



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Viral pathogenesis and central nervous system infection

Lynda A. Morrison and Bernard N. Fields

Both host defense and viral genetic factors influence the development of viral infection and disease. Due to the presence of the blood-brain barrier, infection of the central nervous system creates additional complexities in interactions between a virus and its host. Stages in viral pathogenesis defined as (1) virus entry, (2) spread, (3) tropism, (4) virulence and injury to the host, and (5) the outcome of infection are discussed for viral infections in general and those aspects unique to infections of the central nervous system. Information about neuronal physiology and function has also been revealed through studying virus infection. An increased understanding of viral pathogenetic mechanisms and host response to infection raises interesting possibilities for vaccine development and for basic studies in neurology and neurobiology.

Key words: virus / infection / pathogenesis / central nervous system

VIRAL PATHOGENESIS has been defined as the process by which a virus causes disease in a susceptible host.¹ Several stages in pathogenesis can be identified that represent unifying themes in this process. All viruses must successfully penetrate the host's barriers to entry, undergo primary replication and then spread to their ultimate target tissue. Any virus able to cause disseminated infection has the potential to infect the CNS. Viruses infecting the CNS can either circumvent the blood-brain barrier by entry into peripheral nerve endings and axonal transport into the CNS, or they can invade from the blood stream by infection of or transport across the vascular endothelium in the CNS, in regions of greater permeability, or by passive transport in infected monocytes. But with all potentially neurotropic viruses successful invasion of the CNS is rare, limited by host defenses, the mechanics of the blood-brain

barrier and possibly by a need for a critical threshold of virus at an appropriate location. For viruses successfully penetrating the nervous system, the viral properties of neurotropism and neurovirulence determine which host cell populations are infected and the extent of injury, respectively. Here we examine these stages in viral pathogenesis and the unique obstacles posed by the nervous system to virus infection and to virus clearance. Both host defense and susceptibility factors and viral genetic mechanisms influence these stages in pathogenesis and the ultimate manifestation of disease; viral infection of the CNS cannot be understood without an understanding of many aspects of the nervous system itself.

Entry into the host

All body surfaces can be traversed by viruses and different neurotropic viruses use each of the potential entry points¹⁻³ (Table 1). The entry point permissive for a particular virus is determined by the genetics and biochemistry of the virus and the physicochemical environment of the host portal. Entry of arboviruses through the skin requires mechanical transmission through the outer layer of dead, keratinized cells into the underlying epithelium, dermis or blood stream.¹⁻³ Membranes that cover other body surfaces are moist, with an outermost layer composed of living, dividing cells that provide a much more hospitable environment for virus entry.⁴ Several herpesviruses are usually spread by contact with oral and pharyngeal surfaces, where a mucous film and the flow of saliva represent the only barriers to attachment. Viruses that are washed into the stomach and intestine encounter bile salts, acid pH and enzymatic activity, all of which can affect virus structure and thereby alter its infectivity and survival potential. In the harsh gastrointestinal environment, the outer capsid proteins of the enterovirus are major determinants of virus stability. Viruses entering the respiratory tract, such as influenza, rhinovirus and measles, may be spread in saliva or by oronasal inhalation in aerosols.⁵ Resistance to dessication while in aerosols

*From the Department of Microbiology and Molecular Genetics, and the Shipley Institute of Medicine, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115, USA
©1991 by W. B. Saunders Company
1044-5765/91/0302-0001\$5.00/0*

Table 1. Depth of viral penetration into the host

Depth:	Epithelium: confined to body surface	Subepithelium: may remain local or become systemic	Systemic: begins at body surface, then spreads
Potential to invade CNS	-	+	+
Site of entry			
Respiratory tract	Influenza ^a Parainfluenza Coronavirus ^b Rhinovirus	Reovirus ^c	Measles Rubella Rabies virus Papovavirus? Herpes simplex virus Cytomegalovirus Epstein-Barr virus Mumps Lentivirus (Visna)? Varicella zoster virus
Oropharynx			
Intestinal tract	Rotavirus Parvovirus	Enteroviruses ^d Reovirus ^c Coronavirus ^c Adenovirus ^f	
Trans-dermal	Papillomavirus		Arbovirus Rabies virus Arenavirus? Herpes simplex virus Lentivirus (HIV)
Genital tract	Papillomavirus		
Conjunctiva	Adenovirus	Enteroviruses Herpes simplex virus	

^aConfined to epithelium in mammals; ^bRespiratory infection in man; ^cInfects only young animals and infants; ^dMany strains confined to the intestine but others invade the nervous system; ^eIntestinal infection in some animal species; ^fCertain serotypes cause systemic infection; ?Route of entry uncertain.

