Review Article

Viral infections of the nervous system

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Neurotropic viruses cause a number of important infectious syndromes including encephalitis, myelitis, meningitis, and radiculopathy. In this review, the biology of conventional and unconventional viruses is examined. The host immune response to viruses is discussed, and patterns of viral pathogenesis are explained. The clinical features, laboratory findings, management of important viral infections, such as herpes simplex encephalitis and epidemic encephalitis, are presented. Post-infection syndromes, such as the Guillain-Barré syndrome, and chronic viral infections, such as those causing progressive multifocal leukoencephalopathy and subacute sclerosing panencephalitis, are discussed. Current knowledge concerning the nature of unconventional virus-like agents of the spongiform encephalopathies, including kuru and Creutzfeldt-Jakob disease, is summarized. Finally, viral infections of immunocompromised patients and the possible role of viruses in the newly described acquired immunodeficiency syndrome (AIDS) are examined.

KEY WORDS - encephalitis - post-infection syndrome - unconventional virus - acquired immunodeficiency syndrome - subacute sclerosing panencephalitis - progressive multifocal leukoencephalopathy

In the past 20 years, there has been a significant change in the fundamental thinking about viral infections of the nervous system. New information has accumulated and exciting concepts have evolved concerning a variety of central nervous system (CNS) clinical syndromes. The clinical syndromes resulting from acute, persistent, latent, chronic, and slow viral infections are now better understood. Moreover, the insights and techniques of modern virology have also stimulated research into such processes as multiple sclerosis, Guillain-Barré syndrome, and myasthenia gravis as well as into degenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis, and parkinsonism. The definitive role of viruses in these degenerative and immune-mediated diseases has not been established. However, research in both human and experimental viral diseases has increased our understanding of these complex processes.

The outcome of a viral infection is dependent on a variety of factors. Whether the infection is clinically inapparent or apparent relates to both the nature of the invading organism and the host response. The size of the inoculum and the virulence of the viral strain as well as the portal of entry and the site of primary multiplication are also of critical importance. The host factors collectively may be called “susceptibility.” One must differentiate between “susceptibility to infection” and “susceptibility to disease.” The exposure of the nonimmune host to the invading organism will result in an infection. This exposure may occur in any setting. Air-borne infection can be acquired while making rounds on a pediatric service; eating in the local restaurant can introduce enteroviruses; and one may become infected by an arthropod-borne virus while on safari in east Africa. “Susceptibility to disease” takes on another dimension. In this situation, the virulence of the virus and the host factors are paramount. Host factors include barriers such as skin and mucosal surfaces, the immune response, and the vulnerability of specific cells and tissues. Genetic influences, or “predisposition,” also play a role in susceptibility to diseases. These include host proteins which serve as membrane
Acute CNS syndromes include meningitis, encephalitis, poliomyelitis, transverse myelitis, and myeloradiculitis, as well as a number of parainfectious immune-mediated processes that affect both the CNS and the peripheral nervous system. Those diseases with more protracted courses include chronic infections such as progressive multifocal leukoencephalopathy (PML), subacute sclerosing panencephalitis (SSPE), progressive rubella panencephalitis (PRP), which are described in detail later in this report, and a bevy of rarer syndromes seen mostly in the immunoincompetent host due to cytomegalovirus, herpes simplex virus (HSV), varicella-zoster virus, adenoviruses, and enteroviruses. Creutzfeldt-Jakob disease, caused by an unconventional agent, is also a transmissible disease with a protracted clinical course. Herpes simplex encephalitis (HSE) appears to be, at least in most instances, an activation of a latent infection producing an acute clinical syndrome. Rabies virus usually has a long incubation period; however, it ends in an acute fulminant illness. Thus, virus-related CNS diseases occur in many different clinical patterns. Both the incubation period (short or long) and the period of apparent disease (acute, subacute, or chronic) are highly variable, and virtually all possible combinations of incubation and disease type occur with the viral conditions just mentioned.

This paper reviews the subject of neurotropic viruses by providing fundamental information on viral structure and replication. The role of specific epidemiological and host factors in CNS disease is also explored. This includes an overview of the immune response, the blood-brain barrier (BBB), and basic tenets of CNS cell tropism as they relate to viral disease. Finally, the clinical features of a few of the more important syndromes, and their diagnosis and treatment, are addressed.

**Nature of Viruses**

Viruses that affect animals have been divided into two categories. In one group are those viruses with a well defined protein structure and a nucleic acid genome; these are termed “conventional” agents. In the other group are the “unconventional” agents; that is, those viruses in which the protein structure and nucleic acid genome have not been demonstrated. The conventional viruses are the classic agents such as measles, mumps, and poliovirus, whereas the unconventional agents are those causing Creutzfeldt-Jakob disease and kuru.

**Conventional Viruses**

**Morphological Features.** One can think of conventional viruses as a foreign nucleic acid which needs to parasitize a host cell, and of which the immediate goal is replication.8 The nucleic acid for each virus has a specific configuration and is either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). The nucleic acid is entwined and/or surrounded by proteins, and
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the resulting mature viral particle is called a "virion." The simplest virion consists only of a protein shell ("capsid") surrounding the nucleic acid core interwoven with protein ("nucleocapsid"). Such viruses are called "naked" virions and include naked RNA viruses such as enteroviruses and naked DNA virions such as adenoviruses and papovaviruses, the latter agents being associated with PML. If the capsid is surrounded by a lipid bi-layer, the virion is called an "enveloped" virus. In this case, the envelope is derived from the membrane of infected cells and consists of lipid synthesized by the cell plus proteins that have been specified by the viral genome. The envelope is acquired as the nucleocapsid buds from cellular membranes. In an incompletely understood process, viral proteins are inserted into the lipid bi-layer as the host cell proteins are simultaneously excluded from the region that will become the envelope of the budding virus. Herpesviruses acquire their envelopes from nuclear membranes, togaviruses (for example, St. Louis encephalitis virus) from vesicles derived from the membranes of the endoplasmic reticulum, and myxoviruses and related viruses, such as, influenza, mumps, and measles, from plasma membranes.

Conventional viruses have a variety of sizes and shapes. Some are as small as 20 nm (a ribosome is 25 to 30 nm), and some as large as 400 nm, such as the smallpox agent. Shape also is highly variable. For example, among enveloped viruses the rhabdoviruses (rabies) are bullet-shaped, the coronaviruses have petal-shaped projections resembling the solar corona, and the poxviruses are brick-shaped. By contrast, naked viruses have a cubic (icosahedral) symmetry.

**Multiplication Cycle.** The multiplication of a virus consists of the following steps: adsorption of the virus to a specific cell, penetration into the cell, uncoating of the protein shell surrounding the nucleic acid, transcription and replication of the viral genetic material, translation to produce proteins, assembly of the virus, and release of the virion into the environment. This cycle varies with the virus type and involves complicated interactions between the virus and the cell.

The initial step of infection, the adsorption of the virion to the plasma membrane of a cell, is a major determinant of virus tropism for specific cells. This virus-receptor interaction is currently the subject of intense study. As an example, the adsorption of paramyxoviruses is associated with a specific glycoprotein designated "HN." This protein projects from the outer surface of the viral envelope and has both receptor-binding activity (hemagglutination) and neuraminidase activity.

The receptors themselves appear to be, for the most part, glycoproteins. In some cells, the viral receptor appears to be part of the MHC. In experimental rabies infection, the receptor is closely associated with or identical to the acetylcholine receptor. If this proves to be a general phenomenon, it will correlate viral neurotropism and viral attachment to a normal and very specific cell constituent.

