Preface

A 2003 editorial in the well-renowned journal *Science* was entitled "Forensic Science: Oxymoron?." An oxymoron is a rhetorical figure in which an epigrammatic effect is created by the conjunction of incongruous or contradictory terms. This short article questioned both the reliability and validity of forensic sciences, alleging a lack of such criteria as error rate, adequate testing, regular standards and techniques, as well as a general lack of acceptance within the field. The will of those involved in death investigation was also questioned, calling for an improvement in the quality of their work in a scientific setting by noticing "Both these public interests—security and justice—would be furthered by a more scientific and reliable technology for analyzing crimes. The mystery here is why the practitioners don't seem to want it!."

From this editor's point of view it is generally impossible to quantify the pain of tortured victims and, without a doubt, the violation of human rights cannot be measured by biostatistical methods. However, police investigators and forensic pathologists have evidenced and documented ethnic cleansing in war zones and thus testified against war criminals in order to continually protect human rights over the past decade. Physical evidence of torture is properly analyzed where based in a scientific setting. Following regular standards and techniques for the identification of human remains, forensic pathologists and anthropologists are able to identify those who are killed by terroristic acts as opposed to civilian deaths. The components of weapons of mass destructions are analyzed by means of modern forensic science techniques. A harmonization of autopsy rules has gained worldwide popularity, providing highly scientific international standards. However, it is probably relatively easy to doubt the methods used in forensic death investigation when one has no insight into real forensic casework. But to doubt the will of those practitioners doing the field work is beyond any serious discussion.

One year after the appearance of the first volume of *Forensic Pathology Reviews*, this series has gained considerable attention within the forensic and medicolegal scientific community worldwide, which is, among other things, reflected in the efforts of 25 researchers from nine different nations representing four continents who have contributed to this third volume of the series. Most of the authors are *the* leading authorities in their particular fields of research. The

chapters in this volume, once again, provide the reader with a profound scientific and practical knowledge on a broad variety of different topics.

Chapter 1 gives the reader a thorough insight into the medicolegal investigation of bodies found in water, focusing not only on victim identification, evaluation of postmortem submersion time, and determination of the cause and manner of death, but also in depth analysis of the pathophysiology of drowning. Chapter 2 devotes attention to human immunodeficiency virus (HIV)-1 infection of the central nervous system in the forensic pathological setting. The forensic pathologist is frequently confronted with HIV-1 infection, especially in the context of drug abuse. In particular, the sampling of specimens for histological examination during autopsy, the neuropathological examination, and the related findings of diagnostic relevance, including the macroscopic and microscopic appearance of opportunistic infections, cerebrovascular complications, and neoplasms associated with the disease, are emphasized. Chapter 3 deals with rare events such as deaths in a head-down position, which most often occur accidentally. The author examines the phenomenology and pathological features of such fatalities, providing new insight into the pathophysiology of inverse body position based on human and animal experiments under true and simulated microgravitational conditions.

Chapter 4 deals with forensic bitemark analysis, giving a comprehensive outlook on promising new areas of research in this field (e.g., the retention of DNA on skin over time and the newly described bacterial fingerprinting technique).

Chapters 5 and 6 are devoted to taphonomic changes of human bodies and their remains, namely the underlying biological processes and resultant postmortem changes that a corpse undergoes during the early postmortem interval. The broad range of variables influencing the morphological picture under which distinctive postmortem changes present, as well as elaborate findings that can serve as a basis for the macromorphological exclusion of a forensically relevant lay time of soil-embedded skeletal remains are provided.

Chapter 7 concerns arrhythmogenic ventricular dysplasia, a disease that plays a significant role that should not be underestimated in daily forensic pathological autopsy practice in cases of sudden death. The illness can lead to lethal cardiac arrhythmia and usually manifests during the third decade of life. Interestingly, regionally higher frequencies of the illness in some countries at least suggest a genetic disposition to the disease. Chapter 8 concerns the postmortem diagnosis of death in anaphylaxis. The authors provide the reader with an up-to-date overview concerning morphological, biochemical, and

immunological investigations toward the diagnosis of anaphylaxis and give helpful guidelines for practical casework.

