REVIEW ARTICLE

The Neuropathology of AIDS

UCLA Experience and Review

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The central nervous system (CNS) has been examined at autopsy in 89 patients who died of the acquired immune dificiency syndrome (AIDS), including 14 patients who died primarily of neurologic complications of the disease. A total of 66 brains (74%) showed siginificant pathologic abnormalities, with opportunistic infections including cytomegalovirus (14) and cryptococcal (11) infections, progressive multifocal leukoencephalopathy (6), toxoplasmosis (6), and histoplasma microabscesses (1). Incidental *Mycobacterium avium-intracellulare* infection was found in 4 cases. Simultaneous CNS infection by more than one microorganism was encountered in 5 patients. Subacute (microglial nodule) encephalitis-related to cytomegalovirus infection or possibly brain infection by the causative agent of AIDS was present in 56 cases. Primary CNS lymphoma was noted in 3 patients. Secondary CNS deposits of lymphoma were found in 1 patient, and another patient had lymphomatoid granulomatosis. Vascular complications were not infrequently seen, and included infarcts secondary to vessel occlusion and disseminated intravascular coagulation in 4 patients and intracranial hemorrhage of variable severity in 13. White matter changes included vacuolar myelopathy (3 cases), central pontine myelinolysis (1 case), and foci of calcified, necrotizing leukoencephalopathy in pontocerebellar fibers of the basis pontis (2 cases). These findings highlight the variety of CNS complications in AIDS, some of which are not associated with clinical manifestations. Nevertheless, characterization of all lesions may be important in understanding the neurologic sequelae of AIDS. (Am J Pathol 1986, 124:537–558)

SINCE its recognition and the original case descriptions in 1981, thousands of individuals have suffered and died of the acquired immune deficiency syndrome (AIDS).[1-4] The social and economic impact of this disease has been tremendous[5]; and, unfortunately, its prevalence continues to increase. While significant advances have been made in understanding etiologic factors,[6-9] effective therapy for AIDS remains elusive and a "cure" seems remote.

Although the clinical spectrum of the disease is reasonably well understood, new aspects of AIDS are continually emerging.[10,11] Central nervous system (CNS) manifestations are a frequent cause of morbidity and mortality in AIDS patients, and examination of the CNS at autopsy discloses a myriad of changes. The purpose of this paper is to present the pathologic changes in the nervous system of 89 AIDS patients, emphasizing recent important findings, and to discuss areas requiring further study.

Materials and Methods

The brains of 89 patients with a clinical diagnosis of AIDS were examined. The spinal cords were also studied in 30 of these patients. Sixty-five cases underwent autopsy at the UCLA Center for the Health Science and 21 at Wadsworth Veterans Administration Hospital, and 3 brains were referred to UCLA from surrounding community hospitals. The patients' autopsy records and clinical charts (when available) were re-

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Table 1—Systemic (Non-CNS) Manifestations of AIDS Found Clinically or at Autopsy in 89 AIDS Patients

Pathologic process	Patients	
	Number	Percentage
I: Infections		
Pneumocystis carinii	68	76
Cytomegalovirus	68	76
Candidiasis	59	66
Herpes simplex virus	29	33
Mycobacterium avium-intracellulare	28	31
Gram positive bacterial sepsis/ pneumonia	16	18
Amebiasis	13	15
Cryptococcosis	10	11
Cryptosporidiosis	10	11
Giardiasis	10	11
Herpes zoster	10	11
Hepatitis B	8	9
Gram negative bacterial sepsis/ pneumonia	3	3
Myobacterium tuberculosis	3	3
Mycoplasma pneumonia	3	3
Toxoplasmosis	3	3
Histoplasmosis	2	2
Aspergillosis	2	2
Actinomyces	1	1
Nocardiosis	1	1
II: Other		
Kaposi's sarcoma	35	39
Lymphoma	6	7
Nonbacterial thrombotic endocarditis	2	2

viewed, and pertinent clinical and pathologic data were extracted from these sources.

Brains and spinal cords were routinely processed. After at least 2 weeks of fixation in 10% neutral buffered formalin, all specimens were cut, examined, and interpreted under the supervision of a neuropathologist (H.V.V., U.T., M.A.V). Routine hematoxylin and eosin (H&E)-stained microscopic sections submitted in most cases included cerebral cortex, hippocampus, deep cerebral gray matter, midbrain, pons, medulla, and spinal cord (when available). Sections of grossly identified lesions were submitted as required. Special stains were performed when thought to be of diagnostic importance except in the first 29 cases, on all of which Kinyoun acid fast staining was performed on at least one random section.

Results

Only 2 of the 89 AIDS patients were female. Risk factors for AIDS included homosexuality (68), bisexuality (11), intravenous drug abuse (11), multiple blood tranfusions (2), and emigration from Haiti (1). The 2 women with AIDS had bisexual male partners. No risk factors were identified in 6 individuals, and 11 patients had multiple risk factors.

Patients ranged in age from 24 to 65 years, with a mean of 40 years. Among the patients studied, most were Caucasians (58), and there were 24 blacks, 6 Hispanics, and 1 Asian. AIDS was diagnosed between 1 and 26 months before death (mean, 7 months).

Only 10 patients presented with significant neurologic signs or symptoms at the time the diagnosis of AIDS was made. However, during the course of their illness, in 29 patients nonspecific neurologic signs and symptoms developed (eg, mild mental status changes, somnolence, poor attention span, confusion, weakness, unsteady gait); whereas 34 had severe neurologic manifestations (eg, seizures, hemiparesis, coma, blindness, findings consistent with meningitis or encephalitis, homonymous hemianopsia). Of those who had the procedure performed, 23 patients showed computerized tomographic abnormalities of the CNS, including 12 with minimal diagnostic changes—predominantly "mild atrophy"—and 11 with severe changes (eg, abscesses, parenchymal infarction, intracranial hemorrhage).

Table 1 summarizes pertinent systemic, nonneurologic clinical and autopsy findings in this series. Opportunistic infections clearly predominated, the lung being the organ most frequently affected. Forty-one patients died directly of pulmonary complications, usually due to *Pneumocystis carinii* or cytomegalovirus (CMV) pneumonia. In addition to those complications listed in Table 1, 35 patients had had a history of hepatitis B, 26 had had prior syphilis, and 27 had had previously treated gonorrhea.

The mean brain weight at autopsy was 1450 g (range, 1175–1800). Forty-one brains had gross abnormalities, and in 15 patients these were relatively minor (eg, slight edema, focal hemorrhage). However, in 26 patients the lesions were significant and included 16 cases with infarcts, necrosis, or abscess formation, 7 cases with prominent meningeal opacification, 1 case of widespread parenchymal hemorrhage, and 1 case with bilateral subdural hematomas.

Significant microscopic abnormalities observed are listed in Table 2, and compared with those in other studies. Only 23 patients had essentially no abnormalities on microscopic examination. Infectious complications clearly predominated in the remaining cases.

Microglial nodules (MGNs) were found in 56 patients, 42 brains showing only a few, scattered MGNs and 14 diffuse, widespread MGN encephalitis. The microglial nodules had variable morphologic characteristics (Figure 1). Although MGN encephalitis may be a direct result of brain infection by the agent that causes AIDS (see Discussion), CMV inclusions were seen in 14 cases: 8 cases had only a few identifiable inclusions, which were also associated with MGNs (Figure 1), and 6 cases had severe necrotizing CMV infection. CMV inclusions were frequently noted in or immediately deep

Table 2—Frequency of Neuropathologic Findings in AIDS in Various Series

Series	Ref	MGN encephalitis	Fungi		Virus			Toxoplasma	Bacteria		Tumors		Vascular		White matter abnormalities	Other
			Cryptococcus	Other	CMV	PML	Other		MAI	Other	Lymphoma	Other	Infarct	Hemorrhage		
UCLA (current) (n = 89)	–	56	11	1 histoplasmosis	14	6	–	6	4	–	3 primary 1 disseminated	–	13	13 (1SDH, 7SAH, 5 IPH)	1 CPM 2 focal pontine leukoencephalopathy 8 Miscellaneous (brain, spinal cord) 3 vacuolar myelopathy	1 lymphomatoid granulomatosis 5 Anoxic-ischemic change Alzheimer II astrocytes, granular ependymitis, calcific vasculopathy
Moskowitz et al (n = 52)	43	5	0	1 unspecified	2	2	1 (?rubeola)	16	–	1 TB 1 *E coli*	1 primary	–	2	4 (2SAH, 2 IPH)	2 CMV-related demyelination	5 Anoxic-ischemic change 1 Alzheimer II astrocytes 1 edema
Welch et al (n = 29)	47	10	3	–	2	–	–	–	–	1 *E coli*	3 primary (2 large cell, 1 Burkitt)	2KS	Yes, but no details	–	–	–
Belman et al (n = 6)	46	2	–	–	1	–	–	–	–	–	–	–	–	–	Yes, including CST degeneration, calcification in 2	2 calcific vasculopathy
Reichert et al (n = 10)	48	4	3	–	3	1	–	1	1	–	1 primary	–	–	1 (IPH)	1 severe demyelination of unknown origin	–
Pitlik et al (n = 6)	49	–	–	1 *Candida*	1	–	1 herpes simplex	2	–	1 *Staph epidermidis*	1 primary	–			–	1 brain atrophy
Niedt et al (n = 51)	50	–	7	1 *Aspergillus* ? *Candida*	12	1	1 herpes (unspecified)	5	–	–	2 primary (1 Burkitt) 1 disseminated	–	–	–	–	–
Levy et al* (n = 128)	52	NS	16	2 *Candida albicans* 1 coccidioidomycosis	?	2	8 herpes simplex 1 varicella zoster	18	NS	1 *Treponema pallidum* 1 atypical myocobacteria	9 primary 2 disseminated	2KS	1	1	–	3 viral myelitis 33 peripheral and cranial nerve abnormalities†
Lemann et al (n = 104)	39	69‡	2	2 *Candida*	34	2	2 herpes simplex 2 varicella zoster	15	–	–	5 primary 3 disseminated	–	–	–	26 vacuolar myelopathy	
Guarda et al (n = 13)	51	–	–	–	2	–	–	1	–	–	1 primary	–	1 (NBTE)	–	1 subcortical necrosis and demyelination	1 CMV in peripheral nerve 1 CMV associated with vasculitis
Sharer et al (n = 11)	53	9§	–	–	1	–	–	–	–	–	–	–	–	–	9 demyelination, gliosis	10 calcific vasculopathy Cerebral atrophy
Sharer and Kapila (n = 8)	60	4‖	2	1 *Nocardia asteroides*	1	1	–	4	–	1 *Salmonella enteritidis*	–	–	1	–	1 microcystic white matter change 1 CPM	–
Total number	507	159	44	10	73	15	16	68	5	7	26 primary 7 disseminated	4	18	19	–	–
% of cases		31.4	8.7	2.0	14.4	3.0	3.2	13.4	1.0	1.4	5.1 primary 1.4 disseminated	0.8	3.6	3.7	–	–

MGN, microglial nodule; NS, not stated; CMV, cytomegalovirus; PML, progressive multifocal leukoencephalopathy; MAI, *mycobacterium avium-intracellulare*; Histo, *Histoplasma capsulatum*; SDH, subdural hemorrhage; SAH, subarachnoid hemorrhage; IPH, intraparenchymal hemorrhage; CPM, central pontine myelinolysis; TB, *Mycobacterium tuberculosis*; KS, Kaposi's sarcoma; CST, corticospinal tract; NBTE, nonbacterial thrombotic endocarditis; ?, indicates that a disease process was found, but the incidence is not given.