After adsorption, the virion penetrates the cell membrane. Most viruses enter the cell via a phagocytic mechanism called "viropexis." In myxoviruses and paramyxoviruses, penetration occurs by fusion and is mediated by means of a protein designated "F protein" which projects from the outer surface of the viral membrane. The F protein is responsible for penetration by inducing fusion between the viral envelope and the plasma membrane. The HSV uses a combination of viropexis and fusion. Regardless of the method of virion penetration, viral glycoproteins can, in many instances, be demonstrated on the cell surface soon after the viral nucleic acid core has entered the cytoplasm. This may allow the immune attack prior to the replication of the virus.

The "uncoating" of the capsid protein appears to be dependent on host cell lysosomal enzymes. This process initiates the transcription and translation of viral nucleic acid coding for all the virus-specific macromolecules. In some situations, the virus shuts down host cell macromolecular synthesis and redirects cellular metabolism toward the synthesis of viral nucleic acid and proteins. However, viral proteins and nucleic acids can also be synthesized without the cessation of host cell processes.

The transcription of specific messenger RNA (mRNA) from viral nucleic acid is a key process in viral multiplication. Different transcription-replication strategies depend on whether the nucleic acid is DNA or RNA, single- or double-stranded, and of negative or positive polarity. Most animal DNA viruses are double-stranded with the exception of parvoviruses, which are single-stranded. The genomes of RNA viruses can also be continuous (non-segmented) or segmented. During RNA viral infection, RNA is either directly translated to virus polypeptides, or a complementary copy is first synthesized and then subsequently translated into viral polypeptides. When the virus RNA is used directly as a messenger, it is designated as having positive (+) strand polarity. Viruses with genomic RNA that must be transcribed to a complementary RNA to form a functional message are called negative (−) strand viruses.

Picornaviruses, including the enteroviruses such as poliovirus, have a positive single-stranded RNA (+SS RNA). The viral nucleic acid is infectious and can serve as an mRNA. Rhabdoviruses (rabies), paramyxoviruses (measles, mumps), and orthomyxoviruses (influenza) are negative single-stranded RNA (−SS RNA). The viral nucleic acid is not infectious, and the virion contains an RNA polymerase that forms complementary mRNA (positive sense). The retroviruses (RNA tumor viruses) contain +SS RNA and have intermediates that are single- and double-stranded DNA "provirus." The virion contains an RNA-dependent DNA polymerase (reverse transcriptase). Reoviruses have double-stranded
segmented RNA and contain an RNA polymerase that transcribes each segment to mRNA.

The translation of viral proteins takes place on ribosomes. Thus, regardless of where nucleic acid is replicated or virus is assembled, protein synthesis occurs in the cytoplasm. Viral proteins are either structural or nonstructural. Structural proteins are morphologically part of the mature particle, whereas nonstructural proteins, usually enzymes such as nucleic acid polymerases, are essential for the viral multiplication cycle but are not part of the virion. The nonstructural proteins are important in replication, transcription, control of host cell macromolecular synthesis, viral assembly, and virion release from cells.

The structural proteins have been the subject of intense study for the past few years. One of the better understood systems is related to the orthomyxovirus and paramyxoviruses in which HN, H, and F are the structural envelope glycoproteins. The M protein is a nonglycosylated internal or matrix protein that plays an important role in the assembly of the virus particle. Recent studies have indicated that an abnormality in the synthesis of the M protein of measles virus is important in SSPE.44 Serological studies have also shown that antibodies to all viral proteins except M appear in the serum of SSPE patients.55 It is not known if the block is at the level of the gene, transcription, or translation, or due to the rapid turnover of the M protein. The result is an inability of measles virus to be assembled, and the outcome is a defective infection resulting in the disease SSPE.

Outcome of Infection. The multiplication cycle of conventional viruses can have a number of outcomes depending on the genetics of the virus and the state of the host cell immune systems. A helpful way to understand host cell-virus interactions is to think of them as being either cytocidal, moderate, or inapparent.120 In cytocidal infections, the cell dies by one or a combination of events. These include inhibition of cellular protein, RNA and DNA synthesis, changes in cell membranes, and the release of lysosomal enzymes. For example, poliovirus causes a cytocidal infection, and the lysis of the cell is associated with viral release.8 As a class, the naked viruses are released by cell lysis.8 By contrast, enveloped viruses may bud through plasma membranes without producing cell death; however, there are usually antigenic changes in the cell membrane. In this so-called "moderate virus-cell interaction," there may be chronic cell dysfunction. Fusion of cell membranes with adjacent cells may occur, or the cell may die as viral antigens become the target of immune attack. If antigens are not expressed on the cell surface, the cell is not a target of immune attack, and the result may be a persistent defective infection.

In the inapparent type of virus-cell interaction, infectious virus may not be expressed at all, but its genetic information may become integrated into the host cell genome or be present in a nonintegrated episomal form. The result may be either neoplasia or a latent infection. In most latent infections, virus cannot be isolated by usual laboratory methods during asymptomatic periods; however, nonspecific "triggers" can activate virus and cause acute disease.109 This is the case in recurrent herpes simplex infections.

Unconventional Agents

The unconventional agents are associated with the subacute spongiform encephalopathies, diseases characterized by a stereotyped noninflammatory vacuolation of CNS cells. These inexorably progressive diseases include kuru and Creutzfeldt-Jakob disease in man, scrapie in sheep and goats, and transmissible encephalopathy in mink.15 The nature of the agents of these "slow" infections continues to be a mystery. Their infectious nature has been demonstrated by experiments in which disease is transmitted by serial passages of tissues from affected animals. Furthermore, it can be shown by titration assays that the total number of infectious units in a diseased animal's CNS exceeds by many orders of magnitude the number of infectious units in the original inoculum. This result provides that the agents are not toxins or inert molecules (the titer would dilute out, rather than increase with passage) but rather are infectious and replicating. They have not been clearly identified by electron microscopy; however, it has been suggested that a 23-nm spherical or icosahedral particle seen in paracrystalline virus-like arrays may be the scrapie agent. These particles have been found in the dendritic processes in brains of scrapie-infected mice.11 These agents have thus far not been shown to possess nucleic acid or to produce cytopathic effects in vitro, or to evoke an immune response in natural or experimental infections. They show unusual properties such as a relative resistance to heat, ultraviolet radiation, ionizing radiation, ultrasonication, nucleases, and formaldehyde, all of which would inactivate conventional viruses under most circumstances. However, agents of the spongiform encephalopathies are moderately sensitive to chloroform, bleach, and other lipid solvents.

Prusiner102 has recently reviewed the possible nature and biology of these unconventional agents. These agents may be any of the following: 1) a small DNA virus; 2) a replicating protein; 3) the result of replication of an abnormal polysaccharide within membranes; 4) a DNA subvirus controlled by a transmissible linkage substance; 5) a provirus consisting of recessive genes generating RNA; 6) a naked nucleic acid similar to plant viroids; 7) an aggregated conventional virus with unusual properties; 8) a nucleoprotein complex; or 9) membrane-bound DNA. Prusiner has presented evidence for the existence of unique proteins which are required for infectivity. He proposed a new term, "prion," to indicate a "small proteinaceous infectious particle." Prions appear to have a molecular weight of about 27,000 daltons. If they are indeed devoid of
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nucleic acid, a possible mechanism of replication must include the activation of host genes. These host genes would then code for prion protein. Alternatively, Prusiner suggested that these agents might code for their own replication by protein-directed protein synthesis or “reverse translation.” The nature of prions remains to be further defined, but the data are promising. Characterization of prions would be a major step forward in our understanding of life processes.

