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The Brain in AIDS: Central Nervous System HIV-1 Infection and AIDS Dementia Complex

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Infection with human immunodeficiency virus type 1 (HIV-1) is frequently complicated in its late stages by the AIDS dementia complex, a neurological syndrome characterized by abnormalities in cognition, motor performance, and behavior. This dementia is due partially or wholly to a direct effect of the virus on the brain rather than to opportunistic infection, but its pathogenesis is not well understood. Productive HIV-1 brain infection is detected only in a subset of patients and is confined largely or exclusively to macrophages, microglia, and derivative multinucleated cells that are formed by virus-induced cell fusion. Absence of cytolytic infection of neurons, oligodentrocytes, and astrocytes has focused attention on the possible role of indirect mechanisms of brain dysfunction related to either virus or cell-coded toxins. Delayed development of the AIDS dementia complex, despite both early exposure of the nervous system to HIV-1 and chronic leptomeningeal infection, indicates that although this virus is "neurotropic," it is relatively nonpathogenic for the brain in the absence of immunosuppression. Within the context of the permissive effect of immunosuppression, genetic changes in HIV-1 may underlie the neuropathological heterogeneity of the AIDS dementia complex and its relatively independent course in relation to the systemic manifestations of AIDS noted in some patients.

IT IS NOW CLEAR THAT INFECTION WITH HUMAN IMMUNODEFICIENCY virus type 1 (HIV-1) is complicated by a dementing neurological disorder, the AIDS dementia complex, which is both a common and an important cause of morbidity in patients in advanced stages of infection (*1*). It was not long after the recognition of AIDS in 1981 that reports began to appear of an unusual encephalopathy in affected patients (*2*). Initial efforts to identify and classify this neurological syndrome were directed toward identifying an underlying opportunistic infection (*3*), but misgivings with this approach arose as more detailed clinical-pathological studies were performed (*1*, *4*) and as a parallel disorder was observed in children, who are less prone to opportunistic brain infections (*5*). Identification of the retroviral etiology of AIDS allowed introduction of the hypothesis that HIV-1 itself might infect the brain and directly cause dementia. This hypothesis, accounting for the frequency and unique character of both the clinical syndrome and its neuropathology, also found support in precedents of retrovirus brain infections of animals that had been studied as models of neurodegenerative disorders. In particular, comparisons were made with visna virus, the prototype lentivirus, which shares considerable biological similarity and some genetic homology with HIV-1 (*6*). This rapidly led to identification of HIV-1 in brains of demented patients, first by Southern blot analysis and in situ hybridization (*7*) and subsequently by other techniques (*8–16*).

Although considerable progress has been made in characterizing and understanding this new neurological disorder, many questions remain regarding both its clinical and biological features (*17*). In this article we review the clinical, epidemiological, and pathological aspects of the AIDS dementia complex and discuss some of the principal unresolved issues regarding its viral pathogenesis.

Clinical Features of AIDS Dementia Complex

Patients with the AIDS dementia complex present with a variable, yet characteristic, constellation of abnormalities in cognitive, motor, and behavioral function (*1*). Perhaps the salient aspects of the

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disorder are the slowing and loss of precision in both mentation and motor control. Early in the illness, patients frequently report that they must keep lists in order to carry out their normal activities and that complex but formerly routine mental tasks take longer and need to be consciously broken down into component steps. Concomitantly, these patients often lose interest in their work as well as in their social and recreational activities. It is this growing apathy along with mental slowing that is frequently mistaken for depression by their associates, yet dysphoria is often absent. Motor symptoms usually lag somewhat behind, but exaggerated tremor or mild gait unsteadiness may be among early complaints, while on examination, slowing of rapid alternating eye and extremity movements and abnormal "release" reflexes are common.

With time, intellectual impairment becomes more pervasive, broadly affecting nearly all aspects of cognition, with further slowing and inaccuracy of performance. Increasing apathy, slowing of speech, and mental impoverishment ultimately may progress to near or absolute mutism and severe dementia. In parallel, gait unsteadiness gives way to frank weakness, general hypokinesia, and incontinence. Variants of the syndrome occur in which particular aspects predominate. Thus, in some patients an agitated mental state with mania or other forms of organic psychosis may occur; in others, weakness with progressive paraparesis dominates the course. Extrapyramidal dysfunction with bradykinesia and postural instability may resemble Parkinsonism, but without the resting tremor.