The series of Belman et al and Sharer et al are exclusively pediatric patients.

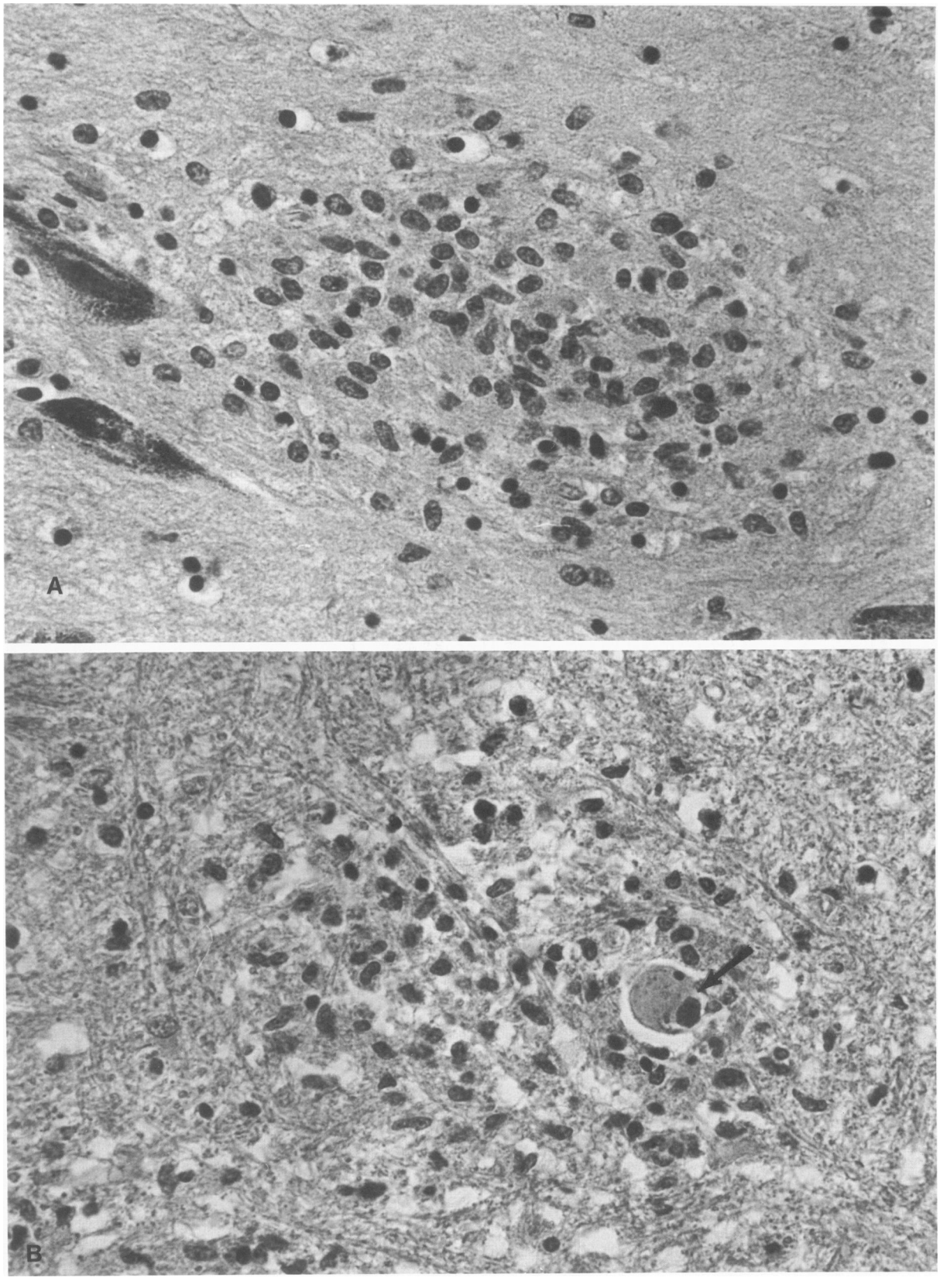
* Not all cases have full pathologic documentation; possible overlap with the study of Welch et al.

† Includes patients with multiple cranial neuropathies (5), Bell's palsy (3), chronic inflammatory neuropathy (12), Herpes zoster radiculitis (6).

‡ Of those with MGN encephalitis, 28 had CMV, 7 had toxoplasmosis, 6 had CMV and toxoplasmosis, 34 had no identifiable organism.

§ Microglial nodules were atypical, often with diffuse inflammation; giant cells were present in 8.

‖ Microglial nodules attributed to *Toxoplasma*, *Cryptococcus* in some cases.


A
B

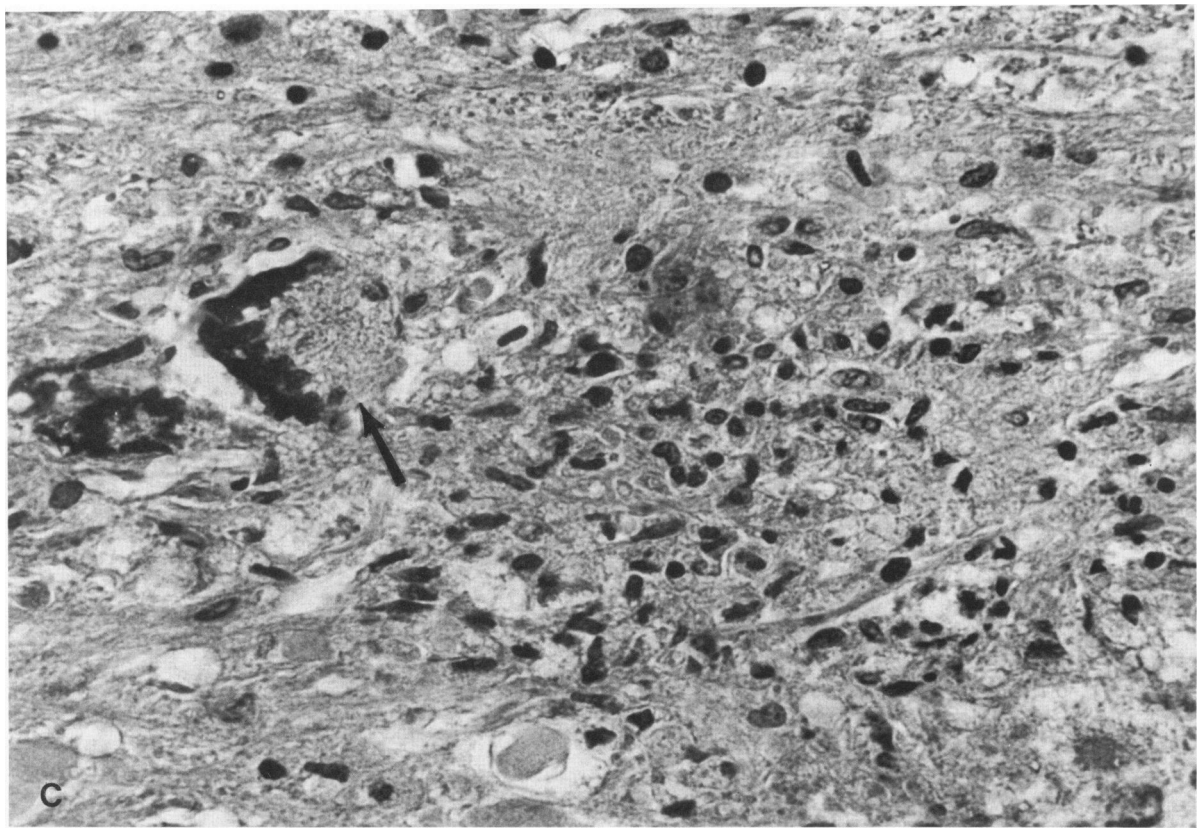


Figure 1—MGN encephalitis. **A**—MGN in substantia nigra (H&E, ×470) **B**—MGN in cerebellum shows a cytomegalic cell with a typical intranuclear inclusion (*arrow*). (H&E, ×470) **C**—MGN with a multinucleate giant cell at one edge (*arrow*). Appropriate stains for microorganisms were negative (H&E, ×470)

to the ependyma (Figure 2) and in one instance were present in and around a large circumscribed area of demyelination in the spinal cord.

Cryptococcal meningitis was found in 11 patients, most of whom also exhibited parenchymal invasion and cyst formation (Figure 3). The inflammatory response to *Cryptococcus* varied from a negligible lymphohistiocytic infiltrate to a significant macrophage (including multinucleate giant cell) response (Figure 4). Six patients had progressive multifocal leukoencephalopathy (PML) (Figure 5), and 6 had toxoplasmosis (Figure 6). Of the 6 patients with *Toxoplasma gondii*, 4 had multifocal necrotic abscesses, whereas 2 had scattered intact cysts within the brain parenchyma with minimal tissue reaction. *Myobacterium avium-intracellulare* (MAI) was incidentally identified in 4 cases (Figure 7), all with systemic MAI infection. MAI organisms were generally found in or near brain foci that had been injured by another disease—eg, CMV encephalitis. A single case of histoplasmosis was seen. Scattered microabscesses containing *Histoplasma* organisms were noted throughout the neuraxis in the setting of multi-organ infection, but were most prominent in the pons (Figure 8).