is an important determinant of virus stability. Viruses infecting the genito-urinary tract, herpes simplex virus (HSV) and human immunodeficiency virus (HIV), are most often spread through sexual activity and are thought to gain entry through small breaks in the integrity of the mucosa, or possibly by uptake at the intact mucosal surface. Infection of the conjunctiva, presumably by direct inoculation from contaminated fingers, can occur with enterovirus 70, HSV and some coxsackie viruses.³

Regardless of the route of entry, viruses must evade local phagocytic cells that make an important contribution to early host defense. Alveolar macrophages and histiocytes of the reticuloendothelial system efficiently phagocytose and eliminate invading viruses, but some (lymphocytic choriomeningitis virus, cytomegalovirus and the lentiviruses visna and HIV) escape destruction by productively infecting these cells.^{1,2,5} Elements of the host immune system, immunoglobulin A in mucous secretions and intraepithelial lymphocytes in the intestine, must also

be avoided.⁴ Thus virus must be transmitted in a form that retains infectivity despite environmental conditions and permits internalization by susceptible cells before being inactivated by mechanical or immune host defenses.

Spread

Tissue invasion

A period of replication in epithelial or subepithelial tissue at the site of inoculation typically occurs, except when virus is directly inoculated into the blood. Whether a virus infection will remain localized at the site of entry or become disseminated is influenced by the temperature of the epithelial surface (e.g. rhinovirus), the propensity of a virus to bud from the apical (influenza) or basolateral (HSV) surface of epithelial cells,^{3,5} and the cell type infected (rotavirus infection of intestinal epithelial

cells versus transcytosis of poliovirus by Peyer's patch M cells)¹ (Table 1). Once a virus infection becomes systemic, spread to the CNS may be accomplished from the blood stream, or by entry through peripheral nerves.

Blood-borne spread

Following replication at the site of inoculation, virus enters the subepithelial lymphatic capillaries and is carried into the blood stream³ where it must survive encounters with phagocytic cells and elements of the immune system. Primary viremia permits the rapid dissemination either of free virus or of blood-cell associated virus to other susceptible tissues:¹ successful penetration of the vascular endothelium and replication in these organs amplifies the infection and augments viremia. Viremia must be of a magnitude and duration adequate to sustain infection and, for some viruses, to permit an assault on the blood-brain barrier.

Replication of some arboviruses in cerebral capillary endothelium precedes viral invasion of the neural parenchyma,⁶ and replication in or passive transport across the endothelium has been postulated for several other viruses, including enteroviruses, arboviruses and retroviruses.^{6,7} Because of its fenestrated endothelium and sparse basement membrane, the choroid plexus is also a target for replication or passive transport of mumps and arboviruses;^{1,3} through it, virus enters the cerebral spinal fluid to infect ependymal cells lining the ventricles and subsequently the underlying brain tissue.^{3,5} Migrating infected monocytes, lymphocytes or leukocytes may be an important vehicle for virus transport into the CNS, especially in lentivirus infection (see Zink and Narayan, this issue,⁸ and refs 9,10).

Neural spread

Neural spread from the periphery to the CNS can be considered as two processes, penetration and propagation. Penetration probably occurs at nerve terminals, either at the site of initial entry into and replication in the host or at a secondary site of replication in extraneural tissues to which virus is disseminated by the blood. Electron microscopic observations have documented accumulation of neuro-invasive rabies virus particles in infected myocytes at neuromuscular junctions and neuromuscular

spindles, followed by entry into motor or sensory nerve terminals.³ Receptors used by viruses may be concentrated at nerve terminals and synapses, facilitating uptake and possibly transport of virus (see below, Tropism).

Once within nerves, propagation is mediated by axonal transport, replication and transsynaptic transfer of virus. HSV, rabies, poliovirus and reovirus are known to spread along nerves by the system of fast axonal transport.¹¹ Transport has been demonstrated both towards and away from the cell body in somatic motor, somatic sensory and autonomic nerves, under various experimental conditions. Bidirectional transport is important in the establishment of, and reactivation from, latency seen with HSV and varicella zoster.^{12,13} Viruses may have a predilection for a subset of nerve types, as evidenced by the more rapid uptake of reoviruses in motor than sensory fibers innervating the footpad¹⁴ and by the restriction of rabies mutants to transport by sensory but not autonomic paths.¹⁵ In contrast to the fast axonal transport of most viruses, the scrapie agent has been postulated to use the system of slow axonal transport.^{3,6,16} Disruption of the neurofilament cytoskeleton that supports slow axonal transport has been observed in scrapie-infected neurons and has been implicated in generation of the spongiform changes that characterize this degenerative neurological disease (see Hope, this issue,¹⁷ and refs 16,18).