Host Responses

A brief review of the immune response might improve understanding of the outcome of acute infections and the establishment of persistent, latent, and chronic infections. The immune responses, both humoral and cellular, require cells with immunological specificity, such as T and B lymphocytes, and cells without apparent antigenic specificity, such as the macrophage. The primary cell of humoral immunity is the B cell (so-called “bursa” or “bone marrow-derived” cell). The T cell (thymus-dependent cell) is the critical lymphoid cell in cell-mediated immunity.

Immunoglobulin (Ig) is the effector molecule of the humoral immune response and is the product of a mature B cell, the plasma cell. A plasma cell secretes Ig of only one class and specificity. The classes of antibody include IgG, IgA, IgM, IgD, and IgE. Immunoglobulin A, IgG, and IgM are most important in viral infections. Immunoglobulin A is present in secretions on the mucosal surfaces of the respiratory and the gastrointestinal tracts where local production of virus-specific antibody can be quite effective in controlling infection. Virus-specific IgG antibodies persist for life, but those of the IgM class appear in primary infection and are short-lived.

Antibodies interact with viruses by combining with virion surface antigens to prevent the attachment to susceptible cells, thus decreasing viral penetration and uncoating. Cytophilic antibodies promote phagocytosis and hence the digestion of viruses. Antibody-antigen interaction can activate the complement system and induce the inflammatory response. The activation of the complement system by enveloped viruses produces lysis of the virus or host cells which bear viral antigens on their surface. Antibodies agglutinate viruses, thus expediting phagocytosis. Finally, antibody can, at least in vitro systems, modulate viral expression on cell surfaces and induce persistent and often defective infections. It has been postulated that this is the mechanism of establishing a defective measles infection in SSPE.

The T cells differentiate from hematopoietic cells under the influence of the thymus. They serve as both regulatory and effector cells: these include the individual activities and interactions of helper (Th), suppressor (Ts), and cytotoxic (Tc or CTL) T lymphocytes. Helper activity is generally defined by an enhancement of Ig production by B lymphocytes. In contrast, Tc cells act to inhibit the production of Ig either by elaborating a soluble product or by making physical contact with the B cell. Functionally, CTL's are distinguished from other T cell types by their ability to kill specific target cells. These cytotoxic or “killer” T lymphocytes are highly antigen-specific, although some CTL’s have nonspecific cytotoxic action.

The development of specific T cell markers has greatly expanded the ability of laboratories to give the clinician a clear idea of defects in immune regulation. T cell subsets can be identified by the presence of antigens defined by mouse monoclonal antibodies. In humans, the OKT4 marker appears on Th, and the OKT8 marker is associated with suppressor and cytotoxic T cells. Monoclonal antibodies to human T cell markers are now commercially available. The development of monoclonal antibodies is discussed later.

Activation of T cells is associated with the release of soluble factors that play a role in the regulation of T cell-mediated immune responses. Some of the more important of these soluble factors, or lymphokines, include interleukin-2, immune or gamma interferon, and granulocyte-macrophage colony-stimulating factor. There are many other lymphokines, but these three are produced principally, if not exclusively, by activated T cells. They appear to participate, in cooperation with cells of the monocyctic linkage, in the control of the proliferation, differentiation, and effector function of specific T cell subsets.

Macrophages are also important in cell-mediated immunity to viruses. They may be activated by lymphokines, the third component of complement, and immune complexes. Macrophages are phagocytic cells that act nonspecifically to present antigens to lymphocytes, effect complement activation, and play a role in interferon production. In addition, macrophages may be related to the establishment of chronic infection. Allison and Sandelin have suggested that viruses that replicate in macrophages without producing a cytopathological effect are associated with chronic infection. Examples of viral replication in macrophages associated with persistent infection include lactic dehydrogenase virus (which produces an anterior horn cell disease), equine infectious anemia virus (which produces an arteritis), lymphocytic choriomeningitis virus (which produces immune complex disease), mouse hepatitis viruses (which produce demyelination), and Aleutian mink disease (which produces a gammopathy and arteritis). The role of the interaction of macrophages and viruses in the establishment of persistent infection is a fertile area of investigation.

The ability of the immune system to respond to certain viral antigens appears to be under genetic control. The MHC, which is termed “HLA” (human leukocyte antigen) in humans and “H-2” in mice, is critical in the cooperation between B cells and T cells. The macrophage and the T cell must also share MHC antigens. The interaction of cytotoxic T cells with viral
immunological surveillance is not well understood. At times, the brain was considered to be an "immunologically privileged site;" however, this concept is being modified. There now appears to be a lymph-like system draining regional lymph nodes as elsewhere in the systemic vascular bed. Exceptions to this rule are in the capillary system found in the area postrema, the hypothalamus, the pineal gland, and the choroid plexus. These areas can be used as entry points by viruses; however, most viruses probably enter the brain by infecting endothelial cells or by diffusion through endothelial cells within pinocytotic vesicles. The movement of substances from blood to CSF differs in some ways from blood-to-brain transport. The movement of substances from CSF to brain is probably by diffusion, since continuous tight junctions are absent among ependymal and pial cells, permitting the entry of proteins and other hydrophilic molecules into the brain from the CSF. Changes in blood pressure, blood pH levels, and osmotic pressure can alter the BBB itself by temporarily opening the tight junctions.

**Viral Action Within the CNS**

In contrast to the spread of viruses via CSF pathways, disseminated through the neuropil is poorly understood. There is apparent cell-to-cell spread, but viruses have not been observed in the extracellular gaps between cells and processes. Viruses probably also spread by way of dendritic and axonal cytoplasmic processes of neurons. Rabies virus appears to spread across the synaptic junctions between neurons.

Once a virus enters and spreads through the CNS, a variety of clinical syndromes are produced. Most viruses are pantropic, producing meningitis or encephalomyelitis. A number of viruses, however, do show specific cellular tropism: poliovirus involves motor neurons; rabies virus selects neurons in the limbic system; mumps and Reovirus infect the newborn infant's ependymal cells; the parvoviruses produce specific loss of granule cells in the cerebellum of newborn rodents and cats; and blue-tongue virus selects the subventricular cells of the forebrain of fetal lambs. In PML, infected oligodendrocytes are produced causing lysis and demyelination, whereas the astrocytes appear to be transformed but generally do not contain mature viral particles. Selective vulnerability of CNS cells may be related to their specific functions and/or their states of metabolism. Central nervous system cells are unique because they are highly differentiated populations with host and growth at a primary extraneural site, viruses spread to the CNS by the blood, or, in rare instances, via the nerves. When entering the CNS by this latter route, the virus can advance by growth in perineural or Schwann cells. Viruses have also been shown to reach the CNS by retrograde axoplasmic flow. This has been demonstrated with HSV, varicella-zoster virus, and rabies. In either situation, viral entry into the CNS requires bridging the BBB.