Formal neuropsychological studies are useful in documenting and serially following disease severity and in understanding the pathophysiological basis of the symptoms and signs (*18–20*). The characteristic abnormalities include difficulty with complex sequencing, impaired fine and rapid motor movement, and reduced verbal fluency, while other verbal abilities, including vocabulary and object naming, tend to be maintained even when the disease is relatively advanced. Also notable in many patients is a discrepancy between their complaints of frequent forgetfulness and their relatively preserved performance on formal memory testing. In general, the neuropsychological impairments become most prominent when some or all of the following demands are placed on the patient: performance under time pressure, problem solving, visual scanning, visual-motor integration, and alternation between two or more performance rules or stimulus sets (*18*, *20*). Although depression may coexist with, mimic, or potentially result from the AIDS dementia complex, clinical evaluations as well as analyses of data from self-report questionnaires indicate that depression does not account for impaired performance on neuropsychological tests that are most sensitive to the AIDS dementia complex. The pattern of clinical and neuropsychological abnormalities conforms to what has been termed a "subcortical dementia," previously applied to patients with progressive supranuclear palsy, Huntington's disease, and Parkinson's disease (*21*).

Computed tomographic scanning and magnetic resonance imaging reveal the common early brain atrophy and, less frequently, abnormalities of the white matter in patients with this disorder (*1*, *22*). A study conducted with positron emission tomography made it possible to distinguish patients with AIDS dementia complex from normal subjects on the basis of patterns of regional brain glucose metabolism (*23*). The metabolic pathology of the disorder was characterized by two patterns of regional covariation, one influenced primarily by subcortical metabolism and correlated with impairment of fine motor control, and the other influenced by cortical metabolism and correlated with impairments in verbal fluency and problem solving. With respect to disease progression, basal ganglion and thalamic glucose hypermetabolism appeared to be an early component of the disorder that was followed later by perturbation of subcortical-cortical relationships and general hypometabolism.

The Epidemiology of HIV-1 Infection of the Central Nervous System

The AIDS dementia complex must be considered in the context of the overall course of HIV-1 infection and the still imprecise picture of other central nervous system (CNS) disorders known or suspected to be related to primary infection of the brain with HIV-1 (Fig. 1). The AIDS dementia complex is the most common of these, but emerging evidence of earlier symptomatic and asymptomatic CNS HIV-1 infection provides an important broader view of the interaction of this retrovirus and the human nervous system.

Early symptomatic infection of the CNS. Although described only as individual cases (*15*, *24*), the CNS may be affected early in the course of HIV-1 infection. Either within the context of the seroconversion-related, mononucleosis-like illness accompanying primary HIV-1 infection, or somewhat later during the "latent" phase, headache, as well as encephalitis, aseptic meningitis, ataxia, and myelopathy have been described. These disorders are monophasic with most resolving in weeks. Although their incidence is probably low, these acute disorders may be underappreciated since they are

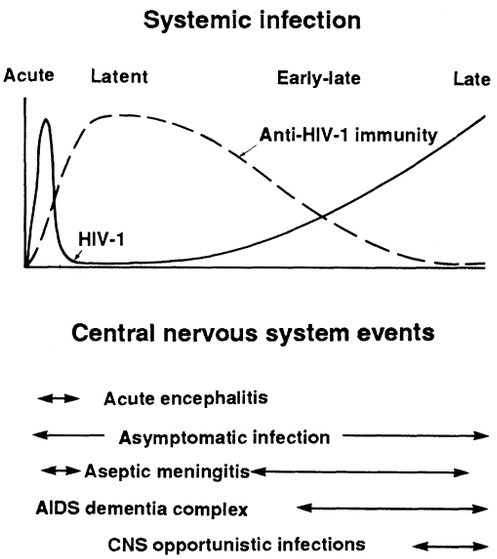

Fig. 1. Stages of HIV-1 infection in relation to the development of the AIDS dementia complex and other neurological complications. In this model, adapted from that proposed for systemic disease by Redfield (*51*), we have divided systemic disease into four phases: an acute phase following initial virus exposure; a latent phase without systemic symptoms or signs; and two later phases, an early-late phase associated with "minor" opportunistic conditions and roughly corresponding to the AIDS-related complex but including also the period when Kaposi's sarcoma may develop, and a final late phase in which major, AIDS-defining, opportunistic infections occur. Using different but conceptually parallel terminology, Redfield relates these conditions to changing virus load and immunity to HIV-1. Thus, acute viremia may be associated with high viral titers in the blood, but this is curtailed as appropriate host immune responses suppress virus replication as in other acute viral syndromes. However, the virus persists and over the course of the latent period, by virtue of its effect on $CD4^+$ lymphocytes and perhaps macrophages, slowly erodes the defenses that protect against opportunistic pathogens as well as HIV-1 itself. At a certain threshold, the balance between the immune response and HIV-1 replication is tipped so that the virus load increases and the rate of immunosuppression accelerates. Present epidemiological and clinical observations allow the CNS complications to be tentatively seen within this pathogenetic framework. Acute encephalitis and aseptic meningitis accompany or soon follow initial viremia and exhibit a similar monophasic time frame, terminating as CNS virus is limited by effective immune defenses. However, asymptomatic infection may persist but without meaningful invasion of the parenchyma or brain dysfunction. Only when immune defenses wane is there substantial invasion and HIV-1 replication in the brain. Hence, the AIDS dementia complex is a relatively late sequela and requires the permissive effect of immunosuppression.