Chapter 9 takes a comprehensive look at gross, microscopical, and genetic findings in the forensic pathological evaluation of fatal pulmonary thromboembolism and the potentially involved medicolegal issues. Chapters 10 and 11 cover aspects of suicide. A profound look at the trends of suicide in the United States during the twentieth century is given in Chapter 10. These trends have altered drastically, especially within the past century and most specifically in the United States. Chapter 11 addresses problems that may arise in the medicolegal investigation of murder–suicides, uncommon events that require careful investigation.

Chapter 12 deals with the investigation of iatrogenic deaths that constitute a substantial forensic contribution to injury prevention, medical audit, and continuing improvement in health care. Iatrogenic injuries such as perioperative hemorrhage, sepsis, trauma, embolic phenomena, cardiovascular and cerebrovascular events, complications associated with anesthesia, interventional radiology and radiotherapy, as well as adverse drug events and reactions are considered in detail. In Chapter 13, thorough information about the use of radiology in medicolegal investigations (e.g., for the location of foreign bodies within the body, documentation of mechanical injuries, identification purposes, or elucidation of child abuse) is provided.

Again, I owe great thanks to my contributors for making their practical and scientific knowledge available.

Michael Tsokos, MD

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HIV-1 Infection of the Central Nervous System

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CONTENTS

SUMMARY

The forensic pathologist frequently is confronted with human immuno-deficiency virus (HIV)-1 infection, especially in the context of drug abuse. After involvement of the lung, the brain is the second most frequently affected organ in HIV-1 infection. Because HIV-1 rarely is the cause of focal macro-scopical lesions, even in severely infected patients, the systematic sampling of specimens for histological examination is required. If focal lesions are present, they are almost always attributed to opportunistic infections, cere-brovascular complications, or neoplasms. Changes primarily attributed to HIV-1 include HIV-1 encephalitis, HIV-1 leukoencephalopathy, and HIV-1 myelitis. Early changes in the course of the infection are characterized by meningeal lymphocytic infiltration and perivascular lymphocytic infiltration. Changes probably attributed to HIV-1 include vacuolar myelopathy and vacuolar leu-koencephalopathy. Opportunistic infections seen in the course of HIV-1 infection include a broad spectrum of viral, parasitic, fungal, and bacterial infections. Furthermore, ischemic stroke and intracranial hemorrhage, as well as lymphoma and Kaposi sarcoma, may be encountered. Despite the introduc-tion of antiretroviral therapies with a greater life expectancy of HIV-1-infected individuals, epidemiological data suggest that involvement of the brain in acquired immunodeficiency syndrome subjects continues to be a frequent autopsy finding. In the brains of HIV-1-infected children, the most common findings are vascular mineralization/calcification, myelin pallor, and gliosis of the white matter as well as inflammatory infiltrates and/or multinucleated giant cells. In contrast to adults, opportunistic infections are comparatively uncommon. The pathogenetic mechanisms induced by HIV-1 infection and leading to the multiple facets of brain damage are not yet clearly understood. The development of brain lesions caused by opportunistic infections and lym-phomas might be explained by the lack of a competent immunological defense system. In contrast, changes caused by direct or rather indirect effects of HIV-1 are more controversially discussed. HIV-1 enters the brain mainly by being passively carried by T lymphocytes and monocytes. Thereafter, perivascular macrophages spread productive HIV-1 infection to neighboring microglia. These are the major cell populations in the brain that are productively infected with HIV-1. They serve as a reservoir for persistent viral infection and repli-cation, a vehicle for viral dissemination throughout the brain, and a major source of neurotoxic products that affect glial function, the blood–brain bar-rier and neuronal function and finally lead to cell death.

Key Words: Central nervous system; forensic pathology; HIV-1 infec-tion; opportunistic infections; pathogenesis.

1. INTRODUCTION

Human immunodeficiency virus (HIV)-1 infection is a serious health problem worldwide, and the forensic pathologist frequently is confronted with this disease, especially in the context of drug abuse *(1–11)*. Intravenous drug abuse is a major risk factor for HIV-1 infection, and several drugs of abuse have been shown to enhance both the HIV-1 entry into the central nervous system (CNS) as well as the effects of HIV-1 on the CNS *(2,6,12–25)*. Similar to HIV-1, many abused drugs tend to affect neuronal function and enhance the microglial activation resulting from HIV-1 infection in some individuals *(26,27)*. Further paralleling HIV-1, some drugs seem to compromise immune function, which in turn may have secondary detrimental effects on the CNS *(28)*.