Three patients had primary CNS lymphomas, which were either localized to deep central gray structures or diffuse within the cerebral hemispheres, cerebellum, and brainstem (Figure 9). The lymphomas all showed the characteristic angiocentric invasion of brain parenchyma, but were not severely destructive. None was clinically diagnosed before death. One patient had secondary seeding of the CNS, with parenchymal invasion (cortex and basal ganglia), from a retropharyngeal primary lymphoma. Another case was found to have typical changes of lymphomatoid granulomatosis, confined to the central gray matter. No evidence of lymphomatoid granulomatosis was found in other organs. No cases of CNS Kaposi's sarcoma were identified, despite the presence of widespread skin and visceral Kaposi's in over 30 patients.

Vascular complications were frequently seen, although these were usually not diagnosed clinically. Included in this study were 13 patients with intracranial hemorrhage (seven subarachnoid, five parenchymal, and one subdural). Infarcts secondary to vascular occlusion from disseminated intravascular coagulopathy and emboli from nonbacterial thrombotic endocarditis were evident in a total of 4 cases.

Foci of demyelination were seen within the spinal cord

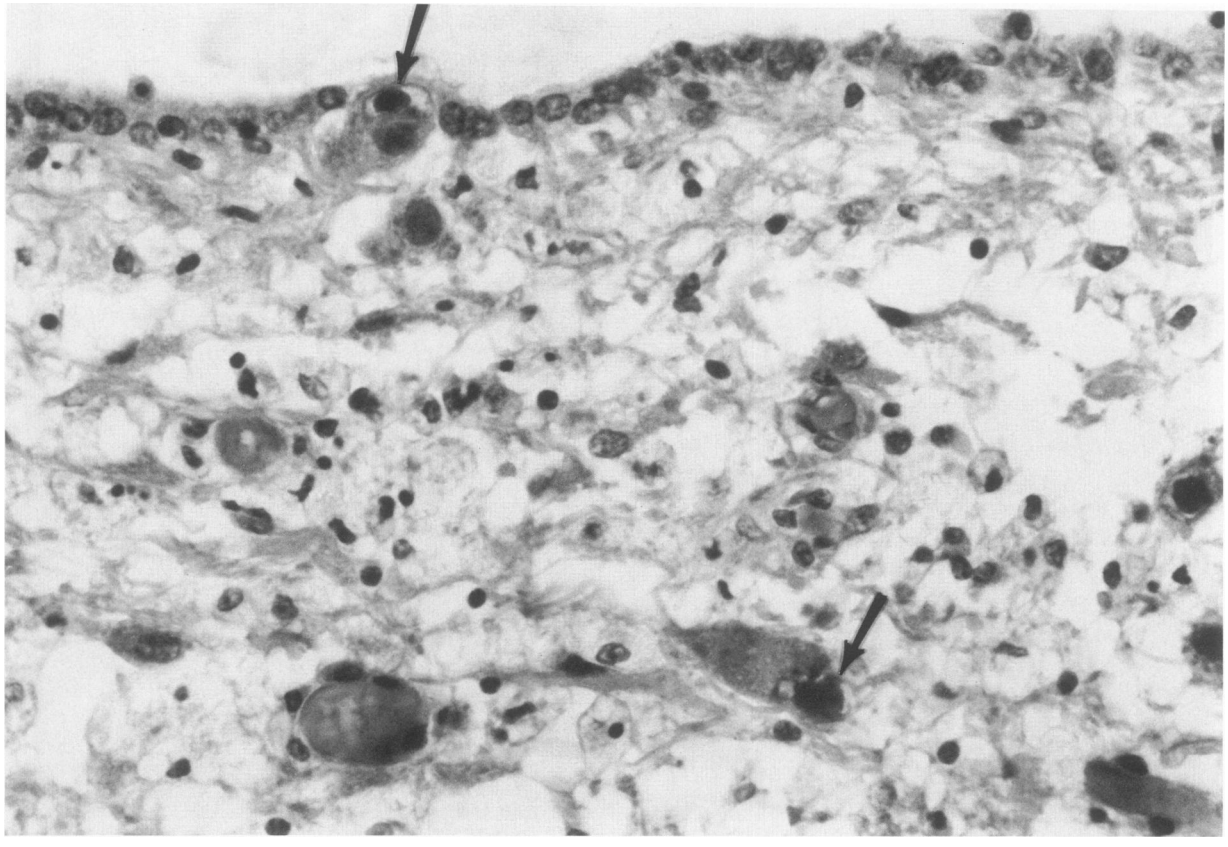


Figure 2—Base of the fourth ventricle (in medulla) shows spongy change and scattered macrophages. CMV inclusions are present in the ependyma and periventricular tissue (*arrows*). (H&E, ×470)

in 6 patients, including 3 cases of vacuolar myelopathy resembling subacute combined degeneration. A case of central pontine myelinolysis (CPM) (Figure 10) and two cases of necrotizing leukoencephalopathy in the pontocerebellar tracts (Figure 11) were identified. The patient with CPM had experienced hyponatremia (serum Na^+ values of 130–132 mEq/l) for approximately one month before his death. Small foci of demyelination were seen in the subcortical white matter of 3 patients.

Several findings of unknown significance (at present) were found, and are listed for the sake of completeness: anoxic-ischemic encephalopathy (always in the context of severe respiratory disease) (5), siderocalcinosis or ferruginization of vessels (Figure 12) in the basal ganglia (10), variable degrees of Alzheimer Type II astrocytosis (10), subependymal gliosis (9), mild focal lymphocytic infiltration of the meninges or around small parenchymal vessels (11), and patchy Bergmann gliosis without significant Purkinje cell loss in the cerebellum (2).

In the 7 patients whose main neurologic diagnosis was that of dementia and in whom no mass lesion was present, one brain showed no gross or microscopic abnormalities, while all the others had some component of MGN encephalitis. In addition, two patients had severe CMV encephalitis, one had focal MAI in addition to CMV, and one patient showed necrotizing leukoencephalopathy in the basis pontis (see above). Two brains with MGNs also showed microinfarcts.

Discussion

The agent that causes AIDS is now generally accepted as being a retrovirus. Though its precise nomenclature is a subject of some debate, the agent is commonly referred to as human T-cell lymphotropic virus Type III (HTLV-III).[9,12–16] A review of the molecular biology of this virus, its mechanism of action, and its effects on the immune system and other tissues is beyond the scope of this paper; moreover, these topics have been extensively discussed.[12–16] More intriguing with regard to the neurologic complications of AIDS is the finding of HTLV-III within the CNS.[17] This has recently been proven by several techniques, including classic transmission experiments using brain tissue suspension from patients with AIDS encephalopathy,[18] isolation of the virus from the cerebrospinal fluid (CSF) and brain of patients with neurologic symptoms,[19,20] as well as Southern blot analysis and *in situ* hybridization for the

presence of HTLV-III.[21,22] Some AIDS patients show synthesis of HTLV-III-specific IgG within the blood-brain barrier (BBB),[23] implying that the etiologic agent is neurotropic as well as lymphotropic. Matters of some debate (see below) are the questions of 1) what, if any, morphologic sequelae follow HTLV-III infection in the CNS/PNS (peripheral nervous system), and 2) what neurologic signs and symptoms the presence of the virus or its genome may elicit in the absence of obvious structural damage to the nervous system.

The most common neurologic or neuropathologic manifestaions of AIDS are consequences of immunosuppression or direct nervous system invasion by HTLV-III. The important role of immunosuppression in causing neurologic syndromes was recognized[24-33] soon after the initial detailed clinical descriptions and case reports of the syndrome appeared.[34-38] The neurologic complications of AIDS can broadly be classified (and will be discussed below) as follows: 1) opportunistic infections, 2) neoplasms, 3) vascular lesions, 4) white matter changes, 5) peripheral nerve and muscle abnormalities, and 6) miscellaneous diseases. Table 2 summarizes the relative frequency with which various types of abnormalities have been recognized in clinicopathologic series. The authors recognize that the table is abstracted from a diverse group of papers in which the extent of sampling of the nervous tissue and interpretation of findings (to name only two variables) undoubtedly differed from study to study, and take responsibility for any inaccuracies the derived information may thus convey. We used only the most current data from each major center, to avoid reduplication of case material and artificially inflated estimates of numbers of different disease processes. Nevertheless, it is important to recognize that 1) more than one abnormality (even of infectious etiology) may be present in the nervous system of a given patient, 2) the frequency with which structural nervous system abnormalities are identified (over 50% of patients) is greater than the prevalence of severe neurologic signs and symptoms in the AIDS population (approximately 30%), and 3) neurologic dysfunction may be the initial manifestation of the disease in approximately 10–30% of patients.[26,27,31,39-41] Neuro-

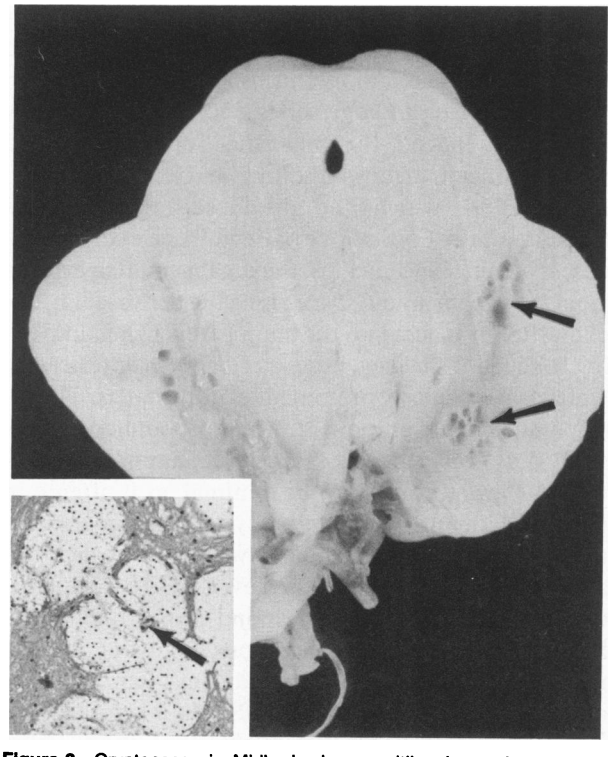


Figure 3—Cryptococcosis. Midbrain shows multilocular cystic structures (*arrows*) that give the substantia nigra a cribriform appearance. Extensive confluent cryptococcomas (**Inset**) in the substantia nigra cause displacement of parenchyma and negligible inflammatory reaction. Blood vessels (*arrow*) at the centers of some lesions suggest organism extension from the subarachnoid space. (**Inset**, H&E, original magnification ×70)