clinically indistinguishable from other acute viral or postinfectious encephalitides, most of which never achieve specific diagnosis.

Asymptomatic infection. In contrast to the apparent rarity of the acute syndromes, early asymptomatic HIV-1 infection of the CNS, or at least of the leptomeninges, is relatively common and may even be the rule. Studies of the cerebrospinal fluid (CSF) have provided a valuable "window" into the biology of HIV-1 infection of the nervous system. Evidence of early infection and local host reactions in the CSF of asymptomatic seropositive patients include: (i) increase in the number of inflammatory cells or protein content and the presence of "oligoclonal" immunoglobulin bands of undetermined specificity; (ii) local, "intrablood-brain barrier" synthesis of antibody to HIV-1; and (iii) isolation of virus or detection of viral antigens (*25, 26*). Although data are limited, even asymptomatic patients may experience an acute phase of infection in which there is detectable virus and host cell reaction in the CSF, as well as a subsequent phase in which virus is reduced or absent but the local production of HIV-1 antibodies continues.

Aseptic meningitis. Aseptic meningitis occurs not only in the setting of seroconversion, but, even more commonly, later in the course of HIV-1 infection, usually as the latent phase progresses to the AIDS-related complex (ARC) or full-blown AIDS (*2, 27*). Both acute and chronic forms of this disorder have headache as their most prominent feature. The CSF again shows a mononuclear pleocytosis, usually with normal glucose and mildly elevated protein, and HIV-1 is readily isolated. This syndrome itself is benign, although it carries an overall poor prognosis and is a harbinger of other AIDS-related complications. Whether or not these patients have a higher incidence or pursue a different course with respect to the AIDS dementia complex is uncertain.

AIDS dementia complex. The epidemiology and course of the AIDS dementia complex are imprecisely defined with estimates being derived principally from clinical and pathological series rather than more representative population-based or prospective analyses. Hence the frequency of this syndrome at each stage of systemic HIV-1 infection remains uncertain. However, if the early monophasic encephalitides are excluded, the AIDS dementia complex appears to be confined to the later phases of systemic infection (Fig. 1). Most cases occur in the setting of systemic AIDS (*1*) as defined by the Centers for Disease Control (CDC) criteria (*28*) relating to life-threatening opportunistic infections. In our own selected clinical experience we have estimated that at the time of AIDS diagnosis perhaps one-third of patients exhibit overt and one-quarter subclinical AIDS dementia complex; these numbers progress to an eventual preterminal prevalence of perhaps two-thirds of patients with clinically significant forms of the disorder and one-quarter with subclinical forms (*1, 29*). Clearly, however, the disorder may develop before the diagnosis of systemic AIDS, and a substantial, though indeterminant, number of patients with "minor" systemic disease (ARC) develop the syndrome (*29, 30*).

The AIDS dementia complex may also develop in the absence of any systemic symptoms, but this is unusual; most, if not all, of these patients have laboratory evidence of immunosuppression. It is important to emphasize that while some reports have described neuropsychological impairment in HIV-1 seropositive individuals without ARC or AIDS, these individuals were not immunologically normal and were probably on the threshold of the later stages of HIV-1 infection (*30*). Furthermore, the definition of impairment in the testing procedures is not firmly established. Thus, the neuropsychological abnormalities reported in these small series should not be extrapolated to the large existing population of seropositive individuals and do not now justify excluding seropositive individuals from employment.

Overall, however, the AIDS dementia complex is one of the most important complications associated with HIV-1 infection. Whether appearing early or late, whether dominating the course of infection or compounding systemic disease, this neurological condition gradually impairs function in work, in daily life, and eventually in self care. The progressive disability of patients with this disorder also has broad societal implications that relate to lost productivity as well as to the costs of long-term assistance and institutional care.