The structure of the BBB is complex. The CNS capillary endothelium is unique in that cells form a continuous nonporous layer with tight junctions between contiguous cells. Hence, cerebral capillaries lack the fenestrations found in the endothelial cells of the systemic vascular bed. Exceptions to this rule are in the capillary system found in the area postrema, the hypothalamus, the pineal gland, and the choroid plexus. These areas can be used as entry points by viruses; however, most viruses probably enter the brain by infecting endothelial cells or by diffusion through endothelial cells within pinocytotic vesicles. The movement of substances from blood to CSF differs in some ways from blood-to-brain transport. The movement of substances from CSF to brain is probably by diffusion, since continuous tight junctions are absent among ependymal and pial cells, permitting the entry of proteins and other hydrophilic molecules into the brain from the CSF. Changes in blood pressure, blood pH levels, and osmotic pressure can alter the BBB itself by temporarily opening the tight junctions.

**Invasion of the CNS by Viruses**

Invasion of the CNS by viruses appears to be inhibited to a degree by the BBB and the blood-cerebrospinal fluid (CSF) barrier which separate the CNS from the systemic circulation. After penetration into
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complex, functionally integrated, cell-to-cell connect-
ions: they possess special metabolic properties, and
have enormous energy requirements.132

Laboratory Diagnosis of Viral Diseases

The criteria used for diagnosis of viral diseases in-
clude the isolation and identification of the virus or
evidence of a serological response to the specific agent.
Unfortunately, isolation may take several days to sev-
eral weeks, and identification of the virus requires
further time. Serological diagnosis is often dependent
on obtaining a convalescent serum. Hence, available
diagnostic methods are often not helpful in the imme-
diate management of acute viral diseases.

Recently, there have been major advances in immu-
nology which will have a significant impact on the
diagnosis of viral disease. The development of mono-
clonal antibodies by the fusion of sensitized lympho-
cytes and mouse myeloma cells (hybridomas) has re-
sulted in the production of a monospecific antibody.
This technique increases the reliability and sensitivity
of immunoassays. The use of monoclonal antibodies
will result in rapid diagnosis by fluorescent identifica-
tion of specific viral antigens in infected cells. Immune
electron microscopy, enzyme-linked immunosorbent
assay, and radioimmunoassay will also be used to study
specimens suspected of having viral antigens.

In most instances, the isolation of virus or the iden-
tification of viral antigen and a fourfold or greater rise
in antibody titer between sera in the acute and conva-
lescent stages assure a specific diagnosis of the virus. In
some patients, only a single serum sample is available
and a high-titer antibody is found. If the suspected
disease is rare, then the single high titer probably reflects
a response to the etiological agent, particularly if the
antibody is of the IgM class. However, one cannot
always be assured of the causal relationship of antibody
increases to the illness as these increases may represent
nonspecific activation. One should also be aware that
it is possible that no virus may be isolated or identified
and that no antibody rise may be seen, even when a
specific virus may be the cause of the illness. There are
many technical reasons for negative isolations, and
some patients do not have a serological change in
antibody concentration.

Analysis of CSF often reveals viral effects on the
brain and meninges during infection. In acute viral
infections, the earliest response may include the finding
of polymorphonuclear leukocytes, but in most immu-
competent individuals the response soon be-
comes mononuclear. Often, T cells are predominant
as the infection progresses. Intracellular viral antigen has
been demonstrated in phagocytes following infection
with HSV, mumps, measles, and varicella-zoster vi-
ruses;30 however, the diagnostic test for these viruses is
not readily available in most laboratories. A selective
elevation of CSF IgG in viral encephalitis is well de-
scribed.30 In some infections, antibody presumably is
secreted by limited numbers of plasma cell clones,
resulting in oligoclonal bands that can be detected by
agarose electrophoresis and isoelectric focusing tech-
tiques. This restricted electrophoretic mobility is well
described in SSPE and PRP. Oligoclonal antibody re-
response has also been found following mumps menin-
gitis and other acute viral illnesses of the CNS.126 The
measurement of antibody within the CSF becomes im-
portant when the normal serum:CSF antibody ratio
is diminished. This assessment should be accompanied
by measurements of the CSF and serum albumin to
determine if the antibody is indeed being produced
within the CSF. B cells have been extracted from the
brains of mice infected with parainfluenza virus, cloned
in vitro, and have been shown to produce monoclonal
antiviral antibody.48

Clinical Syndromes

The clinical manifestations of a CNS viral infection
are a reflection of the nature and type of virus-specific
tropism for CNS cells and the host response to the virus.
The diseases produced can be acute uniphasic illnesses
or subacute chronic diseases as a result of virus invasion
directly into the brain and meninges or they may occur
indirectly from immune-mediated processes aimed at
viral antigens or against altered host antigens. This latter
mechanism has been postulated in postinfection syn-
dromes with CNS and peripheral nervous system de-
myelination. Viruses also seem to be able to trigger
unusual host responses that cause acute disease. Such a
mechanism has been postulated in the pathogenesis of
Reye’s syndrome, in which a mild viral infection is
followed by liver necrosis and brain edema.

Acute Viral Syndromes

Many clinical syndromes can be produced by the
wide spectrum of viruses. The enteroviruses, parti-
cularly echovirus and coxsackie A, have been associated
with benign meningitis, paralytic disease (poliomyeli-
tis), encephalitis, ataxia of childhood, and myositis.2
Mumps has been known to produce meningitis, en-
cephalitis, ataxia, hydrocephalus, myelitis, facial palsy,
cortical blindness, and hearing loss.12,121 The herpes
viruses have been associated with meningoencephalitis
as well as myelitis and radiculopathies. They have also
been implicated in postinfection immune-mediated
syndromes, particularly Guillain-Barré syndrome.1,114
Most of the viruses that infect man can, under certain
circumstances, invade the nervous system.

The most common viral syndromes of man are
meningitis and encephalitis.84 Poliomyelitis is rare to-
day and, when due to poliovirus, occurs in the immu-
nologically compromised or nonimmune host. In most
instances, poliomyelitis is the result of enteroviruses
other than poliovirus.

Meningitis is generally benign and self-limiting. En-
teroviruses remain the most common known cause of
benign or “aseptic” meningitis. Mumps, lymphocytic
Behavioral abnormalities may be prominent in the early prodromata such as fever, headache, and malaise. Because of non-epidemic or sporadic acute viral encephalitides are discussed below. Epidemic and non-epidemic acute encephalitides are all associated with encephalitis. The most important clinical signs, and coma. Encephalitis can be due to any number of agents, and the clinical manifestations depend to a certain degree on the type of virus. Arthropod-borne viruses, enteroviruses, mumps, HSV, rabies, arenaviruses, adenoviruses, and Epstein-Barr virus are all associated with encephalitis. The most important epidemic and non-epidemic acute encephalitides are discussed below.

Herpes Simplex Encephalitis. The most common cause of non-epidemic or sporadic acute viral encephalitis (AVE) in the United States is HSV type 1 (HSV-1). Typically, the illness is preceded by vague prodromata such as fever, headache, and malaise. Behavioral abnormalities may be prominent in the early stages of the disease, prompting inappropriate psychiatric diagnosis. Usually, there is rapid progression to frank neurological signs such as seizures, clouded consciousness or diminished level of consciousness, aphasia, and focal sensory or motor deficits. The CSF usually shows pleocytosis and may reveal raised Ig levels. Herpes simplex encephalitis shows a marked propensity for one or both temporal lobes in about 90% of cases. It is important to try to demonstrate temporal lobe involvement because this strongly suggests the diagnosis of HSE, and may lead to specific therapy. Computerized tomography (CT) may show low-density lesions that enhance. Electroencephalography (EEG) may reveal periodic discharge or slowing in temporal leads. Radionuclide scans often show uptake in the temporal lobes and may be superior to CT scanning in diagnosing HSE.