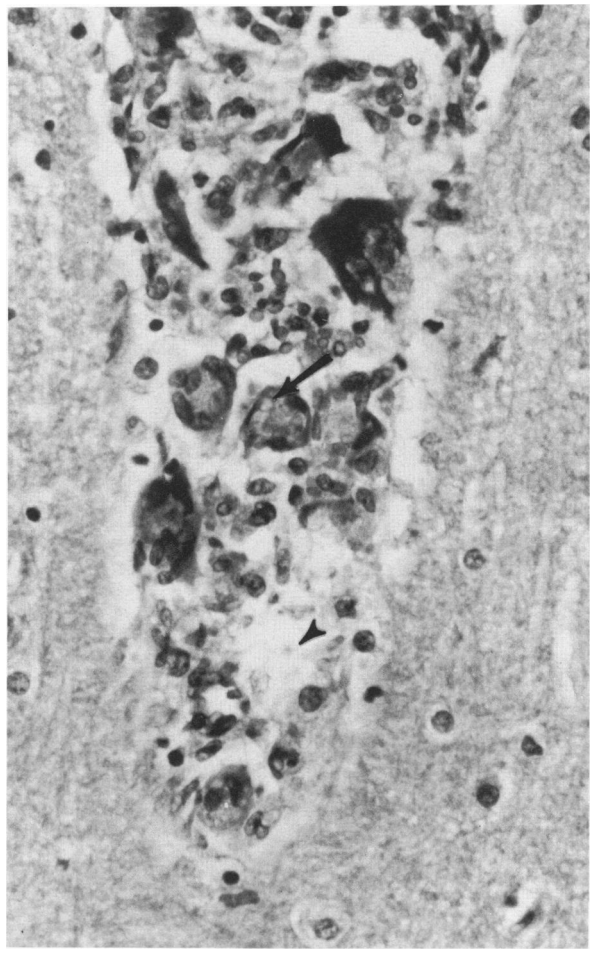


Figure 4—Cryptococcosis. Cerebral cortex. Cryptococci extending along the perivascular space with multinucleate giant cells. Intracellular organisms are visible in many macrophages (*arrow*), and extracellular (*arrowhead*) organisms are present. (H&E, original magnification, ×470)

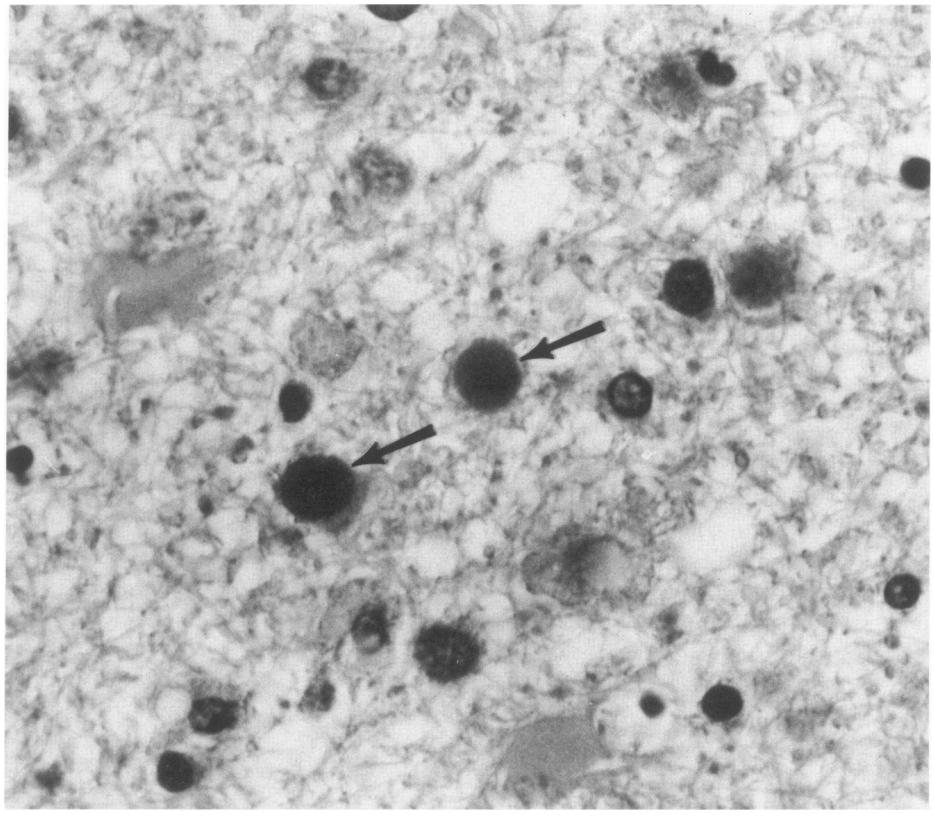


Figure 5—Progressive multifocal leukoencephalopathy. White matter shows hyaline amphophilic intranuclear inclusions (*arrows*). (H&E, ×750)

logic signs and symptoms may be focal (hemiparesis, aphasia) or diffuse (seizures, dementia), depending on the nature of the neuropathologic lesion(s).

Infections

Opportunistic infections of the CNS are the most common specifically identifiable source of neurologic disability and may be caused by one or more of several agents.[40-42] Which of these is most likely to be causing a neurologic syndrome in a given individual depends, to some extent, on the AIDS risk group to which the patient belongs; eg, *Toxoplasma* encephalitis has been rare in our experience, but is common in Haitians and is therefore seen frequently in Florida.[43,44] This serves to emphasize the importance of fully cataloguing the regional variations in all diseases that affect AIDS patients—a phenomenon that in turn may reflect geographic variability in certain AIDS risk factors or evolution of the syndrome. Infections that occur may be caused by agents that are often present in a latent state but producing no symptoms within the patient prior to the onset of AIDS.

Fungi that may produce meningoencephalitis sometimes leading to brain abscesses in AIDS patients include *Cryptococcus neoformans*, *Candida* species, *Aspergillus* species, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*,[41,42] though the first of these microorganisms is the most common fungal pathogen in large series, including the UCLA experience. Indeed, the only other fungus associated with significant neuropathology at UCLA has been *Histoplasma*, which had produced microabscesses throughout the CNS of one patient. In cases of cryptococcal meningoencephalitis, the organism often extends from the subarachnoid space along the perivascular Virchow–Robin spaces into the brain parenchyma, imparting to slices of the fixed brain a cribriform appearance, which is particularly prominent in gray matter. The intraparenchymal component, when pronounced, is described as a cryptococcoma. The inflammatory reaction to *Cryptococcus* may be minimal, as it often is in patients with an intact immune system, although a histiocytic response—occasionally with multinucleate giant cells—is sometimes elicited even in AIDS patients. Occasional AIDS patients respond to antifungal therapy, although relapsing infections following clinical remission are frequent. The organism often produces an infection confined to the CNS; but when the CNS is involved as part of a disseminated infection, *Cryptococcus* may even be identified within specimens of skeletal muscle.[40]

The neuropathologic features of other fungal infections noted in the AIDS population, the most common

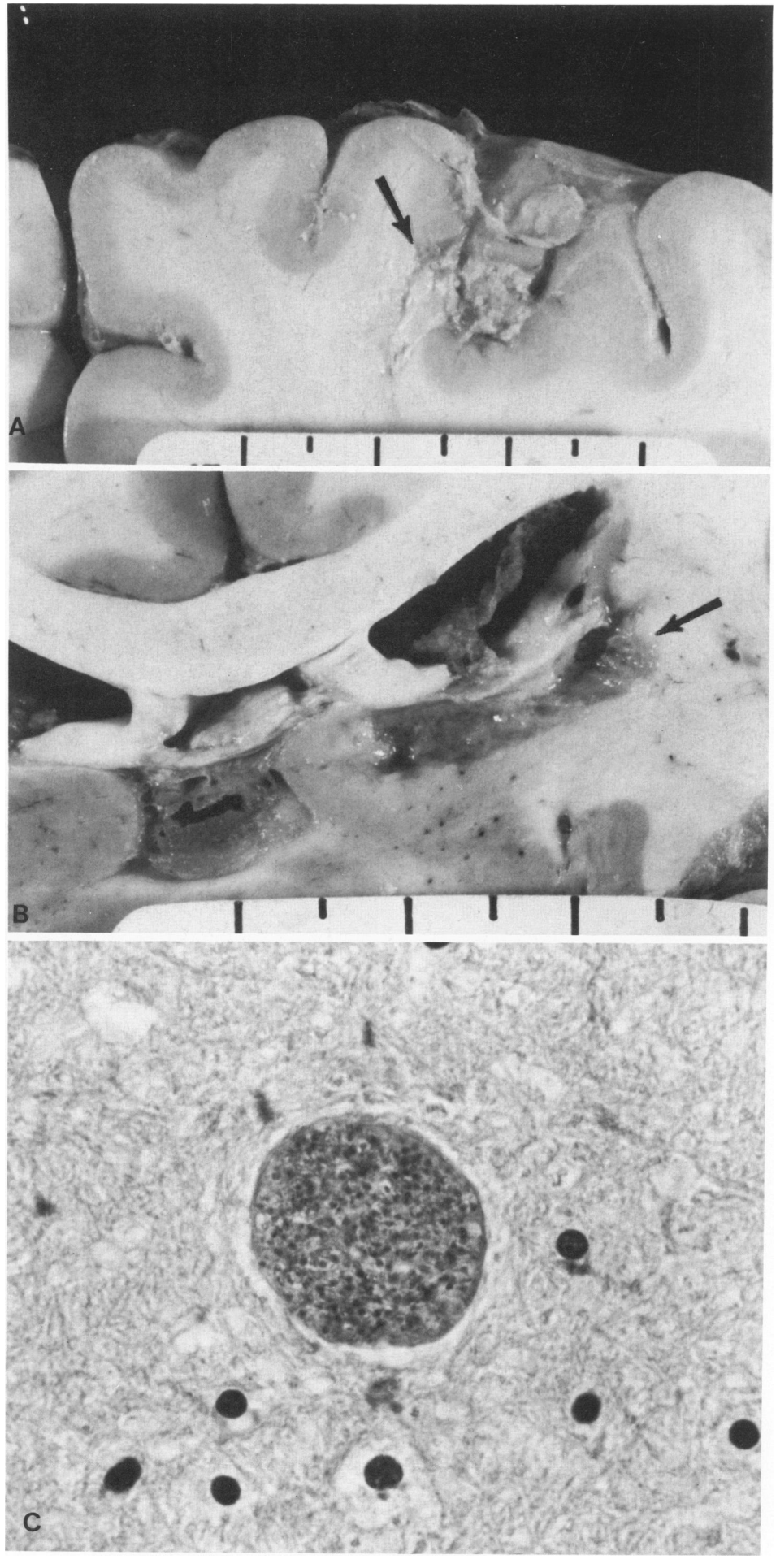


Figure 6—Cerebral toxoplasmosis. **A**—Poorly delineated areas of necrosis at cortex-white matter junction (*arrow*). **B**—Necrosis in periventricular region (*arrow*). **C**—Toxoplasma cyst without parenchymal reaction (**C**). (H&E, ×340)