Pathology of the AIDS Dementia Complex and CNS HIV-1 Infection

The pathological abnormalities in patients with the AIDS dementia complex are variable, and it is not yet clear that the clinical syndrome corresponds to a single etiopathogenetic entity. The principal histopathological abnormalities are most prominent in the subcortical structures, notably in the central white matter, deep gray structures including the basal ganglia and thalamus, the brain stem, and the spinal cord (*4, 31*). There is relative sparing of the cortex. One can divide the histopathological abnormalities into three seemingly discontinuous, but frequently coexisting, sets: diffuse pallor of the white matter, multinucleated cell encephalitis, and vacuolar myelopathy (*4*). The most common of these, diffuse white matter pallor accompanied by astrocytic reaction, involves particularly the central and periventricular white matter and generally parallels in severity the neurological symptomatology (Table 1). Diffuse white matter pallor can also be identified in mild degree in an appreciable number of patients with apparently normal or subclinically altered neurological status, and indeed the presence of atrophy and diffuse pallor in individuals without overt neurological

Table 1. Subclassification of AIDS patients and the dementia complex according to clinical, pathological, and virological findings. The listed frequencies are based on estimates derived from our earlier studies (*1, 4, 7, 13, 52*) but should only be considered tentatively established since some of the observations involved different sets of patients. AIDS patients are divided into three groups on the basis of the presence (groups 1 and 2) or absence (group 3) of clinically overt AIDS dementia complex and the pathological identification of multinucleated cell encephalitis (group 1). The degree of diffuse pallor tends to segregate with the severity of clinical dementia although there is clear overlap among the three groups. The frequencies given for vacuolar myelopathy include only findings previously categorized as grades 1 (severe) and 2 (moderate) and omits mild changes; other workers have remarked on a lower incidence of this abnormality. The HIV-1 detection methods included immunohistochemistry, Southern blot, and in situ hybridization; direct isolations of virus from brain or CSF were not included in the classification.

Clinical-pathological classification	Estimated percentage of all AIDS patients at autopsy	Clinical severity of the AIDS dementia complex	Neuropathology			Approximate percentageof brains with detected HIV-1
			Percentage with multinucleated cells	Diffuse pallor (degree)	Percentage with vacuolar myelopathy	
Group 1	25	Moderate to severe	100	Moderate to severe	40	95
Group 2	50	Mild to moderate	0	Mild to moderate	35	15
Group 3	25	Absent (subclinical)	0	Absent to mild	5	<5

disease provides an additional indication of the high frequency of brain involvement in HIV-1–infected individuals. When pallor is present without multinucleated cells, inflammatory changes are characteristically scant, consisting of a few perivascular lymphocytes and brown-pigmented macrophages accompanying the astrocytosis.

Multinucleated cells are found in a subgroup of patients with more severe clinical disease. In the brains of these patients reactive infiltrates are more prominent and consist of perivascular and parenchymal foamy macrophages, microglia, and lymphocytes, along with the multinucleated cells (Fig. 2A). These infiltrates are most often concentrated in the white matter and deep gray structures, including particularly the basal ganglia, thalamus, and pons. In the white matter, they are often surrounded by focal rarefaction of myelin. In both white and gray matter there is accompanying reactive astrocytosis, but loss of oligodendrocytes or neurons is not characteristic. Additional, but far less common, white matter changes include spongy vacuolation, which may be diffuse or focal. In pediatric cases the pathology is similar except that it also includes a calcific vasculopathy (*5*).

Inflammation with multinucleated cells may also be present in the spinal cord, but in our own experience a vacuolar myelopathy is more common (*4, 32*). The latter pathologically resembles subacute combined degeneration resulting from vitamin B12 deficiency, but serum B12 levels are normal. The vacuolation appears to result from swelling within the layers of the myelin sheaths. Similar changes can also extend into the brainstem of some patients. Although there is a general correlation between the incidence of vacuolar myelopathy and the other pathological abnormalities found in the brain, the myelopathy can certainly occur in the absence of the multinucleated cell–associated changes. Additionally, there is not always a one-to-one correlation between the severity of this myelopathy and that of the brain abnormalities, and no pediatric examples of vacuolar myelopathy have been published. These discrepancies leave very much open the question of whether vacuolar myelopathy is a variant of the process causing the multinucleated cell formation and other brain changes described above or whether it is pathogenetically and etiologically independent. Indeed, the overall pathological diversity underlying the AIDS dementia complex is one of its fundamental puzzling aspects, and a reason to retain the latter term to describe a syndrome until the underlying etiologies and pathogenetic processes are established.

