Absence of evidence is not the same thing as evidence of absence" [87].

Supported by Po-1-NS 26643, from the National Institute of Neurological Diseases and Stroke, The National Institutes of Health.

References

1. Marie P. Sclérose en plaques et maladies infectieuses. Prog Med 1884;12:287–289
2. Bebbe GW, Kurtzke JF, Kurland LT, et al. Studies on the natural history of multiple sclerosis. III. Epidemiologic analysis of the Army experience in World War II. Neurology 1967;17:1–17

3. Dean G, Kurtzke JF. On the risk of multiple sclerosis according to age at immigration to South Africa. Br Med J 1971;3:725–729
4. Sibley WA, Bamford CR, Clark K. Clinical viral infections and multiple sclerosis. Lancet 1985;2:1313–1315
5. Andersen O, Lygner P-E, Bergström T, et al. Viral infections trigger multiple sclerosis relapses: a prospective seroepidemiological study. J Neurol 1993;240:417–422
6. Horvath CJ, Simon MA, Bergsagel DJ, et al. Simian virus 40 (SV40)-induced disease in rhesus monkeys with simian acquired immunodeficiency syndrome. Am J Pathol 1992;140:1431–1440
7. Zurbriggen A, Yamawaki M, Vandevelde M. Restricted canine distemper virus infection of oligodendrocytes. Lab Invest 1993; 68:277–284
8. Lai MMC, Stohlman SA. Molecular basis of neuropathogenicity of mouse hepatitis virus. In: Roos RP, ed. Molecular neurovirology. Totowa, NJ: Humana, 1992:319–348
9. Roos RP, Casteel N. Determinants of neurological disease induced by Theiler's murine encephalomyelitis virus. In: Roos RP, ed. Molecular neurovirology. Totowa, NJ: Humana, 1992: 283–318
10. Skiram S, Topham DJ, Huang S-K, et al. Treatment of encephalomyocarditis virus-induced central nervous system demyelination with monoclonal anti-T-cell antibodies. J Virol 1989;63: 4242–4248
11. Fazakerley JK, Webb HE. Semliki forest virus-induced, immune-mediated demyelination: adoptive transfer studies and viral persistence in nude mice. J Gen Virol 1987;68:377–385
12. Seay AR, Wolinsky JS. Ross river virus-induced demyelination: I. pathogenesis and histopathology. Ann Neurol 1982;12:380–389
13. Del Canto MC, Rabinowitz SG, Johnson TC. Virus-induced demyelination. Production by a viral temperature sensitive mutant. J Neurol Sci 1979;42:155–168
14. Narayan O, Clements JE. Biology and pathogenesis of lentiviruses. J Gen Virol 1989;70:1617–1639
15. Adams JM, Imagawa DT. Measles antibodies in multiple sclerosis. Proc Soc Exp Biol Med 1962;111:562–566
16. Bray PF, Bloomer LC, Salmon VC, et al. Epstein-Barr virus infection and antibody synthesis in patients with multiple sclerosis. Arch Neurol 1983;40:406–408
17. Norrby E. Viral antibodies in multiple sclerosis. Prog Med Virol 1978;24:1–39
18. Salmi A, Reunanen M, Ilonen J, et al. Intrathecal antibody synthesis to virus antigens in multiple sclerosis. Clin Exp Immunol 1983;52:241–249
19. Ohta M, Ohta K, Mori F, et al. Sera from patients with multiple sclerosis react with human T cell lymphotropic virus-I gag proteins but not env proteins—western blotting analysis. J Immunol 1986;137:3440–3443
20. Goswami KKA, Randall RE, Lange LS, et al. Antibodies against the paramyxovirus SV5 in the cerebrospinal fluids of some multiple sclerosis patients. Nature 1987;327:244–247
21. Astrom KE, Mancall EL, Richardson EP Jr. Progressive multifocal leukoencephalopathy. Brain 1958;81:93–111
22. Price RW, Nielsen S, Horten B, et al. Progressive multifocal leukoencephalopathy: a burnt-out case. Ann Neurol 1983;13: 485–490
23. Berger JR, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. Neurology 1988;38:1060–1065