Viral replication occurs once virus particles reach the neuronal cell body. Newly synthesized virion components and virus particles then accumulate at post-synaptic sites, probably reflecting directed transport of virus components analogous to directed budding in polarized epithelial cells (see Entry into the host, above; ref 11). Both rabies and vesicular stomatitis virus accumulate at synaptic terminals and beneath the nodes of Ranvier. When antiviral antibody is added to infected neuronal cultures, vesicular stomatitis virus buds preferentially from the synapses, indicating that exocytosis by neurons may be facilitated at this point.³ Neurons thus transfer virus at synaptic junctions in the periphery. In the CNS, the high density of neurons and glia permits many viruses to spread from cell to cell with less fidelity.

The site of virus inoculation can influence the ultimate distribution of lesions within the CNS, especially for viruses that spread along neural routes. Neurons can transport viruses great distances intra-axonally both to and within the CNS, and the final destinations of a virus will be determined in part by

the particular synaptic connections made with individual neurons whose processes took up virus in the periphery.¹⁹ HSV gaining entry through the genitourinary tract infects and becomes latent in sacral ganglia, whereas HSV entering in the oral mucosa becomes latent in trigeminal sensory neurons.

Though cases of strictly blood-borne or neural spread of viruses to the nervous system have been documented, a combination of the two routes may be used by certain viruses, or under certain conditions. For example, flaviviruses can spread through the blood to exposed neurons of the olfactory bulb which take up and transport the virus into the CNS.²⁰ Studies with poliovirus highlight the complexities encountered in determining whether spread occurs by neural or blood-borne routes. The virus initially replicates in Peyer's patches in the ileum,^{21,22} from whence it enters the lymphatics and the blood stream. Elimination of viremia by administration of passive antibody coincides with blockade of neuronal infection and has been taken as evidence of blood-borne spread. Yet neural spread has been well-documented after experimental peripheral inoculation of poliovirus strains.²¹ Such spread might occur in natural infection through nerve endings in the gastrointestinal tract and through motor nerve terminals in secondarily infected tissues, by analogy to events recently described for reovirus infection

(Figure 1; L. Morrison, R. Sidman and B. Fields, in press).

Tropism

The ability of a virus to infect specific populations of cells within the CNS defines its neurotropism. Neurotropism is influenced by viral genes acting at several steps in the viral replication cycle, and by host cell expression of receptors and enzymatic activities. Distinct patterns of injury and ultimately of disease result from interplay between attributes of the infected host and the infecting virus.

The interaction of viral cell-attachment proteins with specific receptors on host cells regulates viral entry and is a major determinant of viral tropism.^{3,24-26} Several proteins have been identified that normally serve various physiological functions in the host nervous system but that can be usurped by viruses as viral receptors (Table 2). HSV has been recently shown to bind the basic fibroblast growth factor receptor,²⁷ richly expressed in the nervous system. Serotype 3 reovirus binds to a protein possessing biochemical similarity to the β -adrenergic receptor on neurons and lymphocytes,^{3,26} although this may not be its only receptor molecule, or even the main receptor used *in vivo*. The nicotinic

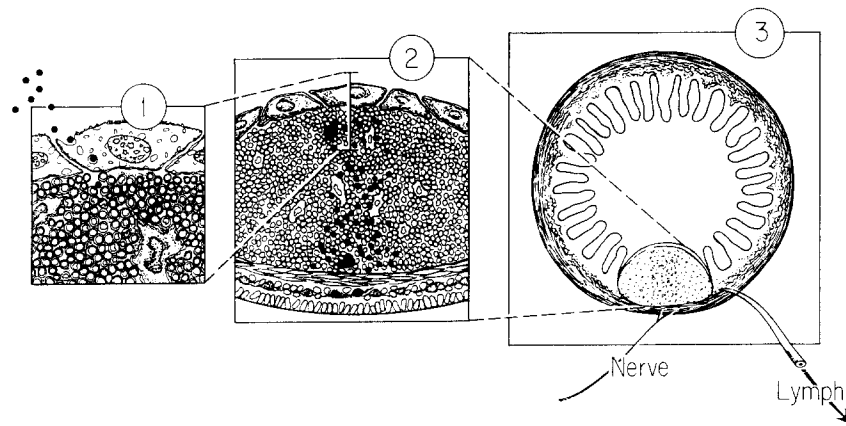


Figure 1. Schematic representation of reovirus serotype 3 entry into the intestinal tract and possible routes of spread from the intestine. (1) Reovirus (and poliovirus) particles are transcytosed by M cells overlying Peyer's patches of the small intestine.^{22,23} (2) Reovirus apparently replicates in mononuclear cells in the Peyer's patch and in adjacent myenteric neurons between the muscle layers beneath the patch. (3) From Peyer's patches in the wall of the small intestine, reovirus enters both efferent lymphatic capillaries and nerves but initially spreads to the CNS through nerve fibers innervating the intestine. Poliovirus also replicates in intestinal tissue²¹ in unknown cell type(s) and similarly has local access to nerve terminals as well as to the blood stream as potential routes of spread to the CNS. The dashed lines indicate where each enlargement fits into the subsequent image.