There is now firm evidence that the AIDS dementia complex, at least when multinucleated cells are present histopathologically, is associated with direct brain infection by HIV-1. Southern blot analysis has shown both a high frequency (comparable to that of lymphatic tissue) and high copy number of proviral DNA in the brains of patients with this pathology, and both integrated and nonintegrated forms of the genome have been identified (*7*). In situ hybridization and immunohistochemical studies have also revealed the presence of viral nucleic acid and antigens within these brains (*8–13*), and HIV-1 has been cultured directly both from brain and CSF of demented patients (*15, 26*). In addition, HIV-1 virions have been detected by electron microscopy (*14*).

In our own experience, the distribution of productively infected cells identified immunocytochemically parallels the neuropathological findings; these cells are most prominent in subcortical structures, although cortical involvement can also occur (*13*). Although there remains some controversy concerning the cell types involved in productive brain infection, there is emerging consensus that macrophages and multinucleated cells derived from macrophages are principal participants (Fig. 2B) (*8, 9, 12, 13, 16*). Although not an invariant finding in HIV-1–infected brains, the multinucleated cells are histological markers of productive HIV-1 brain infection and indeed the multinucleation almost certainly results from direct virus-induced cell fusion in situ; these cells are thus the in vivo counterparts of the syncytial cytopathology characteristic of HIV-1 in cell culture (*33*). Viral antigens have also been detected in other cells with cellular processes (*13*). Many of these cells have been identified morphologically and histochemically as microglia (Fig. 2, C and D) (*12, 34*). Microglia additionally appear to participate in the formation of multinucleated forms (*32*). Whether other cell types in the brain, including astrocytes, oligodendrocytes, neurons, or vascular endothelium are also infected is less clear (*10, 13, 14*). Cell culture studies have demonstrated low-level infection of astrocytic tumor cell lines (*35*), and similar restricted or latent infection of these and other native brain elements has not been ruled out. As with visna virus (*36*), such infection may be pathogenetically important.

Viral Pathogenesis of AIDS Dementia Complex

Unresolved issues of the pathogenesis of the AIDS dementia complex and CNS HIV-1 infection can be considered in the context of three fundamental questions.

1) *What determines progression of HIV-1 CNS infection and its various clinical manifestations at each stage?* There may be genetically determined host differences that influence initial susceptibility to HIV-1 infection and perhaps the speed of disease progression. Likewise, other infections, past or present, may also modulate CNS infection. However, the evolution of CNS infection probably depends principally on: (i) changes in the host immune response to the virus and (ii) changes in the infecting virus.

Progressive immunosuppression is, of course, the hallmark of HIV-1 infection. In addition to conferring vulnerability to opportunistic infections, this immunosuppression also affects the host's defense against HIV-1 (*37*). Waning defenses against HIV-1 and a resultant increase in the "virus load" probably also influence HIV-1 infection of the CNS and provide a framework for interpreting the neurological manifestations at each phase of the evolving infection (Fig. 1). The acute CNS disorders occurring at or near the time of initial exposure to HIV-1 and seroconversion can be viewed as pathogenetically similar to other acute encephalitides and aseptic meningitides caused by organisms that are of relatively low neurovirulence. In most patients, immunological responses effectively reduce or eliminate the virus from the brain, and, mechanistically, CNS dysfunction may relate as much to the inflammatory changes and "bystander effects" as to the virus itself; hence the good recovery.

The subsequent course of asymptomatic CNS infection on the one hand indicates that the virus is "neurotropic" by virtue of its predilection to infect the leptomeninges early and frequently, and on the other hand provides evidence of the low neurovirulence of HIV-1 despite its persistence, at least as long as immune defenses restrict its replication and spread. Neuropathology is mild or absent, and our own studies thus far indicate that productive brain infection is not detected by immunohistochemistry. Invasion and replication of virus within the brain and secondary injury are therefore probably minimal or absent during this phase.

As the degree of immunosuppression increases and the transition from the latent period to the later phases of disease occurs, HIV-1 replication, including that in the CNS, may escape immune control. This probably explains why the AIDS dementia complex begins to appear at this point. In this respect, HIV-1 may be similar to JC virus, which causes progressive multifocal leukoencephalopathy only in the absence of an effective host antiviral response (*38*). In the case of HIV-1, however, it is the same organism that first creates "opportunity" by virtue of its effect on the immune system and then

takes advantage of this opportunity to infect the brain.