24. Richardson EP Jr. Progressive multifocal leukoencephalopathy. N Engl J Med 1961;265:815–823
25. ZuRhein GM, Chou SM. Particles resembling papovavirus in human cerebral demyelinating disease. Science 1965;148:1477–1479
26. Padgett L, Walker DL, ZuRhein GM, et al. Cultivation of papova-like virus from human brain with progressive multifocal leukoencephalopathy. Lancet 1971;1:1257
27. Weiner LP, Narayan O, Penney JB Jr, et al. Papovavirus of JC type in progressive multifocal leukoencephalopathy. Arch Neurol 1973;29:1–3
28. Narayan O, Penney JB Jr, Johnson RT, et al. Etiology of progressive multifocal leukoencephalopathy-identification of papovavirus. N Engl J Med 1973;289:1278–1282
29. Aksamit AJ, Sever JL, Major EO. Progressive multifocal leukoencephalopathy: JC virus detection by in situ hybridization compared with immunohistochemistry. Neurology 1986;36: 499–504
30. Johnson RT, Weiner LP, Narayan O, et al. Progressive multifocal leukoencephalopathy. In: ter Meulen V, Katz M, eds. Slow virus infections of the central nervous system. New York: Springer-Verlag, 1977:99–100
31. Johnson RT, Griffin DE, Gendelman HE. Postinfectious encephalomyelitis. Semin Neurol 1985;5:180–190
32. Johnson RT, Griffin DE. Postinfectious encephalomyelitis. In: Kennedy PGE, Johnson RT, eds. Infections of the nervous system. London: Butterworths, 1987:209–226
33. Gendelman HE. Pezeshkpour GH, Pressman NJ, et al. A quantitation of myelin-associated glycoprotein and myelin basic protein loss in different demyelinating diseases. Ann Neurol 1985; 18:324–328
34. Asaad F. Measles: summary of worldwide impact. Rev Infect Dis 1983;5:452–459
35. von Pirquet C. Das verhalten der kutanen tuberkulin-reaktion wahrend der Masern. Dtsch Med Wochenschr 1908;34:1297–1300
36. Hirsh RL, Griffin DE, Johnson RT, et al. Cellular immune responses during complicated and uncomplicated measles virus infections of man. Clin Immunol Immunopathol 1984;31:1–12
37. Griffin DE, Moench TR, Johnson RT, et al. Peripheral blood mononuclear cells during natural measles virus infection: cell surface phenotypes and evidence for activation. Clin Immunol Immunopathol 1986;40:305–312
38. Tamashiro VG, Perez HH, Griffin DE. Prospective study of the magnitude and duration of changes in tuberculin reactivity during complicated and uncomplicated measles. Pediatr Infect Dis J 1987;6:451–454
39. Graves M, Griffin DE, Johnson RT, et al. Development of antibody to measles virus polypeptides during complicated and uncomplicated measles virus infections. J Virol 1984;49:409–412
40. Griffin DE, Ward BJ, Jauregui E, et al. Immune activation during measles. N Engl J Med 1989;320:1667–1672
41. Ward BJ, Johnson RT, Vaisberg A, et al. Spontaneous proliferation of peripheral mononuclear cells in natural measles virus infection: identification of dividing cells and correlation with mitogen responsiveness. Clin Immunol Immunopathol 1990;55: 315–326
42. Griffin DE, Cooper SJ, Hirsch RL, et al. Changes in plasma IgE levels during complicated and uncomplicated measles virus infections. J Allergy Clin Immunol 1985;76:206–213
43. Griffin DE, Hirsch RL, Johnson RT, et al. Changes in serum C-reactive protein during complicated and uncomplicated measles virus infections. Infect Immun 1983;41:861–864
44. Griffin DE, Ward BJ, Juaregui E, et al. Immune activation during measles. β-2 microglobulin in plasma and cerebrospinal fluid in complicated disease. J Infect Dis 1992;166:1170–1173