Clinical signs are not specific for HSE. Fever, alteration of consciousness, headache, hemiparesis, and memory loss occur with equal frequency in HSE-positive cases and in cases in which it was clinically suspected but not proven by brain biopsy. Seizures occurred with equal frequency in both groups, but focal seizures were more common in proven cases of HSE. Focal EEG abnormalities, particularly with rapidly changing patterns, have had the highest correlation with proven cases. When biopsy-positive and biopsy-negative cases were compared, focal EEG abnormality occurred in 81% versus 59%, brain scan localization in 50% versus 14%, and a positive CT scan in 59% versus 22% of cases, respectively.

The pathogenesis of HSE is imperfectly understood. Serological data from the National Institute of Allergy and Infectious Diseases (NIAID) collaborative antiviral study group suggest that as many as 30% of HSE cases may be caused by primary infection. However, virological studies have demonstrated latent HSV infection in a very high percentage of randomly selected human trigeminal ganglia at autopsy. From these investigations and from experimental models, it appears that the viral genome is sequestered in neurons. During the latent period, neither mRNA nor viral antigens are prominent. Activation by stress, immunosuppression, irradiation, concurrent disease, or other factors result in the expression of the genome. The mechanism of axoplasmic transport of virions has been invoked to explain recurrent herpes labialis. Similarly, activation of trigeminal foci may sometimes lead to dissemination of the virus along the floor of the middle fossa, and perhaps this process explains the marked temporal lobe involvement in HSE.

The clinical picture described above and the demonstration of temporal lobe involvement strongly suggest HSE. Nevertheless, the experience of the NIAID collaborative study has shown that, upon further investigation, one-half of such patients will not have HSE. At present the "gold standard" of diagnosis is brain biopsy. Fully 95% of patients diagnosed as having HSE by all means together (autopsy, serological investigation, electron microscopy, CSF antibody study) will have a positive biopsy. Although other non-invasive tests are under investigation, at present none of these is reliable in establishing the diagnosis early in the course of disease when treatment may be effective. Furthermore, the NIAID study showed that almost one-half of the patients with a clinical picture suspicious of HSE but with brain biopsies negative for HSV were later diagnosed by biopsy and further studies as positive for HSV. Many of these conditions (namely, bacterial abscess, tumor, toxoplasmosis, tuberculosis, cryptococcosis, Reye's syndrome) are treatable; others, such as different types of AVE, might have been made worse by treatment for HSE.

Because of the above-mentioned considerations, most authorities suggest that brain biopsy be recommended for patients with the clinical picture of HSE. The specimen should be processed for routine histology, HSV isolation by tissue culture methods, and immunofluorescent microscopy for HSV antigens. The biopsy processing should also include isolation attempts for bacteria, tuberculosis, and fungi. Serum and CSF should be obtained (at the acute and convalescent stages) for determination of HSV antibody levels. It is important that the biopsy be taken from a site that clinical and laboratory studies have shown to be in-
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Involved in the disease process, even if this means obtaining the biopsy specimen from the dominant temporal lobe. It is difficult to know the contribution that the biopsy procedure makes to the morbidity and mortality of these patients who already have extensive neurological involvement; the NIAID study identified only three of 182 patients who had acute complications due to biopsy. In order to avoid herniation of tissue at the biopsy site, it is important to control increased intracranial pressure (ICP) and to adequately visualize the surgical field.

Treatment of HSE with adenine arabinoside (ARA-A, vidarabine) reduces the mortality rate from approximately 70% to about 40% at the 1-year follow-up evaluation.136-137 Outcome depends highly on the patient's level of consciousness at the time treatment is instituted, and it therefore is essential to perform neuradiographic studies and obtain a brain biopsy as early as possible. Lethargic patients do best and comatose patients worst after treatment. Treatment with ARA-A should start at the time of or immediately after the brain biopsy, at a dose of 15 mg/kg of body weight every 24 hours. If the results of the biopsy confirm HSE, therapy should be continued for 10 days; conversely, ARA-A should be discontinued in biopsy-negative patients as soon as these results are available from the laboratory. The mean biological half-life of ARA-A is 3½ to 5 hours, and CSF levels are approximately one-third those found in plasma.80 Adverse reactions with ARA-A have been reported in patients having preexisting liver disease and impaired renal function. Manifestations have included jitteriness, tremor, and myoclonus, all of which are reversible with discontinuation of the drug. Concomitant treatment of raised ICP by surgical decompression or administration of mannitol and barbiturates may be necessary. The use of ICP monitors may be helpful in guiding therapy in this regard. The use of dexamethasone in cases of HSE has not been adequately studied, but it probably should not be administered in cases in which the diagnosis is uncertain or in which antiviral agents are not given simultaneously.

The NIAID collaborative study group is currently investigating a second-generation drug, acyclovir. Acyclovir is preferentially taken up by HSV-infected cells and therefore has a lower toxic potential for normal uninfected cells.

The work-up and treatment of a suspected case of HSE is a formidable task. Physicians who lack laboratory support may wish to refer cases promptly to a center that is participating in the NIAID study. If a decision is made not to refer such patients or if transportation to a study center is impractical, one may wish to treat blindly those patients with strong clinical evidence for HSE (that is, without brain biopsy), since it makes little sense to obtain a biopsy that cannot be processed properly. Treatment with ARA-A should also be considered in cases where clinical suspicion of HSE is high but informed consent for biopsy is not forthcoming. It should be recognized, however, that many suspected cases of HSE, as pointed out above, in fact turn out not to be HSE upon complete evaluation. Adenine arabinoside must be administered with large fluid volumes, and this may unnecessarily complicate the management of patients with AVE not due to HSV. Another potential advantage of brain biopsy is the discovery of diseases which were not expected clinically, many of which have specific treatments.

One should also be aware of the recent reports of recurrent HSE after antiviral treatment. In one case, the patient was treated with cytosine arabinoside (ARA-C) and recovered.38 Fifty-four days after the initial episode of encephalitis, the patient relapsed with a subacute progressive encephalitis. A biopsy at that time resulted in recovery of HSV-1, and treatment with ARA-A was begun.36 The patient relapsed after 2 months, was treated again, but died 4 months later. The basis for these two relapses is not well understood. There has been a report of resistance of HSV to acyclovir in a child with immunodeficiency.29 The possibility of relapses and selection of resistant viruses makes it critical to be certain of the diagnosis of HSE at the initial presentation and to continue therapy for the prescribed period.

Rabies. The rabies virus continues to manifest itself sporadically in the United States.35 Transmission of the virus is via saliva, usually from animal bites. The relative geographic compartmentalization of rabies predominantly to a single animal species is of interest. Rabies occurs in skunks in California, and little or no rabies is seen in foxes there. In the southeastern United States, the disease occurs in foxes and rarely is found in skunks or rabbits. In South and Central America, rabies is prominent in dogs and cattle. It can be transmitted by the bite of the vampire bat, and air-borne transmission can also occur in bat caves. The only known recent human-to-human transmission has been by means of corneal transplantation.

The incubation period can be from days to months, with the disease becoming apparent after more than 6 months in as many as 10% of cases. Signs include fever, agitation, convulsions, difficulty in swallowing, lacrimation, salivation, and confused mental state. There have been two reported cases of survival in man.56,100 The diagnosis can be made by immunofluorescent staining of corneal smears (50% of cases are positive); skin and buccal mucosal biopsies are less effective.75 Brain tissue from man or animal is inoculated into mice, which are generally positive for antigen between 3 to 14 days post-inoculation. Autopsy specimens from the mice may show pathognomonic neuronal cytoplasmic inclusions, the Negri bodies.