Although immunosuppression appears to have a necessay permissive influence on the development of the AIDS dementia complex, it may not account for discrepancies in the coevolution of systemic and CNS disease noted in some patients. Thus, some patients develop multiple opportunistic infections and have minimal circulating $CD4^+$ T lymphocytes yet remain neurologically intact, while others show progressive neurological deterioration over many months to years but develop few or no major opportunistic infections. Such differences provide a clinical basis for examining whether there are neurotropic variants of HIV-1 that more readily infect brain macrophages, microglia, or other neural cell types. Likewise, differences in viral strains may contribute to the heterogeneity of disease patterns and pathologies. One can speculate, for example, that some viral strains may be more likely to cause aseptic meningitis than the AIDS dementia complex, or that some will induce vacuolar change in the spinal cord while others will cause only multinucleated cell encephalitis. Genetic drift with genesis of variants of HIV-1 may, in fact, be more important in causing these different pathologies than in determining overall vulnerability of the nervous system. Virus strain differences may also explain apparent geographic differences in pathology. In attempting to establish the relevance of neurotropic variants of HIV-1, therefore, one needs to consider not only the presence of neurological disease but also its pathological substrate. The virus is well known to have a high mutation rate and to show marked polymorphism (*39*). Not only do isolates differ from one patient to another, but several isolates from a single patient may differ from each other. Putative neurotropic variants have, in fact, been reported, with differing cell tropisms, cytopathology, and patterns of replication in cell culture (*16, 40*). However, in the absence of more direct model test systems, the biological and pathogenetic importance of these changes remains speculative.

2) *Why (and how) is the brain infected*? This question is of particular interest because productive HIV-1 brain infection appears to be confined principally to macrophages, that is, cells extrinsic to the brain, and to a lesser extent to microglia, their counterpart resident in the brain. Why then the apparent selection of the brain as a target? Perhaps there is less selectivity than we now recognize, and CNS infection is, in fact, only part of a generalized infection, attracting attention because of its functional importance. Another alternative is that chronic leptomeningeal infection or nonproductive infection of astrocytes or other neural elements may initiate involvement of the brain parenchyma. The brain has been shown to contain messenger RNA corresponding to the CD4 molecule that serves as the receptor for HIV-1 on lymphocytes (*41*). However, the cells expressing this determinant in brain, and its role in brain infection, remain to be clarified. If the permissiveness of macrophages and microglia is under immune control, the end stage of CNS involvement with multinucleated cell encephalitis may simply represent amplification by these elements of latent or indolent (astrocytes, oligodendrocytes, neurons) or extraneural (leptomeninges) infection.

It has also been suggested that monocyte-derived macrophages become infected peripherally prior to migrating into the CNS: the "Trojan horse" hypothesis (*36*). The large number of infected macrophages in some brains imply that (i) infected monocytes selectively migrate into the brain, (ii) latent infection of monocyte/macrophages is selectively activated in the brain, or (iii) there is secondary spread of HIV-1 to these permissive cells within the brain. Although each of these mechanisms may operate, we favor the third as the dominant one. Similarly, microglia are probably infected in situ, although there is still some controversy about the timing of