45. Ward BJ, Johnson RT, Vaisberg A, et al. Cytokine production in vitro and the lymphoproliferative defect of natural measles virus infection. Clin Immunol Immunopathol 1991;61:236–248
46. Johnson RT, Griffin DE, Hirsch RL, et al. Measles encephalomyelitis: clinical and immunological studies. N Engl J Med 1984; 310:137–141
47. Lebon P, Boutin B, Dulac O, et al. Interferon-τ in acute and subacute encephalitis. Br Med J 1988;296:9–11

48. Griffin DE, Ward BJ, Juaregui E, et al. Immune activation during measles: β2-microglobulin in plasma and cerebrospinal fluid in complicated and uncomplicated disease. J Infect Dis 1992; 166:1170–1173
49. Moench TR, Griffin DE, Obriecht CR, et al. Distribution of measles virus antigen and RNA in acute measles with and without neurologic involvement. J Infect Dis 1988;158:433–442
50. Esolen LM, Ward BJ, Moench TR, et al. Infection of monocytes during measles. J Infect Dis 1993;168:47–52
51. Centers for Disease Control. Pneumocystis pneumonia—Los Angeles. Morb Mortal Week Rep 1981;30:250–252
52. Centers for Disease Control. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California. Morb Mortal Week Rep 1981;30:305–308
53. Ho DD, Rota TR, Schooley RT, et al. Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. N Engl J Med 1985;313:1493–1497
54. Levy JA, Shimabukuro J, Hollander H, et al. Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms. Lancet 1985;2:586–588
55. Shaw GM, Harper ME, Hahn BH, et al. HTLV-III infection in brains of children and adults with AIDS encephalopathy. Science 1985;227:177–182
56. Resnick L, DiMarzo-Veronese F, Schüpbach J, et al. Intra-blood-brain-barrier synthesis of HTLV-III-specific IgG in patients with neurologic symptoms associated with AIDS or AIDS-related complex. N Engl J Med 1985;313:1498–1504
57. Gonda MA, Wong-Staal F, Gallo RC, et al. Sequence homology and morphologic similarity of HTLV-III and visna virus, a pathogenic lentivirus. Science 1985;227:173–177
58. McArthur JC. Neurologic manifestations of AIDS. Medicine 1987;66:407–437
59. Johnson RT, McArthur JC, Narayan O. The neurobiology of human immunodeficiency virus infections. FASEB J 1988;2: 2970–2981
60. Navia BA, Cho E-S, Petito CK, et al. The AIDS dementia complex: II. Neuropathology. Ann Neurol 1986;19:525–535
61. Petito CK, Navia BA, Cho E-S, et al. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. N Engl J Med 1985;312:874–879
62. Schmidbauer M, Huemer M, Cristina S, et al. Morphological spectrum, distribution and clinical correlation of white matter lesions in AIDS brains. Neuropathol Appl Neurobiol 1882;18: 489–501
63. Power C, Kong P-A, Crawford TO, et al. Cerebral white matter changes in acquired immunodeficiency syndrome dementia: alterations of the blood-brain barrier. Ann Neurol 1993;34:339–350
64. Becker PS, Griffin JW, McArthur JC, et al. Vacuolar myelopathy in human immunodeficiency virus (HIV) infection: central remyelination. J Neuropathol Exp Neurol 1989;48:383 (Abstract)
65. Genis P, Jett M, Bernton EW, et al. Cytokines and arachidonic metabolites produced during human immunodeficiency virus (HIV)-infected macrophage-astroglia interactions: implications for the neuropathogenesis of HIV disease. J Exp Med 1992;176: 1703–1718
66. Lipton SA. HIV-related neurotoxicity. Brain Pathol 1991;1: 193–199
67. Kennedy PGE, Narayan O, Ghotbi Z, et al. Persistent expression of Ia antigen and viral genome in visna-maedi virus-induced inflammatory cells: possible role of lentivirus-induced interferon. J Exp Med 1985;162:1970–1982