The best treatment is prevention. In the event of exposure, the wound should be cleaned and the patient vaccinated with a vaccine approved by the Center for Disease Control and given immune serum therapy.
Rabies Ig should be obtained from humans. The preferred vaccine is human diploid cell rabies vaccine rather than duck embryo vaccine. Regardless of the interval from exposure, the treatment should be given as soon as possible after the diagnosis is suspected.

Other Causes of Acute Viral Encephalitis. Additional causes of sporadic AVE include enteroviruses (for example, coxsackie virus, poliovirus, and echoviruses) as well as measles, mumps, rubella, chicken pox (varicella), Epstein-Barr virus, lymphocytic choriomeningitis virus, arthropod-borne viruses (described below), and other viruses. These viruses do not as a rule show the predilection for temporal lobe involvement seen in HSE. In the absence of a clinical picture of HSE and in the presence of clinical features suggesting one of the above viruses, brain biopsy does not play the central role that it does in suspected HSE. Treatment with ARA-A is not indicated in these diseases except in cases associated with the disseminated varicella-zoster virus. Theoretically, due to fluid overload this drug may even worsen these conditions, as noted above. Diagnosis is made by serological studies, associated systemic infections, and isolation of the virus. There is at present no established therapy for these viruses other than meticulous supportive care, including control of increased ICP as well as fluid and electrolyte balance.

Epidemic Encephalitis. Epidemic AVE is a major world-wide problem. In the Americas, the most common causes of epidemic AVE are the arthropod-borne viruses. These agents may also at times cause sporadic cases of AVE. Most of these viruses are transmitted from hosts such as wild birds by insects, usually mosquitoes, to horses and man, in whom clinical symptoms of encephalitis are evident. These infections usually are not seen in winter months when arthropod vectors are diminished or absent. The clinical features of these infections have recently been reviewed by Monath. The most common cause of epidemic AVE in the United States is the St. Louis encephalitis virus. In the 1975 outbreak, 1815 cases were reported. The St. Louis encephalitis virus occurs throughout North America and is most common in the Ohio-Mississippi River basin. The ratio of inapparent infections to evident infections is about 1:355 during epidemics, and the case fatality rate is between 10% and 20%. Another cause of epidemic encephalitis is Venezuelan equine encephalitis. Outbreaks of this infection have originated in South and Central America and then spread to the southwestern United States. The virus commonly causes an influenza-like illness. Approximately 4% of infected individuals develop AVE, and 20% of these cases are fatal. Eastern equine encephalitis usually occurs along the Gulf or Atlantic Coasts. The inapparent:apparent ratio is low, and there is a high fatality rate. Fortunately, this severe disease is rare by comparison to other arthropod-borne AVE's. Western equine encephalitis occurs, as the name implies, in the western and central parts of North America. During epidemics, as much as 1.7% of the population in the area may be infected. However, the incidence of overt disease is low and the fatality rate is 3% to 7%. The California group of viruses, particularly the La Crosse strain, is a significant cause of encephalitis in the upper midwestern and the eastern United States. Since 1945, only three cases of AVE due to these viruses have actually been identified in California itself. The illness is mild, with a fatality rate of less than 1%.

The above instances of arthropod-borne virus AVE require an insect vector and are not transmitted directly from human to human. Except in the rare event of laboratory accidents, the patient or his tissues do not represent a great hazard of infection. By contrast, several arenaviruses produce hemorrhagic fevers with neurological involvement. Junin and Machupo viruses cause Argentine and Bolivian hemorrhagic fever, and Lassa virus causes Lassa fever. These diseases are highly contagious, and suspected cases should be kept under the strictest isolation conditions.

There is no specific treatment for patients with epidemic AVE. It is important to identify cases and make a definitive diagnosis when possible in order that proper public health measures can be instituted. Early application of insecticides during the outbreak of western equine encephalitis in North Dakota in 1975 significantly reduced the attack rate in infected areas. Effective equine vaccines are available for eastern, western, and Venezuelan equine encephalitis; human vaccines are still experimental.

Post-Infectious Encephalomyelitis

Post-infectious or parainfectious syndromes have been described in both the CNS and peripheral nervous system. These illnesses occur in close temporal relationship to viral infections. Infectious agents are rarely recovered or identified in neural tissues. The pathology is suggestive of an immune-mediated disease and is believed to be caused by a host immune attack triggered by infection and directed against nervous tissue. The microscopic findings consist of perivascular cellular infiltrates, primary demyelination, and on occasion, frank hemorrhage.

In the CNS, the parainfectious syndromes are generally associated with viral infections related to an influenza-like illness. The childhood illnesses such as measles, rubella, mumps, and varicella were often seen with parainfectious syndromes but, since these illnesses are now rare except for varicella, most cases of parainfectious encephalomyelitis remain without a specific diagnosis. The signs and symptoms of the initial infection appear to run a typical course, and, for the most part, the patient is not severely ill. If there is an associated rash such as in measles or rubella, it has usually diminished by the time acute neurological symptoms and signs appear, typically 7 to 10 days after the first febrile illness. These signs may be sudden in onset and may consist of confusion, changes in consciousness,
seizures, and focal neurological signs. Meningeal irritation may be present, and the CSF may show elevated pressure with CSF monocytes. A minority of patients experience a rapid and fatal course. The remainder recover in 3 to 6 weeks with little or no residual neurological signs. The mortality rates vary with the associated virus. Mumps and varicella have low mortality rate, usually less than 5%, but measles has a mortality rate as high as 40% in some series.

Varicella-associated acute cerebellar ataxia continues to be a problem, and makes up about 50% of the post-infectious syndromes associated with chickenpox. Limb ataxia is most prominent and can be associated with papilledema, vomiting, tremor, dysarthria, and nystagmus. The CSF may be normal or have mild pleocytosis. This illness occurs 5 to 10 days after the onset of rash. Varicella has also been associated with a subacute myelitis. In the elderly patient who has had shingles, a progressive myelitis may develop. This can occur from 6 days to 6 weeks following the rash, and appears to be an immune-mediated syndrome, although in some cases the virus seems to invade the cord directly. A recent report describes a successful treatment with ARA-A.

Other parainfectious syndromes include Guillain-Barré syndrome, acute paralytic brachial neuritis, and syndromes associated with the chronic and relapsing polyneuropathies. Association of these syndromes with viruses has been clearly documented in case of Epstein-Barr virus, cytomegalovirus, HSV, coxsackie A and B, echoviruses, measles, mumps, rubella, influenza, and rabies.

The pathogenesis of these diseases is not completely understood. However, most of the syndromes appear to be immune-mediated. Several mechanisms by which viruses could induce an immune-mediated pathology have been suggested. Shared antigenic determinants may exist between viruses and normal host cell membrane constituents. Cross reactivity has been suggested between measles virus and myelin basic protein (MBP), and monoclonal antibody to HSV has been found to cross-react with viral and cellular antigens (S Wroblewska, personal communication, 1983). Another mechanism involves virus-induced release of sequestered host cell antigens. These may be internal antigens which are released following virus-induced cell lysis, or they may be "neoantigens" which, because of viral infection, are expressed on the cell surface. These antigens are not recognized as such. A third mechanism which is currently receiving attention is the so-called "bystander effect." This term has been applied to the destruction of tissue that is adjacent to an immune reaction to nearby viral antigens. This was originally proposed as a mechanism of nonspecific cytolysis in the presence of heterologous antigen and sensitized lymphocytes. More recently, CNS demyelination was produced in sensitized guinea pigs following the local injection of tuberculin-purified protein derivative. A number of virus-induced experimental models of both CNS demyelination (Theiler's virus, a murine picornavirus) and peripheral nervous system demyelination (Marek's virus, an avian herpes virus) have been attributed to the bystander effect. This effect has been ascribed to the action of proteolytic enzymes such as neutral proteases released from activated macrophages. Dal Canto and Rabinowitz have suggested that the bystander effect may cause the similar pathological patterns in both central and peripheral nervous systems in syndromes produced by different and often unrelated viruses.