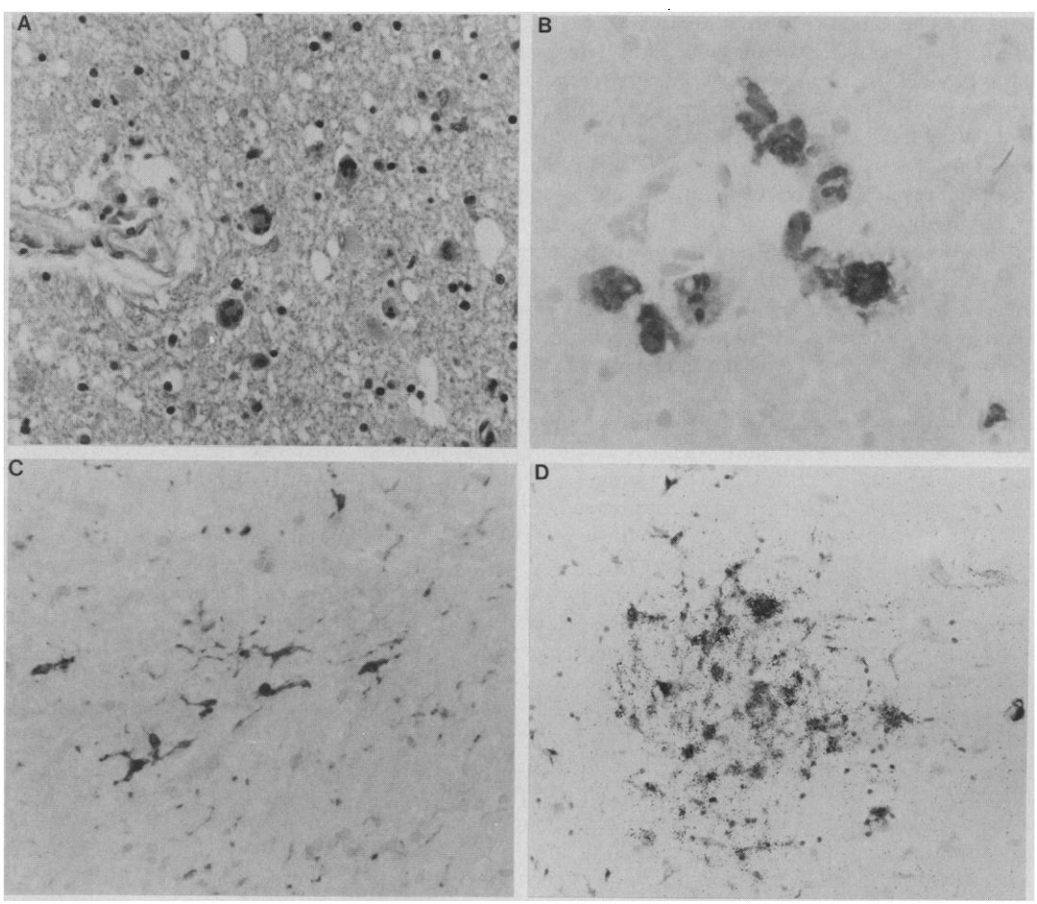

Fig. 2. HIV-1 infection of brain. (**A**) A section of deep, white matter showing spongy vacuolation, astrogliosis, and several multinucleated giant cells. Perivascular mononuclear cells are also present (hematoxylin eosin, ×425). (**B**) Infection of perivascular multinucleated cells with HIV revealed by an immunoperoxidase technique (*13*) with the use of a monoclonal antibody to core protein, p25, (avidin-biotin immunoperoxidase with hematoxylin counterstain, ×550). (**C**) The same protein, p25, is present in pleomorphic microglia with elongated cytoplasmic processes (avidin-biotin immunoperoxidase with hematoxylin counterstain, ×375). (**D**) In situ hybridization with a ^{35}S-labeled RNA probe (*8*) to detect HIV-1 RNA which is colocalized in cells binding the lectin *Ricinis comminis* agglutinin I (*34*), a marker of macrophages and microglia (lectin histochemical preparation with hematoxylin counterstain, ×250).

their ontogeny (*42*). Thus, many questions remain. Some of the most important include: Does cell-free virus in blood infect the brain by way of endothelial cells? Does the CSF become infected via the choroid plexus, as with visna virus, with the virus spreading secondarily to the brain parenchyma? What determines the distribution of virus and tissue injury within the brain so that productive infection involves most prominently the deep gray structures and white matter? Is this related to target cell vulnerabilities or to the route of entry?

3) *How is the CNS injured by infection?* The mechanisms underlying the neurological dysfunction of the AIDS dementia complex are far from clear. The paucity or absence of productive infection or lysis of neurons, oligodendrocytes, or astrocytes indicates processes other than simple destruction of these essential cells. In the subset of patients with multinucleated cells in the brain (group 1 in Table 1), the subcortical distribution of HIV-1–infected cells conforms to that of the neuropathology. Microfoci of infected macrophages, microglia, and derivative multinucleated cells are frequently accompanied by local edema and, uncommonly, frank demyelination. This pattern suggests that indirect mechanisms of tissue damage predominate and relate to the release of toxic substances by infected cells. These may be cell-coded products, for example, cytokines such as tumor necrosis factor or enzymes with bystander effects on surrounding tissue (*43*); and they may be released either as part of the physiological cellular reaction to infection or as a result of virus-induced alteration of cell metabolism. Alternatively, products of viral genes may be toxic to surrounding uninfected tissue. Recently, a model of this type of indirect effect was delineated that involved the HIV-1 envelope glycoprotein gp120 interfering with the activity of a neurotrophic factor, neuroleukin, with which it has partial sequence identity (*44*).

Thus far we have detected productive infection immunohistochemically in only a minority of patients without mulinucleated cells and with pathology restricted to diffuse white matter pallor (group 2 in Table 1). The pathogenesis of infection and brain injury in these patients, therefore, is even less clear than in group 1 patients. Perhaps the insensitivity of current methods prevents detection of underlying latent or indolent infection in which there is limited transcription of viral genes yet impaired cell function. Although the cellular substrate of the nearly ubiquitous brain atrophy in these patients is not yet defined, indolent or intermittent brain HIV-1 infection, or even toxins released into the CSF by leptomeningeal infection or into the blood by systemic infection, might reduce brain myelin by an effect on oligodendrocyte metabolism. The diffuseness of the white matter pallor in these patients suggests a generalized toxic process. The functional integrity of neurons or astrocytes might be similarly affected by toxins. Wiley and colleagues have suggested that HIV-1 infection of endothelial cells might result in altered vascular permeability (*10*).