68. Wesselingh SL, Power C, Glass JD, et al. Intracerebral cytokine messenger RNA expression in acquired immunodeficiency syndrome dementia. Ann Neurol 1993;33:576–582
69. Tyor WR, Glass JD, Baumrind N, et al. Cytokine expression of macrophages in HIV-1-associated vacuolar myelopathy. Neurology 1993;43:1002–1009
70. Margulis MS, Soloviev VD, Schubladze AK. Aetiology and pathogenesis of acute sporadic disseminated encephalomyelitis and multiple sclerosis. J Neurol Neurosurg Psychiatry 1946;9: 62–74
71. Bychkova EN. Viruses isolated from patients with encephalomyelitis and multiple sclerosis. I. Pathogenic and antigenic properties. Vopr Virusol 1964;9:173–176
72. Gudnadottir M, Helgadottir H, Bjarnason O, et al. Virus isolated from the brain of a patient with multiple sclerosis. Exp Neurol 1964;9:85–95
73. Palsson PA, Pattison IH, Field EJ. Transmission experiments with multiple sclerosis. In: Gajdusek CJ, Gibbs CJ Jr, Alpers M, eds. Slow, latent and temperate virus infections. Washington, DC: US Government Printing Office, 1965:49–54
74. Carp RI, Lucursi PC, Merz PA, et al. Decreased percentage of polymorphonuclear neutrophils in mouse peripheral blood after inoculation with material from multiple sclerosis patients. J Exp Med 1972;136:618–629
75. Ter Meulen V, Koprowski H, Iwasaki Y, et al. Fusion of cultured multiple sclerosis brain cells with indicator cells—presence of nucleocapsids and virions and isolation of parainfluenza-type virus. Lancet 1972;2:1–5
76. Field EJ, Cowshall S, Narang HK, et al. Viruses in multiple sclerosis? Lancet 1972;2:280–281
77. Mitchell DN, Porterfield JS, Micheletti R, et al. Isolation of an infectious agent from bone-marrows of patients with multiple sclerosis. Lancet 1978;2:387–390
78. Wrobleska Z, Gilden D, Devlin M, et al. Cytomegalovirus isolation from a chimpanzee with acute demyelinating disease after inoculation of multiple sclerosis brain cells. Infect Immun 1979; 25:1008–1015
79. Burks JS, Devald BL, Jankovsky LD, et al. Two coronaviruses isolated from central nervous system tissue of two multiple sclerosis patients. Science 1980;209:933–934
80. Melnick JL, Seidel E, Inoue YK, et al. Isolation of virus from the spinal fluid of three patients with multiple sclerosis and one with amyotrophic lateral sclerosis. Lancet 1982;1: 830–833
81. Vagabov RMA, Skortsoa TM, Gofman YP, et al. Isolation of the tick-borne encephalitis virus from a patient with multiple sclerosis. Acta Virol 1982;20:403
82. Koprowski H, DeFreitas EC, Harper ME, et al. Multiple sclerosis and human T-cell lymphotropic retroviruses. Nature 1985; 318:154–160
83. Perron H, Geny C, Laurent A, et al. Leptomeningeal cell line from multiple sclerosis with reverse transcriptase activity and viral particles. Res Virol 1989;140:551–561
84. Bergström T, Andersen O, Vahlne A. Isolation of herpes simplex virus type 1 during first attack of multiple sclerosis. Ann Neurol 1989;26:283–285
85. Johnson RT. Viral aspects of multiple sclerosis. In: Vinken PJ, Bruyn GW, Klawans HL, eds. Handbook of clinical neurology. Amsterdam: Elsevier, 1985:319–336
86. Johnson RT, Gibbs CJ Jr. Koch's postulates and slow infections of the nervous system. Arch Neurol 1974;30:36–38
87. Dyson FJ. Unfashionable pursuits. In Hanle H, ed. Alexander von Humboldt foundation, bi-national colloquium for Humboldt awardees in cooperation with the Institute for Advanced Study, Princeton, New Jersey, August 23–26, 1981. Bonn: Bad Godesberg, 1982:29–40