Table 2. Cellular receptors and viral cell-attachment proteins

Family	Virus	Receptor	Cell-attachment protein
Picornaviridae	Polio	Ig superfamily protein ^a	VP1, VP3
	Rhinovirus	ICAM-1	VP1, VP3
Togaviridae	Semliki Forest	histocompatibility antigens ^a	E1, E2
	Lactate dehydrogenase	Ia antigens	E1, E2
Coronaviridae	Mouse hepatitis	100-110 kDa protein	E1, E2
Rhabdoviridae	Rabies	acetylcholine receptor ^a	G
	Vesicular stomatitis	gangliosides ^a (phosphatidyl serine)	G
Paramyxoviridae	Influenza A	sialic acid	HA
Reoviridae	Reovirus serotype 3	β -adrenergic receptor-like protein ^a	σ 1
Retroviridae	Rotavirus	300 kDa protein ^a	VP4
	HIV	CD4	gp120
Herpesviridae	Epstein-Barr	complement receptor 2	gp350, gp220
	HSV-1	heparin sulfate proteoglycan ^a basic fibroblast growth factor receptor ^b	gB, gC, gD/gH ^b

^abest evidence concerning receptors; others controversial.

^bevidence not definitive.

acetylcholine receptor, localized on muscle cells in the region of neuromuscular junctions, has been identified as a receptor for rabies virus. Phosphatidyl serine may function as an alternative receptor for rhabdoviruses,^{5,26} indicating that lipid molecules (and carbohydrate residues) as well as proteins can serve as neurotropic virus receptors. Other molecules acting as receptors for neurotropic viruses are listed in Table 2. Specific interactions with receptors may regulate binding of a particular virus at epithelial surfaces and vascular endothelium as well as nerve terminals, and may explain to some degree tissue specificity and differential susceptibility to infection.

Numerous viral cell-attachment proteins have also been identified (Table 2) by analysis of genetic reassortant, genetic recombinant and mutant viruses.^{3,13} The neurotropism of serotype 3 reovirus has been mapped using reassortant progeny viruses to the S1 gene that encodes the σ 1 protein (see Tyler, this issue²⁸). Viruses with mutations in their cell-attachment protein can escape antibody-mediated neutralization of their infectivity and such mutant viruses have been isolated for the study of individual residues involved in neurotropism. Neutralization-escape mutants of rabies virus have a single amino-acid substitution in the envelope glycoprotein, G, that serves in viral cell-attachment. All show greatly decreased virulence compared to the parental virus and some are restricted in tropism for certain nerve fiber types.^{3,6,15} Mutants of a murine coronavirus

selected with antibody against the E2 envelope protein revealed that a single amino-acid substitution in the E2 molecule determines loss of tropism for neurons without change in tropism for oligodendrocytes.^{6,26} Little is known about the murine coronavirus receptor protein on neurons or its similarity to the receptor on oligodendrocytes.

X-ray crystallographic analysis of the poliovirus virion has provided a detailed molecular view of a ligand in virus-receptor molecular interactions. The analysis has revealed a series of peaks in the VP1 protein surrounded by a broad valley composed of VP1 and VP3 that forms the receptor binding pocket (see Almond, this issue²⁹; ref 13). Other members of the picornavirus family are known or postulated to have cell-attachment proteins of similar topology.

Transcriptional regulatory elements are an important post-receptor-binding determinant of viral tropism.^{5,30} An enhancer element confers tissue-specific expression for JC papovavirus in human oligodendrocytes. Similarly, promoter elements of some neurotropic murine retroviruses determine their species-specificity. On the other hand, host cells that lack enzymatic activities required for maturational cleavage of viral proteins or completion of the virus replicative cycle (as observed for poliovirus) will not be productively infected, thereby limiting tropism.^{5,25}

A number of host factors modulate viral tropism and virulence, influencing viral pathogenetic potential and ultimately the potential for CNS

infection.^{3,31} Many neurotropic viruses more readily infect the young. This has been shown to variously result from the immaturity of the immune response, reduced capacity to produce interferon, increased susceptibility to infection of some cell types, and age-specific nature and distribution of receptor proteins^{2,3} (see Coyle, this issue³²). Genetic determinants of disease susceptibility have been found for infection of mice with strains of most neurotropic viruses, in at least one case of coronavirus reflecting lack of a gene encoding a virus receptor protein. Determinants have been linked to histocompatibility genes that regulate immune responses only in chronic diseases of immunopathological etiology. Last, sex of the host and nutritional status can influence resistance to infection. The selective vulnerability of different species or one species at different ages, coupled with viral determinants of neurotropism, may explain differences in clinical manifestations of CNS disease.