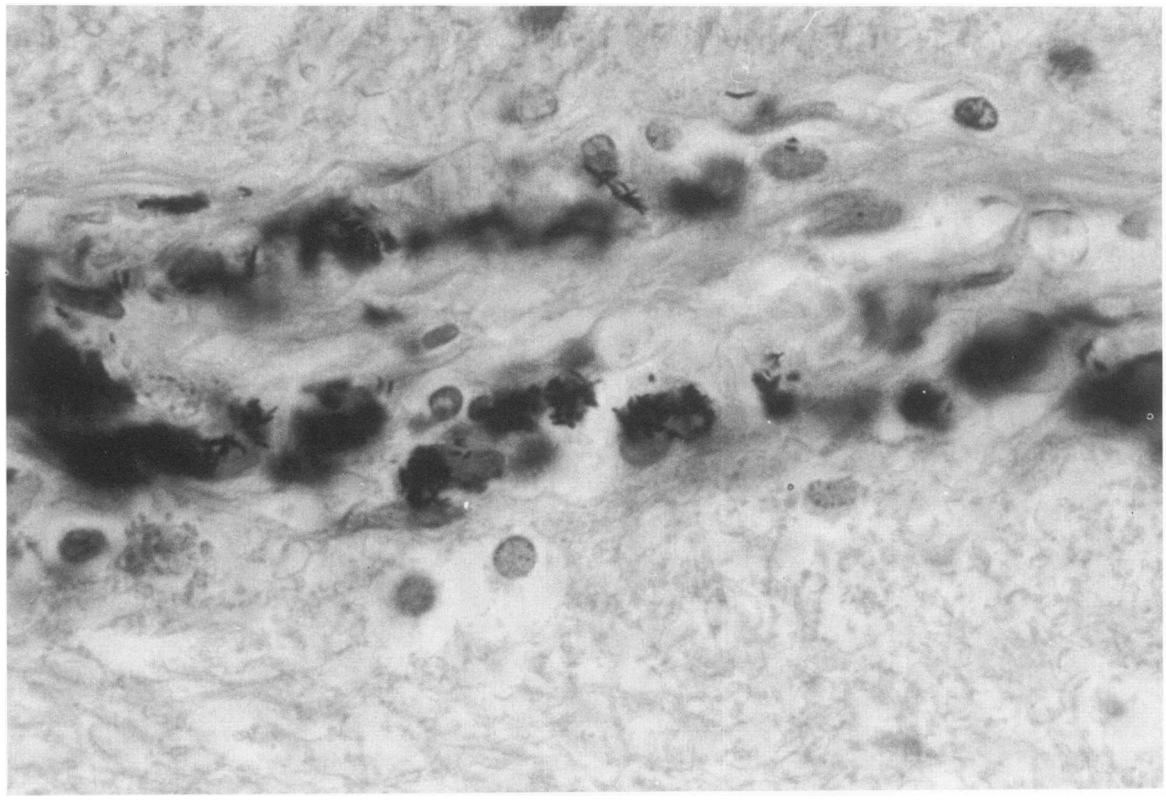


Figure 7—Mycobacterium avium-intracellulare. Perivascular histiocytes contain abundant acid-fast rodlike organisms typical of MAI. Surrounding parenchyma normal. (Oil immersion, acid-fast, ×1130)

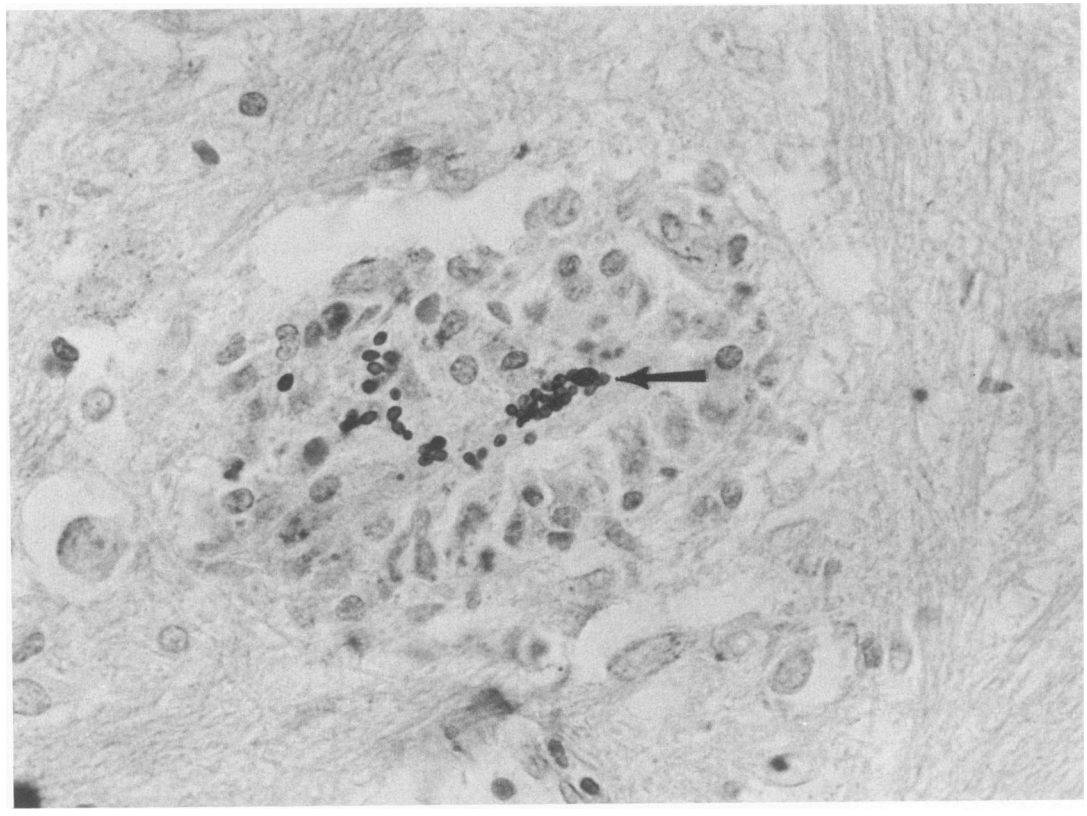


Figure 8—Histoplasmosis. Microglial nodule in basis pontis with characteristic organisms (*arrow*). (Grocott's methenamine silver, ×470)

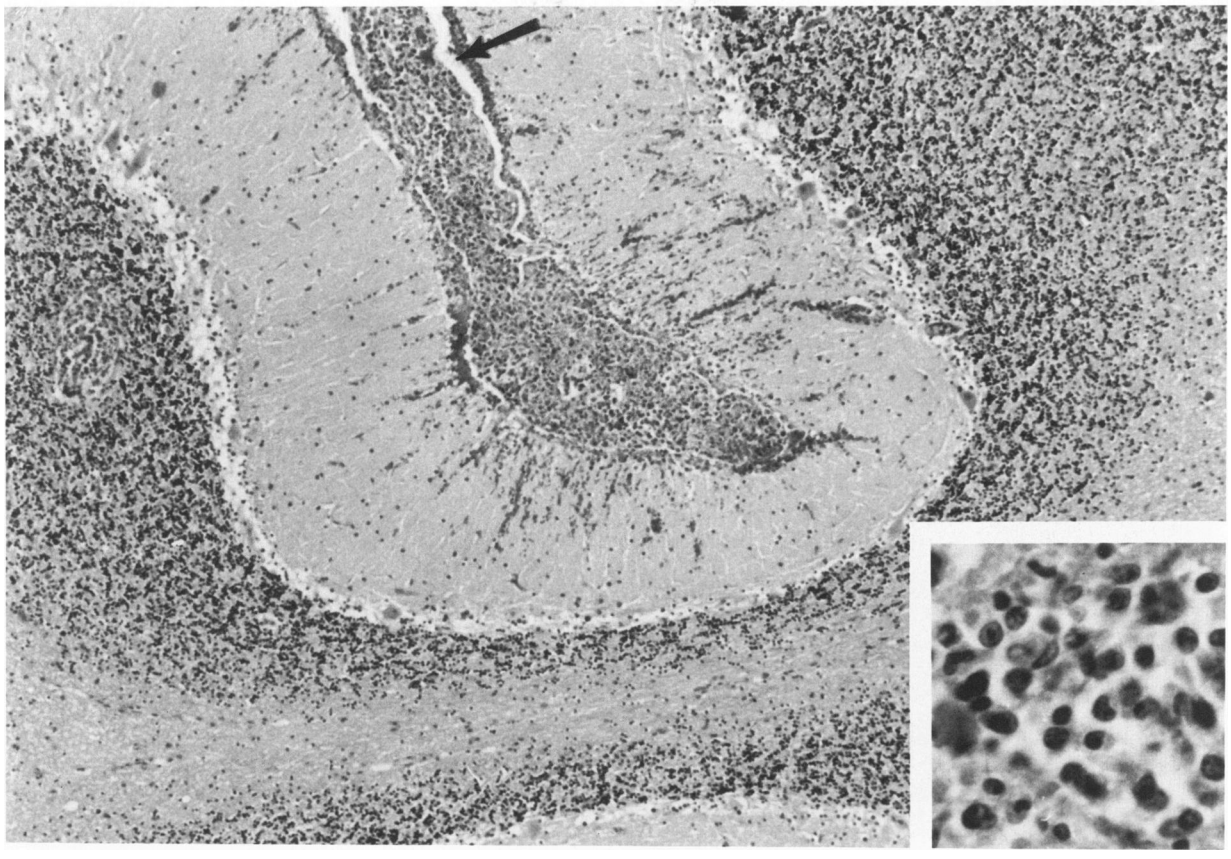


Figure 9—Section of cerebellum shows lymphoma in subarachnoid space (*arrow*) with extension along perivascular spaces into molecular layer. (H&E, ×70) **Inset**—Cytologic atypia of tumor in subarachnoid space. (×470)