The most interesting data on post-infectious demyelination has been from Johnson, et al., who have studied measles in Peru. In their studies, eight of 17 patients with measles encephalomyelitis had lymphocyte responses to MBP. Myelin basic protein is the etiological factor in experimental allergic encephalomyelitis, a well studied laboratory model of autoimmune-mediated demyelination. It has also been found in the CSF in a majority of patients. In comparison, no virus was isolated from the CNS, measles antigen was not demonstrated in the brain, and no evidence of intrathecal synthesis of measles antibody was demonstrated. The MBP was seen early in the disease and suggests immune-mediated disease directed at host cell antigens, most likely due to abnormal immune regulation. Lymphocyte responses to MBP in single cases of encephalomyelitis after rabies vaccine or following varicella or rubella infections were similar to those seen after measles. A common immune-mediated mechanism appears to be present in post-infectious demyelination.

**Subacute Sclerosing Panencephalitis**

Subacute sclerosing panencephalitis has always been a rare disease, but it has almost disappeared from the United States since the introduction of the live measles vaccine program. Most victims have had an early exposure to natural measles infection in the first 2 years of life. Subacute sclerosing panencephalitis is usually seen in children between the ages of 5 and 17 years, although cases in older persons have been described. There is generally an early decline in intellectual function with failure in school, followed by the development of myoclonus as well as focal and generalized seizures. The patient then progresses to severe neurological deficit, coma, and death. The entire course can be as brief as 6 weeks, but on rare occasions has been as long as 10 years. The diagnosis is made by the clinical course, an abnormal EEG with a burst-suppression pattern, and the CSF findings. The serum and CSF titers of measles virus antibodies are markedly elevated, and the CSF IgG level is increased and segregates into oligoclonal IgG. The pathology consists of a mild degree of perivascular inflammation, cytoplasmic and nuclear inclusions in neurons, astrocytes, and oligodendroglia, and neuronal loss, gliosis, and demyelination.

Subacute sclerosing panencephalitis is a chronic destructive measles infection. Recently it has been suggested...
that the virological defect in SSPE may be related to the matrix (M) protein of the virus. Experimental studies in hamsters with SSPE show that nucleocapsid and M proteins appear during acute infection, but M disappears coincident with the appearance of serum antibodies to measles. 63 The disappearance of cell-free virus in the weanling hamster correlated with the appearance of measles serum antibody. 17 It has been suggested that the host antibodies acting at the cell surface cause a selective change in M protein, inhibiting the production of complete infectious virions but allowing an accumulation of viral components that gradually destroy the cell. 22

There is no definitive treatment of SSPE. However, there has been a report of improvement with the antiviral agent Inosiplex (isoprinosine). 119 In other studies, Inosiplex has not been found to be beneficial. 53 Recently, a CT study of a case of slowly advancing SSPE revealed progressive abnormalities despite clinical improvement with Inosiplex. 21 The drug is administered in a 70-mg/kg daily dose and has been administered for as long as 56 months.

**Progressive Rubella Panencephalitis**

Progressive rubella panencephalitis is a slow progressive illness caused by rubella virus. It has been described in patients who have had congenital rubella 124,130,140 and in those with a history of postnatal rubella. 76 All patients have developed clinical signs between the ages of 8 and 19 years, and all have been male. Some have had residual static neurological defects from earlier infections, while others have been free of symptoms. The disease presents with intellectual deterioration, seizures, and ataxia. The course is insidious, and the findings indicate widespread CNS involvement with optic atrophy, retinitis, cerebellar abnormalities, spasticity, and dementia. The disease lasts from 4 to 10 years. The CT scan is not particularly helpful, but the CSF is diagnostic. There may be monocytosis and elevated protein. There are increased IgG and oligoclonal bands. 127 Antibodies to rubella are present in the CSF, and the serum:CSF ratio is diminished, indicating the production of antibody to rubella within the CNS compartment. The pathology shows a panencephalitis with perivascular inflammatory changes. 141 A frank vasculitis appears to underlie some of the active lesions. On occasion, brain biopsy has yielded rubella virus; however, recovery of the virus has usually not been achieved. Rubella has also been isolated from circulating blood monocytes in one case. Neither viral antigens nor virions have yet been demonstrated in brain tissue of patients with PRP.

The pathogenesis of PRP is not completely understood. However, circulating immune complexes have been found in the serum of two patients. 28 These complexes are composed of rubella-specific IgG and rubella antigen. The questions raised by circulating immune complexes are important. The vasculitis and pathology could be the result of immune complex disease directed at viral antigen in the brain, or the immune complex could be producing defects in the immune response which allow rubella to persist and produce a cytolytic infection within the CNS.

**Spongiform Encephalopathies**

We have already reviewed the more exciting aspects concerning the nature of the etiological agents in the spongiform encephalopathies. The two human diseases associated with these unconventional agents are kuru and Creutzfeldt-Jakob disease. Kuru was first described in 1957 as endemic in the Fore natives of the eastern New Guinea highlands. 45 The disease was found in adult women and children of both sexes. The clinical picture includes ataxia and tremors, followed by death in 3 to 6 months. It has been suggested that the disease was associated with a ritual cannibalism practiced by the natives. The decline in the frequency of this disease since that rite was discontinued supports the hypothesis. 45 It is probable that the disease was transmitted by inoculation through cuts and bruises rather than via the oral route.

Creutzfeldt-Jakob disease is the best known disease caused by the unconventional agents but, even so, its incidence is only one to two cases per million population. It is known throughout the world and affects all populations. 16 Patients have a rapidly progressive dementia with myoclonus, ataxia, lower motor neuron weakness, loss of vision, and seizures. The "incubation" or "latency" period appears to be not less than 7 months, and possibly decades. 16 The CSF is normal, and the CT scan is not diagnostic. The EEG may show burst-suppression patterns at some time during the course of the illness. 111

In the brains of patients with Creutzfeldt-Jakob disease, there is widespread neuronal loss and status spongiosus. Membrane-bound vesicles are seen in dendrites and axons of the neuropil. There are a striking astrogliosis, amyloid deposits, and argentophilic plaques in the cerebrum and basal ganglia, but very little inflammation is seen. We have seen two cases recently with rather atypical features. One patient presented with focal seizures and EEG evidence of temporal lobe status epilepticus. The second patient was a women with a progressive dementia and no evidence of myoclonic jerks, seizures, focal signs, or an abnormal EEG. The clinical course was 10 weeks, and the diagnosis was made at autopsy.