Neurovirulence

The efficiency with which a virus can multiply and extend infection after it has invaded the nervous system, its neurovirulence, determines in part the extent of injury suffered by the host. The effectiveness of the host response and the resulting immunopathology also play a role.

Although each virus has evolved its own genetic determinants of virulence, some generalizations can be drawn. Outer capsid and envelope glycoproteins are frequently implicated as virulence factors because changes in their amino-acid sequence usually weaken their infectivity (attenuation), although this may be a subtle reflection of altered tropism. Genetic reassortants between virulent and avirulent strains of bunyaviruses and reoviruses have also been used to identify determinants of neurovirulence by segregation of phenotype with a particular viral gene.³ Genetic recombination between strains of poliovirus and of HSV have similarly been used to identify genes critical for neurovirulence.⁵ More than one region of a viral protein identified as a virulence factor may be important³ and, when neurotropism and neurovirulence are determined by the same protein, changes in that protein can have multiple and dramatic effects on the resulting infection. In studies of Theiler's murine encephalomyelitis virus, a model of human demyelinating disease (see Nash, this issue³³), variants selected with

antibody to the VP1 protein possess tissue-specific alterations in extent and duration of infection and in capacity to induce demyelination.¹³ But not all changes in viral genes are attenuating: mutations causing reversion to neurovirulence have been identified in poliovirus isolates from the feces of recipients of the attenuated trivalent oral vaccine.³⁴

Mutations in genes encoding proteins other than those of the capsid or envelope can also result in attenuation, for example, sequences encoding a retroviral core protein or in the 5' noncoding region of poliovirus RNA.³⁴ Transacting transcriptional activators may play a role in determining virulence, exemplified by a mutant of HIV with a defective tatIII gene that shows reduced replication and cytopathic effect.^{3,6} Importantly, neurovirulence may be under multigenic control and determinants of virulence may differ depending on the host species infected.³

CNS injury resulting from viral infections

Viral infections of the nervous system can have very severe consequences because the neurons vital to host function and survival cannot be replaced once injured or destroyed; the effect of even minor damage may be catastrophic.² Furthermore, once infection in the CNS has begun, the reduced permeability and dense structure of the blood-brain barrier which often impedes the initial spread of virus to the CNS may reduce the capacity of the host to resolve infection and limit injury.⁹

Injury at a cellular level may be directly due to virus infection, occurring when cytopathic effect is significant enough to damage irreparably the plasma membrane (lysis) or to arrest metabolic activity by inhibition of protein, RNA or DNA synthesis, e.g. poliovirus, vesicular stomatitis virus and herpesvirus, respectively.^{35,36} Viruses such as rabies may alter nerve impulse conductance without histologically perturbing infected neurons.¹⁹ Accumulations of virus capsids or even individual viral proteins may in themselves be toxic. The sequence homology between HIV gp120 envelope protein and certain essential neurotransmitters and neuropeptides has evoked the hypothesis that competitive binding of gp120 may block normal neuronal function (see Tillman and Wigdahl, this issue³⁷). gp120 also mediates another potential form of direct injury by virus, syncytium formation. Indirect injury to cells has been postulated to occur by release of

toxic 'factors' from neighboring cells damaged by infection.³⁶

Systemic injury occurs by both direct and indirect mechanisms as well. The consequences of infection vary with the location and function of tissue injured by the virus: for example, motor neuron destruction in poliomyelitis results in paralysis; demyelinating reactions to virus infection cause incoordination; and virus infections of cells in the developing nervous system produce a variety of congenital abnormalities and neurological diseases (see Coyle, this issue,³² and refs 19,38). Indirect mechanisms of viral injury to the host CNS include the actions of interferons,³⁹⁻⁴¹ and the virus-specific cellular and humoral immune response (see Sedgwick and Dörries, this issue,⁴² and refs 2,40,43).