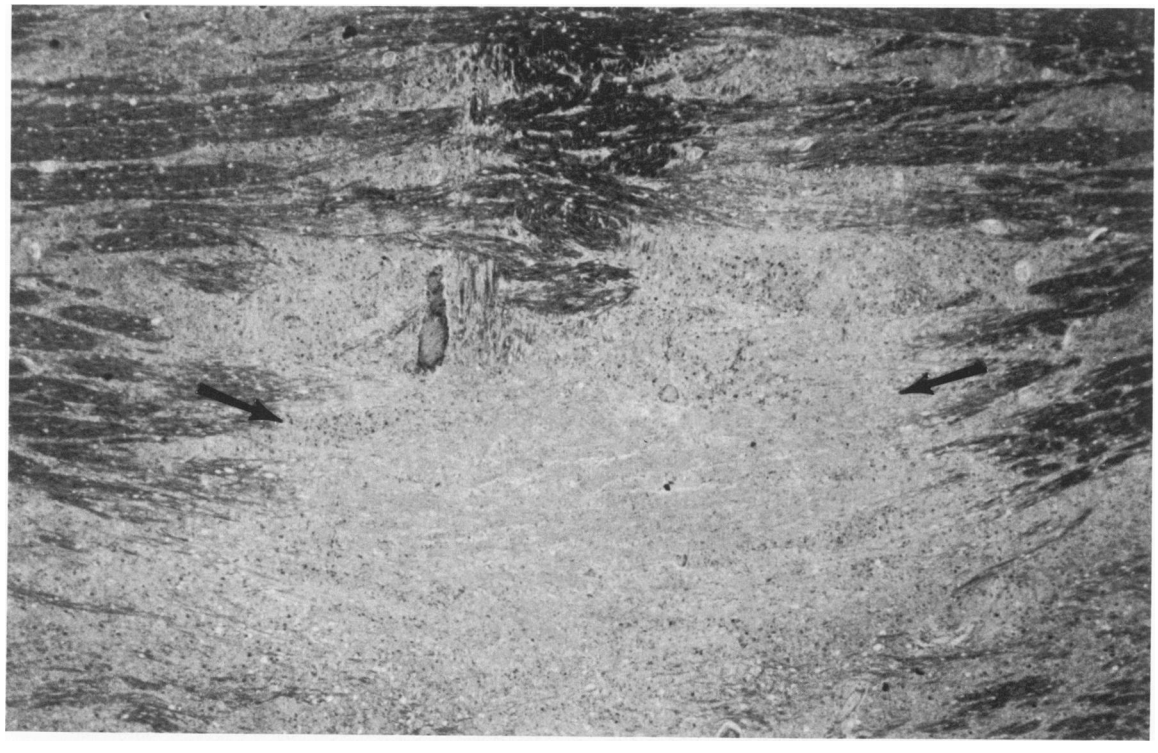


Figure 10—Central pontine myelinolysis. Central region of basis pontis shows demyelination (*arrows*) of pontocerebellar fibers, with relative preservation of axons. (Myelin stain, ×25)

Figure 11—Focal pontine leukoencephalopathy. Basis pontis shows heavily calcified axons within pontocerebellar fiber band (*arrow*). (H&E, ×180)

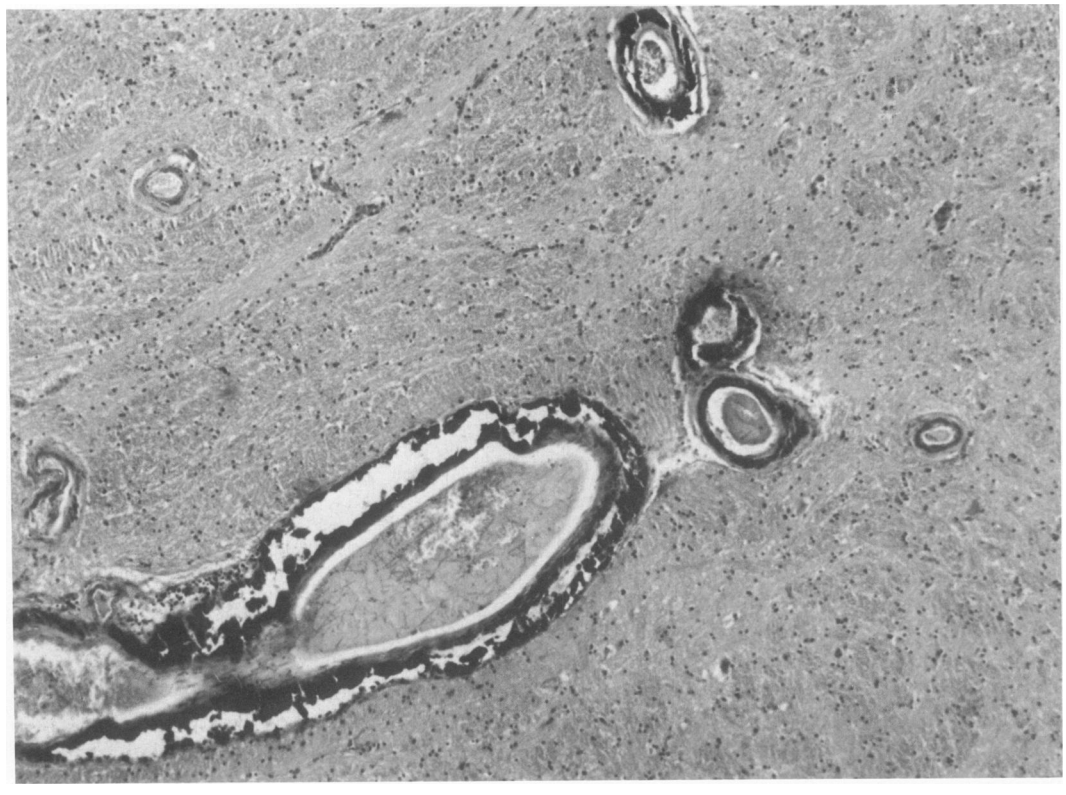


Figure 12—Section of basal ganglia shows marked siderocalcinosis of small and medium size vessels. Media is replaced by calcified material, but vessels are patent. (H&E, ×70)

of which appears to be *Candida*, show no morphologic hallmarks unique to this risk group – ie, they may present as a meningoencephalitis or brain abscess. The predicted increase in frequency of coccidioidomycosis in AIDS patients in Southern and Central California,[42] where this pathogen is endemic, has not yet materialized. Disseminated infection with this organism has been reported in patients immunosuppressed from other causes.[45]

Just as *Cryptococcus* holds preeminence as the most likely fungus to cause neurologic morbidity in AIDS, so cytomegalovirus (CMV) is by far the leading opportunistic viral pathogen.[39-42,46-53] This is not surprising in light of data from one series showing that all patients with AIDS or the related chronic lymphadenopathy syndrome had evidence of active or recent-onset CMV infection.[38] Again, interesting geographic disparities are observed: CMV nervous system infection has been found in approximately one-third of cases in which autopsies were performed in one study from New York,[39] in 20% of cases at UCLA and New York University,[40,50] but in only 4% of cases in Miami.[43] A more recent report from Miami, however, gives a higher figure of 16%.[54] Likewise, CMV infection of the brain is reportedly somewhat uncommon in San Francisco.[47] This variation may have several explanations. In our experience, the likelihood of discovering CMV in neural tissue increases with the amount of tissue directly sampled, even from asymptomatic patients. Characteristic nuclear and cytoplasmic CMV inclusions may be noted in only an occasional section from a brain that usually, however, shows evidence of a low-grade MGN encephalitis. Indeed, the relationship between CMV infection and MGN encephalitis is a crucial one and has been extensively discussed in contexts other than AIDS, eg, when seen in immunosuppressed dialysis patients.[55,56] In a previous report,[40] we stressed the fact that MGN encephalitis was present very commonly in association with CMV inclusions demonstrable in other viscera at necropsy, a finding that is not unique to AIDS.[55,56] This observed association appears valid in our updated series. The argument could be made that CMV inclusions would be found in many or even most of the MGN foci if detailed analysis of serial or subserial sections were undertaken, or that evidence of latent CMV infection might be present if immunoperoxidase and/or *in situ* hybridization techniques were used to detect the virus or its genome.[57] At present, the link between all cases of MGN encephalitis and CMV infection is circumstantial, but in at least selected patients the association appears well founded.[58,59] Some groups now believe that the low-grade AIDS encephalitis is directly related to HTLV-III infection of the brain.[53] It must always be kept in mind that other microorganisms may also cause an otherwise typical MGN encephalitis.[39,60]

Another possible reason for the scarcity of CMV encephalitis in some geographic areas is the presence of other overwhelming, often life-threatening infections, eg, by *T gondii*.[43] However, evidence from all major centers indicates that multiple opportunistic infections may coexist in a given patient. One patient at UCLA was found to have widespread severe CNS toxoplasmosis and disseminated CMV encephalitis, both often discovered in the same brain regions, and similar cases have been reported by others.[54,60]

That CMV should be a common opportunistic pathogen in AIDS is not surprising in view of its ubiquity in the adult population and its high prevalence in the gay community.[61] In the brains of AIDS patients, CMV may be found as an occasional characteristic inclusion in the presence of MGN encephalitis (see above), or may cause significant necrosis and inflammation. The brain may appear normal at autopsy or brain cutting, or it may show changes like those in infection of newborn or infant brain, with ventriculitis, periventricular necrosis, and vasculitis.[62] The virus tends to localize in the ependyma and subependymal regions. A recent case report using *in situ* hybridization methods has demonstrated that morphologically normal neurons and glia may be latently infected by CMV.[63] Whereas this detailed report supports the hypothesis that CMV moves from the ventricles into CNS parenchyma and disseminates within the brain by contact of infected cell bodies, others claim that the portal of entry may be the capillary endothelium or BBB.[64] Rarely, characteristic CMV particles are found on ultrasturctural evaluation of affected brain.[65] The virus is notoriously difficult to culture from CSF. CMV inclusions have been found in regions of demyelination within both the CNS and ventral spinal nerve roots, suggesting that the virus may cause the myelin loss.[63,66] This observation is the more intriguing in view of the frequency with which a variety of white matter lesions are noted in AIDS brains (see below). In one instance,[51] CMV infection was seen with inflammation and fibrinoid necrosis of meningeal vessels, but this is exceptional. Imaging techniques tend to underestimate the degree of CMV encephalitis eventually found when tissue is examined.[54]

Whereas CMV may produce neuropathology that is relatively subtle, PML, caused by papovaviruses, is occasionally the cause of death in AIDS patients. Most series report 1 or 2 AIDS patients with fulminant PML, and we have encountered 6 such patients.[39-43,47-52] A handful of case reports has documented appropriately detailed clinical histories and pathologic findings.[67-70] The neuropathology of PML in AIDS is similar to that seen in non-AIDS cases. Ill-defined asymmetric areas of demyelination, bizarre astrocytes, and amphophilic oligodendroglial intranuclear inclusions are prominent in all cases, and occasionally severe tissue necrosis fo-

cally mimicking the appearance of an infarct is present. Ultrastructure of the virions is characteristic, but the light-microscopic picture is usually sufficient for diagnosis. Immunocytochemical stains may show papovavirus (JC or SV-40 related) antigen.[69]

Other viruses that rarely produce neurolgic dysfunction in AIDS include those of herpes simplex (Types I and II) and herpes zoster.[42] Details of the neuropathology of the herpes simplex virus (HSV) in AIDS have not, to date, been published. A single case in which herpes zoster encephalomyelitis was documented with the use of electron microscopy, immunoperioxidase staining and Southern blot analysis of extracted cerebral DNA, showed patchy areas of necrosis and demyelination in the brain—foci suggestive, at first glance, of PML[71] A single example of encephalitis believed to be consistent with rubeola infection has been reported.[43] Viral myelitis related to combined CMV and HSV-II infection has rarely been seen.[52,72] Furthermore, a host of clinical neurologic conditions has been collected under the rubric "viral-related syndromes,"[41] often without adequate proof of viral origin. These include polyradiculoneuropathy, cranial neuropathy, and aseptic meningitis.[41,73] Meticulous necropsy, biopsy, or cerebrospinal fluid cytologic studies may reveal the specific cause of many or all of these conditions.