The infectious agent has been found in the brain, spinal cord, CSF, cornea, spleen, lymph node, and lung. It has also been found in the leukocyte fraction of experimental animals. 16 There have been spontaneous transmissions in man via a corneal transplant, 38 suspected transmission from intracerebral placement of electrodes, 41 and possible transmission during intracranial surgery. 13 Obviously, patients with degenerative CNS disease are not suitable organ donors. Biopsy and autopsy of such patients should be carried out with care and only when the diagnosis is in doubt. Clearly, sur-
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gical instruments, EEG needles, and body fluids should be handled with caution and sterilized adequately. To our knowledge, no nurse, attendant, spouse, or physician has contracted Creutzfeldt-Jakob disease by being in contact with patients with this disorder. There is no reason to have special isolation wards for such patients. Gloves are recommended in handling infected tissues, needles, and body fluids but not in routine care of patients. Needles and needle electrodes should be autoclaved (121°C at 15 lb/sq in. for 1 hour), incinerated, or carefully discarded. Adequate disinfection is achieved with 5% hypochlorite, 0.03% permanganate phenolics, and iodine solutions. There remains no effective treatment for Creutzfeldt-Jakob disease other than supportive care and treatment of seizures.

Viral Complications of Immunodeficiency

As noted above, the host response is perhaps the major determinant of the outcome of viral infection. In man, the competence of the immune response has been affected by a considerable number of factors. Impairment of responsiveness may be due to either an inherited genetic defect or to an acquired deficiency. The acquired defects are becoming increasingly important and have occurred in patients with malignancies and infections and in those receiving immunosuppressive and cancer chemotherapeutic agents. The complications are varied, and include bacterial, parasitic, fungal, and viral infections. The opportunistic infection is greatly dependent on the nature of the underlying immunological defect. In man, opportunistic viral infections have been due to cytomegalic virus, varicella-zoster virus, HSV, Epstein-Barr virus, measles, papovaviruses, enteroviruses, and adenoviruses. The syndromes have included encephalitis, meningitis, myelitis, PML, and polyradiculoneuritis. These diseases have exhibited both an acute onset and an indolent progressive course lasting from months to years.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a subacute demyelinating disease that is caused by human papovaviruses. It is an opportunistic infection that occurs most often in an immunocompromised host. It has been described in association with lymphoproliferative and chronic granulomatous diseases and in patients during therapeutic immunosuppression, particularly after renal transplantation. It does occur in patients without underlying disease.

Patients with PML develop multifocal neurological signs that typically result in a progressive course and death in 6 months to 1 year, although some patients have been reported to survive for up to 5 years. Frequently, the disease is first apparent in one cerebral hemisphere; it usually localizes to the occipital lobe and then progresses to the rest of the brain. The neurological signs include hemianopsia, hemiparesis, dysphasia, and cerebellar and brain-stem signs. The course is afebrile, and the CSF is usually normal. Serological studies produce variable results and are of little help in diagnosis. The CT scan is most useful. Typically, there is a low-density nonenhancing lesion involving the white matter and sparing the cortex. This lesion, appearing in an immunosuppressed patient with normal CSF findings, is almost always diagnostic of PML. Nevertheless, it may still be necessary to perform a biopsy on the patient. Toxoplasmosis may imitate the lesions in such a patient; however, in this case, the CSF is not normal and some enhancement may be evident on CT scanning.

The pathological picture shows foci of demyelination with axonal sparing, oligodendrocyte loss, and marked astroglial proliferation. Around the foci of myelin loss, there are enlarged oligodendrocytes with intranuclear inclusions. Immunofluorescent studies show viral antigen in the oligodendrocytes, and electron microscopic examination of the inclusions shows paracrystalline arrays of papovavirus virions. All but a very few cases of PML are due to the human papovavirus, JC. Viruses antigenically similar to simian virus 40 have also been isolated from two patients with PML, and have been antigenically identified in the CSF in a patient with PML. Antibody to JC virus is widespread in human populations, and it is not clear if the virus is persistent or latent in the CNS of asymptomatic patients.

The pathogenic mechanism of PML is thought to be the selective infection of a susceptible CNS cell, the oligodendrocyte, producing lysis and demyelination. The JC virus, like other papovaviruses, has neoplastic potential in experimental animals, but thus far it has not been associated with human tumors. The alteration of astrocytes in PML is very suggestive of a malignant transformation, and some astrocytes have been shown to contain viral DNA indicating a latent “non-permissive” infection.

The treatment of PML has not been satisfactory. There have been case reports of some improvement with ARA-C, although no extensive studies have been done. Correction of the immunoincompetence, at least in renal transplantation patients, has not altered the clinical course of the PML.

Acquired Immunodeficiency Syndrome

Recently, a new disease has been described as “acquired immunodeficiency syndrome” (AIDS). In the past several years, 312 of 827 patients with AIDS have died, and three or four new cases are reported each day. The susceptible populations include male homosexuals, drug abusers, hemophiliacs, children in close contact with adults having the disease, and Haitians, particularly those who have recently immigrated. The patients with this disease have cutaneous anergy, a decrease in the number and activity of helper T cells, and a normal or increased number of suppressor T cells. Thus, the helper/suppressor cell ratio is reversed.

The most common viral complications have been
disseminated herpes simplex with meningitis and encephalitis, cytomegalovirus retinitis with blindness, and PML. The nonviral CNS complications have included toxoplasma abscess, Cryptococcus neoformans meningitis, Candida albicans infection, and tuberculosis. The etiology of AIDS is unconfirmed. It is probable that an infectious agent such as a retrovirus plays a role. A common epidemiological feature linking Haitians, drug abusers, homosexual men, and hemophiliacs is the high incidence of hepatitis B virus markers. Both Epstein-Barr virus and cytomegalovirus are known to cause immunosuppression and a reversal of the helper/suppressor cell ratio not unlike that seen in AIDS. Tubuloreticular structures seen on electron microscopy have been described in mononuclear leukocytes in the blood and lymph nodes of AIDS patients. Recently, a new structure, the vesicular rosette, has been revealed by electron microscopy in the cytoplasm of lymph node cells in homosexual men both with and without AIDS. All the patients had lymphadenopathy. The nature of these configurations is not yet evident.

Conclusions

Considerable strides have been made in understanding the nature of multiplication of viruses and the host's response to viral infection. The application of the techniques of molecular biology to the study of the pathogenesis of viruses has led to new insights into the mechanisms of latency, persistence, and antiviral agents. Improved antiviral medications may be expected. New technology, such as recombinant DNA and hybridoma monoclonal antibody production, will produce the tools for sensitive and rapid diagnostic methods as well as for possible therapeutic interventions when human hybridomas are available. Hybridomas producing human antibodies will be useful in modulating the immune response for clearing viruses and correcting immunoincompetent states as well as for interfering with immune-mediated parainfecitious processes. Vaccination programs have eliminated many of the post-infectious childhood syndromes, as well as SSPE, and new vaccines for varicella-zoster virus, herpes zoster virus, and other agents are on the horizon.

Many problems still remain in the diagnosis and treatment of CNS viral diseases. Biopsy of the brain represents a proven means of rapid diagnosis, and neurosurgeons need to give careful thought to techniques that will provide adequate tissue from involved areas with minimum harm to the patient. Even with future use of specific antiviral agents, the widespread administration of interferon, and the use of new antinflammatory agents, many patients will die of cerebral edema, blood pressure instability, respiratory failure, and cerebrovascular accidents precipitated by the many CNS viral diseases. The ultimate factors in the recovery of patients with viral encephalitides will be early diagnosis combined with high-quality supportive and nursing care.

L. P. Weiner and J. O. Fleming

Addendum

In a recent article (Popovic M, Sarnagadharan MG, Read E, et al: Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 224: 497–500, 1984), a member of the human T-cell leukemia virus family has been closely linked to AIDS and seems a likely etiological agent of the disease.

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