Paradoxically, the elaborate system of host response to virus infection that may be protective outside the CNS can be destructive when generated within this normally isolated compartment,^{1,43} where cell lysis and complement activation may injure the host while helping to clear virus. Virus replication in macrophages or immunocompetent T or B cells can also induce immune dysregulation.^{41,43} Last, autoimmune reactions may be provoked by viral infections, resulting in indirect injury to the host even without continued presence of virus.^{41,44} Autoimmunity can be triggered in genetically susceptible individuals by non-specific inflammatory stimuli that alter immune regulation or by cross-reactivity between the viral inducing agent and normal host proteins (molecular mimicry).^{44,45} Exposure of normally sequestered antigen due to virus-induced cytolysis and destruction or dysfunction of suppressor T cells have also been postulated as mechanisms in the development of autoimmune reactions.⁴¹ Autoimmune demyelination reactions, initiated in the CNS against nervous system antigens, are especially prevalent.⁴⁶

Outcome of CNS infections

Several outcomes are possible in viral infections of the CNS that do not acutely result in death. Virus may be effectively cleared from the CNS, may remain latent in the nervous system and cause recurrent disease, or may produce persistent disease. Clearance is thought to be highly dependent on the immune response, though limitation of viral replication and the type of disease produced can be influenced by nonspecific factors. Failure to clear varicella zoster, cytomegalovirus, adenovirus and

measles infections in natural cell-mediated immunodeficiency states suggest that T cell responses may be more important than antibody in eventual clearance of many infections.¹ Successful clearance may still leave the host impaired, depending on the nature and severity of the injury sustained.^{9,10} A chronic autoimmune reaction may continue even after virus clearance.

When latency is established by some viruses, the viral genome remains within the nervous system after acute infection ceases. No infectious virus is produced until reactivation occurs and the absence of viral protein products transcribed during latency may permit the infected cell to escape immune surveillance. Capacity for latent infection in the nervous system is characteristic of the herpesviruses, HSV and varicella zoster (see Stevens, this issue,⁴⁷ and refs 12,13).

Persistent viral infections, in contrast to latency, are characterized by continued production and shedding of virions from infected cells. They are especially prevalent in CNS tissues,⁹ possibly because these contain non-dividing cells, are isolated behind the blood-brain barrier, have low expression of major histocompatibility complex proteins and may permit increased generation of defective viruses.¹⁹ Immune responses are usually generated and maintained but are ineffectual in clearing virus.⁴⁸ As a result, chronic immune reactions may contribute much of the tissue injury.⁴³ Possible mechanisms of establishment and maintenance of persistent infection are listed in Table 3.

Persistent infection takes many forms. In lymphocytic choriomeningitis virus infection of newborn mice, chronic production of virus occurs without serious detriment to cells.⁴³ Most persistent virus infections, however, cause demyelination and/or degeneration in the CNS. Lentiviruses can establish persistent infections that cause progressive neuronal degeneration, though visna and HIV apparently do not persist directly in neurons (see Zink and Narayan, and Tillman and Wigdahl, this issue^{8,37}). Other slow infections with immune-mediated injury that result in degenerative CNS disease include JC virus infection (the causative agent of progressive multifocal leukoencephalopathy), measles infection (resulting in subacute sclerosing panencephalitis, see Schneider-Schaulies and Liebert, this issue,⁴⁹ and refs 6,16,19), and slow infections such as scrapie, Kuru and Creutzfeldt-Jakob disease that are postulated to be incited by small proteinaceous infectious particles lacking nucleic acid (see Hope, this issue,¹⁷ and ref 16).

Table 3. Mechanisms of viral persistence**I. Virus avoids immunological surveillance**

- A. Viral protein expression
anti-viral antibody-induced capping and modulation
only low-affinity antibody induced
- B. MHC expression
modulated by virus proteins
modulated by lymphokines/monokines
very low in neurons
- C. Congenital infection establishing tolerance

II. Virus abrogates lymphocyte/macrophage function

- A. Immunosuppression
generalized
selective
- B. Infected lymphocytes/macrophages
or bone marrow precursors
- C. Lymphokine/monokine-induced alteration of host
gene transcription

III. Altered virus or virus replication

- A. Incomplete or defective viruses generated
- B. Variants or mutants generated
- C. Expression of viral gene products diminished
- D. Replication-inhibitory lymphokines/monokines
stimulated

Future potential

A more thorough understanding of these stages in pathogenesis of viral CNS infections may engender new or more effective measures for prevention of disease. Development of more efficacious vaccines is a primary objective but requirements for protection from individual viruses differ.^{40,50} Knowledge of pathogenetic stages of each virus may reveal points of greatest vulnerability and will help to determine requirements for stimulating immunity with a minimum of immunopathological side effects. Ideally, infection by any virus with potential to invade the CNS should be stopped before entering the nervous system.