The only protozoal-parasitic nervous system infection to be described in AIDS patients, but one that is seen with alarming frequency, is that due to *T gondii*. *P carinii*, a common cause of pneumonia in these individuals, has never been convincingly demonstrated in the CNS, PNS, or CSF. A single patient with cysticercosis[43] may have developed this infestation before contracting AIDS. Clinical, radiologic, and pathologic details of cerebral toxoplasmosis in AIDS worldwide have been extensively described.[44,74-93] The following conclusions have emerged. The parasite, with some exceptions,[80] affects primarily the CNS and causes protean clinical manifestations, as is the case in other immunocompromised patients.[94] Cerebrospinal fluid from infected patients is usually nondiagnostic: modestly elevated protein, a slight pleocytosis, and normal glucose are observed, and the organism is very rarely cultured. Primary *Toxoplasma* infection is accompanied by serum IgM elevation followed by a relatively rapid (within 1–4 months) decline, whereas IgG rises slowly and persists in high titers for long intervals. However, the *absence* of rising antibody titers cannot be used to exclude recent infection or reactivation of latent infection,[85] although a fourfold rise between acute and convalescent sera in a neurologically ill patient is helpful in management.[82,89] Significant peripheral eosinophilia has been noted in at least 2 patients.[91] Although imaging techniques show characteristic lesions, the picture is not specific, and biopsy of abnormal regions is strongly recommended in patients who can withstand the procedure.[74,80] *T gondii* abscesses localize around the ventricles (in basal ganglia and thalamus) and peripherally at the cortex–white matter junction and usually cause pronounced cerebral edema.[92,93] Characteristic pathologic changes include a central necrotic zone with few organisms, an intermediate region with vascular congestion and endothelial hyperplasia, intense inflammation, patchy necrosis, both intracellular and extracellular tachyzoites, and a peripheral or outer zone with relatively little inflammation, fewer tachyzoites, and more common encysted *T gondii* organisms.[92,93] One group has classified the lesions as necrotizing, organizing, or chronic.[93] Scattered free tachyzoites in the neuropil are implicated in active infection, whereas encysted organisms are seen in the quiescent state. Vascular change may be prominent in cerebral toxoplasmosis and includes fibrinoid necrosis and fibrin thrombi in vessels as well as intense perivascular cuffing by mononuclear inflammatory cells. In non-AIDS *Toxoplasma* encephalitis, this perivascular inflammation may be the dominant component and can be seen with very few or no organisms present.[95] It is said to resemble the characteristic picture of congenital *Toxoplasma* encephalitis, in particular when noted in a periventricular distribution. It is vital to keep this possibility in mind in surgical neuropathology, because an important differential diagnosis of cerebral mass lesions in AIDS patients includes *Toxoplasma* and lymphoma, in which the tumor is characteristically angiocentric.[60] In toxoplasmosis, an unusual noninflammatory cellular thickening of small and medium sized vessel walls occurs with effacement of the media and adventitia.[44] In our experience, free tachyzoites or encysted organisms are scarce in relation to the amount of tissue necrosis and inflammation, even in untreated cases. We have also noted occasional encysted *T gondii* in the brain without any detectable necrosis or parenchymal reaction ("latent" infection).[40] *T gondii* organisms can be seen on routine hematoxylin-eosin or Giemsa stains, but the diagnositc yield is increased by use of a peroxidase–antiperoxidase staining procedure.[74,96] Intraperitoneal injection into mice of tissues thought to harbor *Toxoplasma* can be carried out with the diagnosis confirmed by means of subsequent smears of peritoneal fluid.[82]

Toxoplasmosis in AIDS is most commonly seen in Florida, where a large percentage of the affected patients is Haitian.[43,44] One group has noted that cerebral toxoplasmosis appears more commonly in AIDS patients than in other immunoincompetent individuals.[89] Good symptomatic improvement of affected patients after therapy with sulfadiazine and pyrimethamine has been reported.[93] An association between systemic

mycobacterial infection and CNS toxoplasmosis has been described in Haitian AIDS patients.[60]

"Conventional" bacterial infections producing meningoencephalitis in AIDS are rare. *Nocardia* species and *Listeria monocytogenes* are mentioned as potential CNS pathogens in AIDS,[41,42] because extraneural infection with each has been documented. One case of brain abscess secondary to *Nocardia asteroides* and *Salmonella enteritidis* has been reported.[60] Meningitis and microabscesses caused by *Escherichia coli* have occurred,[43,47] as has a polymicrobial brain abscess in which one of the identified organisms was *Staphylococcus epidermidis*.[49] A single case of syphilitic meningoencephalitis has been presented.[52] One brain with a well-circumscribed abscess caused by *Mycobacterium tuberculosis* immediately adjacent to a focus of *Toxoplasma* encephalitis has been illustrated.[43] More common is the finding of *Mycobacterium avium-intracellulare* (MAI) within the brain. We have always found the organisms as an incidental observation, usually within histiocytes in a perivascular distribution in patients with MAI septicemia and nearby CNS necrosis, usually due to CMV. Undoubtedly their prevalence in the CNS is underestimated, because acid fast stains must be performed on random brain sections to locate the microbe. However, there is no evidence that it produces neurologic morbidity.[26]

Neoplasms

Lymphoma is the only primary brain tumor that occurs with unexpectedly high frequency in AIDS patients.[26,39,40,43,47-52,97-101] Many of the CNS tumors are large-cell or immunoblastic ("histiocytic") lymphomas, similar to those noted in non-AIDS immunocompromised individuals. Occasional patients have Burkitt lymphomas[47,50,102] a finding of special interest given recent evidence that some CNS lymphomas in non-AIDS patients may be related to Epstein-Barr virus infection,[103] and that active Epstein-Barr virus infection is nearly universal in AIDS patients.[38] The CNS (usually subarachnoid space) can be involved in cases of disseminated visceral lymphoma, and extradural spinal cord compression by lymphoma or plasmacytoma has been described.[26] CSF examination is helpful in diagnosis when some component of either primary or disseminated lymphoma is in the subarachnoid space. CNS lymphoma may be an incidental necropsy finding. We have also encountered one patient in whom a lesion localized to the deep central gray matter, without extraneural occurrence, showed typical features of lymphomatoid granulomatosis.[40] The pathologic features of the latter also resembled vascular changes frequently seen in pediatric AIDS.[53]

Because multifocal Kaposi's sarcoma is so common in this condition[104]—indeed, it is a component of the diagnostic criteria—the incidence of cerebral Kaposi's is remarkably low.[105] Pathologically documented examples are few.[47,52,106] In regions (eg, Africa) where Kaposi's sarcoma is a common tumor in non-AIDS patients, this rarity of cerebral metastases persists.[107] Though the origins of this tumor (with or without AIDS) are controversial, it appears to arise in many locations simultaneously and to originate from endothelium, possibly lymphatic endothelium.[106,108] Its scarcity in the brain, which lacks lymphatic channels, is therefore not unexpected. Even cerebral microvascular endothelium is structurally and functionally much different from extra-CNS endothelium.[109,110] The cases of Kaposi's in brain thus probably represent metastases from unusually aggressive primary lesions, rather than part of a multifocal neoplasm, a view supported by the finding of cerebral Kaposi's only in the presence of pulmonary metastases.[106]

Vascular Lesions

A variety of vascular lesions has been seen in the brains of AIDS patients.[26,40,43,48,52,60] These inlcude intraparenchymal, subarachnoid, and subdural hemorrhages and infarcts. The vascular abnormalities form a varied group, but are rarely the cause of death. Hemorrhages, when present, sometimes have a peculiar distribution, eg, favoring white matter tracts.[40] Infarcts are often secondary to the presence of nonbacterial thrombotic ("marantic") endocarditis,[51,111,112] because AIDS occurs most commonly at an age when intrinsic cerebrovascular disease is not a contributing factor. Disseminated intravascular coagulation has occurred in a few patients, with resultant hemorrhages and infarcts. Patchy or diffuse changes of anoxic/ischemic encephalopathy are an expected finding in individuals in whom severe respiratory embarrassment antemortem is almost the rule.

White Matter Abnormalities

Disease within white matter tracts of the brain and spinal cord, often in the absence of an obvious infectious agent, is commonly recognized. A tentative classification of white matter alterations (leukoencephalopathy) is presented in Table 3.

Some forms of damage to white matter are identical in topography and nature to those seen in non-AIDS patients, eg, those found in progressive multifocal leukoencephalopathy. Others are so closely apposed to characteristic viral inclusions, or cells that are shown to contain viral protein and/or genome by appropriate techniques, that the conclusion they are being caused

Table 3—White Matter Lesions in AIDS

	References
Secondary to known infectious agent	
Progressive multifocal leukoencephalopathy	26, 39–43, 67–70
CMV-related demyelination	66
Herpes zoster encephalomyelitis	71
Idiopathic	
Poorly demarcated patchy demyelination and gliosis	26, 40, 46, 48, 53
Vacuolar myelopathy	114, 115
Multifocal long tract degeneration	116
Calcification of white matter (predominantly pediatric)	46
Focal pontine leukoencephalopathy	120
Central pontine myelinolysis	60, present report
Progressive diffuse leukoencephalopathy (with giant cells;? papovavirus)	117

by a specific viral infection becomes compelling. This is the case with demyelination in a patient with herpes zoster encephalomyelitis[71] and that often associated with CMV.[66]

More commonly, no such clue to the pathogenesis of white matter lesions exists. Many reports[26,40,46,48,113] have noted patchy ill-defined areas of demyelination and gliosis involving several regions of the brain. These areas are seldom as distinctive or large as the plaques of demyelination noted in multiple sclerosis. Often, they are inapparent on cut slices of brain and are noted only on histologic sections, where they may, however, be numerous in a given case.