The vacuolar myelopthy has also not yet been related to direct HIV-1 infection in the regions of the spinal cord showing myelin changes. In particular, oligodendrocytes that elaborate and maintain the vacuolated myelin have not been shown to be productively infected. A murine retrovirus in which neuronal vacuolation occurs in the absence of apparent virus infection of the neurons themselves provides a precedent for secondary pathogenic effects of infected cells on neighboring cells or of nonproductive infection (*45*).

Therapeutic Rationale and Prospects

The evidence that the AIDS dementia complex is caused either partially or wholly by direct HIV-1 brain infection and that the virus frequently invades the CNS early in the course of systemic infection even in the absence of symptoms provides the rationale for seeking antiviral drugs that can penetrate the blood-brain and blood-CSF barriers (*46*). The CNS may be considered a possible reservoir for infection, much as it provides a sanctuary for leukemic cells. However, the clinically quiescent or latent phase of infection that appears to continue as long as host antiviral defenses are intact suggests that therapies capable of restoring immune function might also be important in preventing or reversing CNS symptomatology.

What can be expected of antiviral chemotherapy in the AIDS dementia complex? The relatively bland neuropathology in some patients, the prominent affliction of white rather than gray matter, and the major involvement of cells other than neurons, astrocytes, and oligodendrocytes in productive infection all provide a theoretical background for the hope that neurological injury may be reversible. We have observed spontaneous substantive improvement in some patients, and preliminary data reported by others suggest that the antiviral nucleoside zidovudine (AZT, azidothymidine) may be capable of ameliorating the AIDS dementia complex (*47*). Further studies are now needed to confirm these findings and to establish the overall impact of such therapy, including its long-term prospects.

Additional Implications of the AIDS Dementia Complex

The role of HIV-1 in the AIDS dementia complex has rekindled interest in the involvement of other viruses, particularly retroviruses, in neurological disease. This has already resulted in the discovery that another retrovirus, human T-lymphotropic virus type 1 (HTLV-1), is associated with a progressive myelopathy referred to in certain equatorial regions as tropical spastic paraparesis (TSP) and in Japan as HTLV-1–associated myelopathy (*48*). One report also suggested an association of HTLV-1 or a related virus with multiple sclerosis (*49*), but this has not been confirmed by others (*50*). Nevertheless, HIV-1 infection of the CNS and the AIDS dementia complex provide a novel view of human viral pathophysiology and strong justification for considering retroviruses in other neurological and psychiatric disorders of unknown etiology.

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Education to Prevent AIDS: Prospects and Obstacles

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A number of obstacles thwart effective education to prevent AIDS in the United States. These include the biological basis and social complexity of the behaviors that must be changed, disagreement about the propriety of educational messages to prevent AIDS, uncertainty about the degree of risk to the majority of Americans, and dual messages of reassurance and alarm from responsible officials. Long-term protection of an individual from infection requires extreme changes in risk-taking behavior. Partial shifts toward safer practices may be epidemiologically important in retarding the rate and extent of spread of infection. Though some striking changes in behavior have occurred, especially in homosexual populations in areas with high prevalence of AIDS, educational efforts to date have succeeded more in raising awareness and knowledge about AIDS than in producing sufficient changes in behavior. The United States has yet to mount a nationwide comprehensive, intensive, and targeted education program to prevent AIDS.

TODAY, MOST AMERICANS VIEW THE ACQUIRED IMMUNODEficiency syndrome (AIDS) as the most serious health threat confronting the United States (*1*). Approximately 50,000 Americans have been diagnosed with the disease since 1981 (*2*). More than half are dead, and no one with AIDS has yet been cured. While researchers seek more effective therapies and biological preventives, education and behavior change have been repeatedly and correctly cited as the only available means of curtailing the spread of the human immunodeficiency virus type 1 (HIV-1) responsible for AIDS.

Extensive epidemiologic investigation has affirmed the principal means by which HIV-1 is spread—blood, sex, and birth (*3*). In the United States, the major groups who have developed AIDS are men exposed by homosexual contact, intravenous drug users who use contaminated needles, hemophiliacs and blood recipients prior to institution of protective measures, and the offspring of infected mothers.

The virus can be transmitted sexually from men to women and

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