Characterization of neurotropic virus infections also offers interesting possibilities for studying structure and function of the nervous system. Basic neurological and neuroscience research has begun to benefit from using the strongly neurotropic rabies, HSV and pseudorabies viruses for tracing neural pathways.⁵¹ More speculative is the use of attenuated neurotropic viruses for delivering foreign proteins into regions of the CNS defined through studies of viral pathogenesis. Foreign genes can be packaged

by many viruses and may be selectively expressed, permitting intracerebral production of pharmacological agents or neurotransmitters. Thus studies of viral pathogenesis of the CNS may offer tools for the future as well as an understanding of disease states.

Acknowledgements

The authors are grateful to Dr K Tyler for much helpful advice and discussion, and for reviewing this manuscript. Work on the manuscript was supported by Public Health Service grants AI08207-02 and program project 5 P50 NS16998 from the National Institutes of Health.

References

1. Johnson RT (1982) *Viral Infections of the Nervous System*. Raven Press, New York
2. Mims CA, White DO (1984) *Viral Pathogenesis and Immunology*. Blackwell, Oxford
3. Tyler KL, Fields BN (1990) Pathogenesis of viral infections, in *Virology*, 2nd edn (Fields BN, Knipe DM, Chanock RM, Hirsch MS, Melnick JL, Monath TP, Roizman B, eds), pp 191-240. Raven Press, New York
4. McNabb PC, Tomasi TB (1981) Host defense mechanisms at mucosal surfaces. *Annu Rev Microbiol* 35:477-496
5. Tyler KL (1989) Pathogenesis of neurotropic viral infections, in *Handbook of Clinical Neurology* 56, *Viral Disease* (McKendall RR, ed), pp 25-49. Elsevier, Amsterdam
6. Tyler KL, McPhee DA (1987) Molecular and genetic aspects of the pathogenesis of viral infections of the central nervous system. *CRC Crit Rev Neurobiol* 3:221-243
7. Beilke MA (1989) Vascular endothelium in immunology and infectious disease. *Rev Infect Dis* 11:273-283
8. Zink M, Gorrell MD, Narayan O (1991) The neuropathogenesis of visna virus infection in sheep. *Semin Neurosci* 3:125-130
9. Johnson RT, McArthur JC, Narayan O (1988) The neurobiology of human immunodeficiency virus infections. *FASEB J* 2:2970-2981
10. Fauci AS (1988) The human immunodeficiency virus: infectivity and mechanisms of pathogenesis. *Science* 239:617-622
11. Kristensson K (1982) Implications of axoplasmic transport for the spread of virus infections in the nervous system, in *Axoplasmic Transport in Physiology and Pathology* (Weiss DG, Gorio A, eds), pp 153-158. Springer, New York
12. Roizman B, Sears AE (1987) An inquiry into the mechanisms of herpes simplex virus latency. *Annu Rev Microbiol* 41:543-571
13. Kennedy PGE (1990) The use of molecular techniques in studying viral pathogenesis in the nervous system. *Trends Neurosci* 13:424-431
14. Flamand A, Gagner J-P, Morrison LA, Fields BN (1990) Penetration of the nervous system of suckling mice by mammalian reoviruses. *J Virol* 65:125-131
15. Kucera P, Dolivo M, Coulon P, Flamand A (1985) Pathways of the early propagation of virulent and avirulent rabies strains from the eye to the brain. *J Virol* 55:158-162
16. Matthews WB (1987) Slow infections, in *Infections of the Nervous System*, *Neurology* 8 (Kennedy PGE, Johnson RT, eds), pp 227-246. Butterworths, London
17. Hope J, Baybutt H (1991) The key role of the nerve membrane protein AP in scrapie-like diseases. *Semin Neurosci* 3:165-171