Of greater interest are various forms of long tract degeneration that occur in the CNS in AIDS. The best described of these is a type of spinal cord degeneration with morphologic similarities to subacute combined degeneration.[114,115] This has been found in as many as 25% of AIDS patients.[39] Its relatively low incidence in our series may reflect the simple fact that the spinal cord is often not removed in autopsies on AIDS patients at our center. The myelopathy typically involves dorsal columns and lateral corticospinal tracts and consists of symmetric vacuolation of the affected white matter with the presence of lipid-laden macrophages. The vacuolation is not, however, confined to specific white matter tracts. Axonal disruption is noted in regions of severe vacuolation, and the vacuoles are surrounded by thin sheaths of myelin and seem to arise from edema within the myelin lamellas. This vacuolar myelopathy has a well-defined clinical correlate, but as yet its exact cause is unclear. Of note is the fact that many AIDS patients with vacuolar myelopathy have dementia and the low-grade MGN encephalitis which is often (see above) associated with CMV infection of the brain. Another demented AIDS patient with a similar low-grade encephalitis was discovered to have multiple areas of myelinated tract degeneration involving bilateral corticospinal, frontopontine, and cerebellar white matter fibers.[116] Microscopically, the lesions showed myelin and axonal damage as well as microcavitation with lipid-laden macrophages. A possible association with adenovirus infection was suggested. A destructive form of progressive diffuse leukoencephalopathy, with multinucleated giant cells (containing HTLV-III?) has been described.[117] It may be caused directly by the AIDS retrovirus, or the latter in combination with papovavirus. Extensive white matter lesions, including focal calcification, have also been noted to be especially prominent in children with AIDS.[46,53] Indeed, the neuropathology of AIDS in the pediatric age group seems to reflect direct HTLV-III virus infection of brain, usually *without* other opportunistic pathogens.[53,118,119]

We have observed a pontine lesion, tentatively designated as focal pontine leukoencephalopathy, in 2 AIDS patients.[120] A less severe form of an identical lesion was found in one patient with a congenital immunodeficiency syndrome. Pathologic assessment showed multifocal areas of vacuolation, axonal injury with swelling, and heavy calcification confined to the pontocerebellar fibers of the basis pontis. The lesions were similar to those described in cancer patients treated by chemotherapy and CNS radiotherapy[121] and, apart from their restricted anatomic localization, resembled a disseminated necrotizing leukoencephalopathy found by others to complicate treatment of CNS leukemia and lymphoma.[122] Of importance is the fact that these two groups of patients were also probably immunosuppressed, given the nature of their primary diseases and therapy. The relationship of this lesion to immunosuppression is, however, unclear. The lesion differs from typical central pontine myelinolysis,[123–125] which we have observed in a single AIDS patient, in several important respects.[120] An abnormality similar to this form of patchy calcified leukoencephalopathy has been briefly described (but not illustrated) in other regions of the neuraxis[26] of AIDS patients.

The complete documentation of these seemingly heterogeneous white matter lesions, which often involve both myelin sheaths and ensheathed axons, is crucial in view of the unanswered question: what cell type(s) in the CNS does HTLV-III invade? The high prevalence of white matter abnormalities, when these are carefully sought at autopsy, provokes the suggestion that oligodendroglia may be one of the infected cell types. Thus it is particularly intriguing to learn that HTLV-III shares morphologic features and nucleotide sequences with a well-characterized lentivirus that causes visna, a degenerative demyelinating condition in sheep.[126]

Peripheral Nerve and Muscle Changes

Peripheral and cranial polyneuropathy commonly occur in AIDS patients, but the clinical features of both are better appreciated than is their neuropathology.[52,127,128] Aside from those cases in which nerve or nerve root involvement occurs secondary to lymphoma or infection (eg, *Cryptococcus*) in the subarachnoid space, there are some patients who have a predominantly inflammatory neuropathy, in some instances similar to the Guillain–Barré inflammatory polyradiculoneuropathy.[128,129] Clinical syndromes of mononeuritis multiplex and distal symmetric sensorimotor polyneuropathy have been described.[127] Biopsies of nerves have shown focal necrosis with macrophages and axonal degeneration, segmental demyelination, and a mononuclear inflammatory infiltrate.[127–129] CMV has been proposed as an agent responsible for demyelination in dorsal and ventral nerve roots and peripheral nerves,[63,66,129] because typical CMV inclusions (and virions on ultrastructual examination) have been seen in demyelinated segments of these tissues and in otherwise normal peripheral nerve.[51] Specific forms of myopathy have not been described in AIDS, although occasional patients have myopathic change[31] or structural evidence of denervation atrophy.[40]

Other Lesions

Calcification of the basal ganglia is often present in AIDS (especially in pediatric cases), though usually it takes the form of calcium and iron deposition in medium size and small ganglionic blood vessels (sidero-calcinosis), without obvious injury to adjacent brain parenchyma.[53,130] Parenchymal calcification is seen in some cases.[46] We have also been impressed by the frequency with which this vascular change appears in the basal ganglia of AIDS brains, but cannot comment on its significance, because a similar change, though usually less severe, is identified in otherwise normal brains from the elderly. Other "minor" pathologic findings ("minor" because we do not yet know their significance) include Alzheimer Type II astrocytosis,[43] a subtle lymphohistiocytic meningeal infiltrate, and patchy perivenous lymphocyte cuffing in several cases. Granular ependymitis or ependymal granulations are common but also occur in otherwise normal brains. In the absence of a cure for AIDS, new forms of neuropathology and new variants of described neuropathology will certainly be seen in this syndrome.

Future Prospects

Several avenues of research, some utilizing simple morphologic tools and imaging techniques, others using modern molecular probes, hold promise for elucidating the pathogenesis and eventual therapy of common central and peripheral neurologic disorders in AIDS patients. Systematic sampling and careful examination of multiple areas of brain, spinal cord, and peripheral nerve from AIDS patients will doubtless reveal new, perhaps surprising, lesions, with or without specific clinical correlates. For example, it would be of interest to document the full extent of white matter abnormalities, in view of pathology that has already been described. If pathologists are guided in tissue sampling by grossly visible lesions, subtle changes are certain to be missed. In general, careful autopsy study of AIDS patients is warranted in view of the frequent discrepancy between premortem and postmortem diagnoses.[99] A comparison of the neuropathologic findings and opportunistic CNS infections in AIDS, given the nature of its highly specific immune defect, with those in other forms of congenital, acquired, or iatrogenic immunodeficiency, might also be illuminating.[131–141] The contribution of animal models of AIDS toward understanding its neuropathologic complications has thus far been minimal,[142–145] though PML has been seen in immunodeficient macaques,[146] and other affected simians have shown nonspecific inflammatory lesions of the brain and meninges.[144,147,148]

Various imaging techniques show promise in the antemortem diagnosis of neuropathology in AIDS patients.[149–153] Important clinicopathologic, computerized tomographic scanning, and magnetic resonance imaging correlations have been made.[151] It is suggested that the latter two methods now be used together to provide complementary data in AIDS patients with neurologic disease. Neither technique is, however, totally sensitive or specific, and biopsy of mass lesions detected by scans is still frequently indicated,[154,155] although in high risk groups where toxoplasmosis is the most common agent producing space-occupying lesions, empirical therapy with anti-*Toxoplasma* agents is sometimes a rational approach.[93,156,157]

One of the most pressing controversies in this field is that of the commonly observed AIDS dementia or encephalopathy.[158–160] The key problems to be resolved in understanding and treating this entity are: 1)What is its relationship to the low-grade, subacute (microglial nodule) encephalitis (see above) and the radiologic observation of brain atrophy? 2) Is it caused by HTLV-III infection within the brain? 3) (a corollary of 2) If it is a function of brain involvement by HTLV-III, what cell population(s) are affected and what will be the long-term sequelae of the infection? In other words, do cells in the neuraxis display selective vulnerability to the HTLV-III agent, as they do for other viruses?[161,162] Indeed, MGN encephalitis itself may reflect HTLV-III, rather than CMV, infection of the neuraxis in some pa-

tients.[113,117] One study of pediatric AIDS, using an immunofluorescent technique, showed cytoplasmic localization of HTLV-III antigen to mononuclear and multinucleated cells (probably macrophages) within foci of MGN encephalitis.[163] Another investigation reached similar conclusions using other techniques,[53,164] and demonstrated HTLV-III-like particles within giant cells by electron microscopy. It is conceivable that such giant cells will become a histologic marker for AIDS encephalopathy, at least in the pediatric age group, because such cells are less common in adult AIDS. More extensive application of immunocytochemical and *in situ* hybridization techniques[165-167] is certain to resolve these matters, though at present the latter technique is problematic in view of the apparently small number of genomic copies of HTLV-III within brain cells. Current clinicopathologic evidence suggests that AIDS encephalopathy does not correspond to a single type of gross or microscopic brain abnormality.[160]

Finally, it will be of interest to learn whether HTLV-III strains that are neurotropic are identical to those that are lymphotropic. Indeed, are different strains of HTLV-III in different geographic regions or risk groups responsible for the heterogeneous neuropathologic changes that are observed? This will be achieved only by further direct isolation and molecular characterization of HTLV-III from the nervous system of AIDS patients. There remains also the issue of how HTLV-III gets into the brain. If one assumes that the virus passes into the CNS through the BBB, does that barrier have receptors and transport mechanisms for HTLV-III, or does focal barrier breakdown allow the agent to enter the brain, perhaps already *within* a bloodborne cell type (ie, the lymphocyte)? Interactions between HTLV-III and cerebral microvascular endothelium (the site of the BBB) will need to be studied by methods that have already been developed to examine the effects of other lymphotropic viruses on cultured endothelium.[168,169] The study may be facilitated by technology that allows for isolation of vertebrate (including human) cerebral capillary cells *in vitro*.[170,171]

One hopes that the neurologic complications of AIDS, and the syndrome itself, will soon no longer be "the unsolved riddle,"[172] but, rather, the riddle with some clearcut solutions.

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