18. Gajdusek DC (1985) Hypothesis: interference with axonal transport of neurofilament as a common pathogenetic mechanism in certain diseases of the central nervous system. *N Engl J Med* 312:714-719
19. Kristensson K, Norrby E (1986) Persistence of RNA viruses in the central nervous system. *Annu Rev Microbiol* 40:159-184
20. Monath TP (1990) Flaviviruses, in *Virology*, 2nd edn (Fields BN, Knipe DM, Chanock RM, Hirsch MS, Melnick JL, Monath TP, Roizman B, eds), pp 763-814. Raven Press, New York
21. Jubelt B, Lipton HL (1989) Enteroviruses, in *Handbook of Clinical Neurology* 56, *Viral Disease* (McKendall RR, ed), pp 307-347. Elsevier, Amsterdam
22. Siciński P, Rowiński J, Warchol JB, Jarzabek Z, Gut W, Szczygiel B, Bielecki K, Koch G (1990) Poliovirus type 1 enters the human host through intestinal M cells. *Gastroenterology* 98:56-58
23. Wolf JL, Rubin DH, Finberg R, Kauffman RS, Sharpe AH, Trier JS, Fields BN (1981) Intestinal M cells: a pathway for entry of reovirus into the host. *Science* 212:471-472
24. Crowell RL, Hsu K-HL (1986) Isolation of cellular receptors for viruses, in *Concepts in Pathogenesis II* (Notkins AL, Oldstone MBA, eds), pp 117-125. Springer, New York
25. McClintock PR, Notkins AL (1984) Viral receptors: expression, regulation and relationship to infectivity, in *Concepts in Viral Pathogenesis* (Notkins AL, Oldstone MBA, eds), pp 97-101. Springer, New York
26. Tyler KL (1987) Host and viral factors that influence viral neurotropism. I. Viral cell attachment proteins and target cell receptors. *Trends Neurosci* 10:455-460
27. Kaner RJ, Baird A, Manukhani A, Basilico C, Summers BD, Florkiewicz RZ, Hajjar DP (1990) Fibroblast growth factor receptor is a portal of cellular entry for herpes simplex virus. *Science* 248:1410-1413
28. Tyler KL (1991) Pathogenesis of reovirus infections of the central nervous system. *Semin Neurosci* 3:117-124
29. Almond JW (1991) Poliovirus neurovirulence. *Semin Neurosci* 3:101-108
30. Serfling E, Jasin M, Shaffner W (1985) Enhancers and eukaryotic gene transcription. *Trends Genet* 1:224-230
31. Tyler KL (1987) Host and viral factors that influence viral neurotropism. II. Viral genes, host genes, site of entry and route of spread of virus. *Trends Neurosci* 10:492-497
32. Coyle P (1991) Viral infections of the developing nervous system. *Semin Neurosci* 3:157-163
33. Nash AA (1991) Virological and pathological processes involved in Theiler's virus infection of the central nervous system. *Semin Neurosci* 3:109-116
34. Almond JW (1987) The attenuation of poliovirus neurovirulence. *Annu Rev Microbiol* 41:153-180
35. Schneider RJ, Shenk T (1987) Impact of virus infection on host cell protein synthesis. *Annu Rev Biochem* 56:317-332
36. Knipe DM (1990) Virus-host-cell interactions, in *Virology*, 2nd edn (Fields BN, Knipe DM, Chanock RM, Hirsch MS, Melnick JL, Monath TP, Roizman B, eds), pp 293-316. Raven Press, New York
37. Tillman M, Wigdahl B (1991) Neuropathogenesis of human immunodeficiency virus infection. *Semin Neurosci* 3:131-139
38. Johnson RT (1988) The viral infections of the developing nervous system: an overview, in *Virus Infections and the Developing Nervous System* (Johnson RT, Lyon G, eds), pp 1-9. Kluwer, Boston
39. Mannering GJ, Deloria LB (1986) The pharmacology and toxicology of the interferons: an overview. *Annu Rev Pharmacol Toxicol* 26:455-515
40. WHO Workshop (1987) Immunological aspects of the prevention of viral diseases. *Bull WHO* 65:1-10
41. Mims CA (1986) Interactions of viruses with the immune system. *Clin Exp Immunol* 66:1
42. Sedgwick J, Dörries R (1991) The immune system response to viral infection of the CNS. *Semin Neurosci* 3:93-100
43. McChesney MB, Oldstone MBA (1987) Viruses perturb lymphocyte functions: selected principles characterizing virus-induced immunosuppression. *Annu Rev Immunol* 5:279-304
44. Sinha AA, Lopez MT, McDevitt HO (1990) Autoimmune diseases: the failure of self tolerance. *Science* 248:1380-1388
45. Oldstone MBA (1987) Molecular mimicry and autoimmune disease. *Cell* 50:819-820
46. Johnson RT, Griffin DE (1986) Virus-induced autoimmune demyelinating disease of the central nervous system, in *Concepts in Viral Pathogenesis* (Notkins AL, Oldstone MBA, eds), pp 203-209. Springer, New York
47. Stevens J (1991) Herpes simplex virus: neuroinvasiveness, neurovirulence and latency. *Semin Neurosci* 3:141-147
48. Oldstone MBA (1989) Viral persistence. *Cell* 56:517-520
49. Schneider-Schaulies S, Liebert U (1991) Pathogenetic aspects of persistent measles virus infections in brain tissue. *Semin Neurosci* 3:149-155
50. Brown F (ed) (1990) *Modern Approaches to Vaccines*. *Semin Virol* 1:1-74
51. Kuypers HGJM, Ugolini G (1990) Viruses as transneuronal tracers. *Trends Neurosci* 13:71-75