Neuropathological examinations show, in up to 95% of the brains, changes that may be attributed to the primary effect of HIV-1 or to opportunistic agents *(29–45)*.

In this chapter, the neuropathological features seen in the brains of patients infected with HIV-1 are reviewed briefly, and representative illustrations are shown. The reader also is referred to the multitude of articles and textbooks describing the neuropathological changes *(6,14,16,29–76)* as well as review articles on HIV-1 and the brain *(34,72,77–110)*. Moreover, changes especially seen in the early stages of HIV-1 infection in adults as well as those seen in the brains of children infected with HIV-1 are described briefly. In the following, the nomenclature and the neuropathology-based terminology as proposed in the consensus report of Budka et al. *(31)* is adopted. The definitions given in this report serve as guidelines for the neuropathological descriptions.

The term "AIDS dementia complex" (ADC) was coined in 1986 *(42,97)* to describe cognitive and motor disturbances frequently encountered in patients infected with HIV-1. The authors suggested that the pathogenesis of ADC was attributed to the changes found in the basal ganglia. Thus, ADC was considered to belong to the class of subcortical dementias. The name ADC was later changed into HIV-1-associated cognitive and motor complex with HIV-1-associated dementia complex (motor)/(behavior) (HAD) and HIV-1-associated myelopathy as its severe manifestations and HIV-1-associated minor cognitive/motor disorder as its mild manifestation *(111)*. It eventually affects up to 30% of untreated adult patients with acquired immunodeficiency syndrome (AIDS *[31,112,113]*). It is characterized by progressive cognitive decline, motor dysfunction, and behavioral abnormalities in 65% of patients *(97,98,101,112,114)*. HAD is the most devastating CNS consequence of AIDS because of its poor prognosis and functional impairment. In some persons

with HAD, the behavioral abnormalities can lead to violence and other criminal behavior *(115)*.

The pathogenesis of HIV-1-induced brain damage is uncertain, and there is evidence that multiple mechanisms leading to neurological injury occur (*see* Section 17). These mechanisms include the role of neurovirulent strains of HIV-1, the potential neurotoxicity of HIV proteins, macrophage/microglia-mediated CNS injury, and altered blood–brain barrier (BBB) permeability *(77,83,84,98,103,105,116–118)*.

Table 1 provides a survey of the neuropathological changes seen in the brains of patients infected with HIV-1. Table 2 summarizes the changes occurring in the peripheral nervous system and skeletal muscles of patients infected with HIV-1, but these are not dealt with in this review. The reader is directed to articles dealing in more detail with the neuropathology of peripheral nervous system and skeletal muscles *(119–127)*.

As a rule in the forensic setting, the HIV status of all persons undergoing autopsy should be determined ahead by enzyme-linked immunosorbent assay analysis of blood samples, which may be obtained from femoral vessels. The precautions in performing the autopsy of a patient who was infected with HIV, including the removal and fixation of the brain, are reviewed elsewhere and should be strictly practiced *(128–133)*. For a thorough neurohistopathological examination, infected cells may be identified by *in situ* hybridization or immunohistochemistry against HIV-1 proteins *(31,134–137)*.

2. EPIDEMIOLOGY

Worldwide, 33 million adults and 2 million children are infected with HIV-1. Despite preventive efforts, the epidemic continues to spread rapidly, and the socioeconomic consequences of the neurological dysfunction caused by HIV-1 infection are of enormous proportions. Most of the affected patients live in developing countries, where anti-retroviral medications are not available.

After involvement of the lung (75–85%), the brain is the second most frequently affected organ (60–80%) in HIV-1 infection *(16)*. The neurological complications of HIV-1 infection are highly stage-specific. Therefore, incidence rates depend on the stage, in which the individual is in, during the course of systemic HIV-1 infection *(70,99)*.

Neurological signs and symptoms are seen in up to 50% of patients infected with HIV-1 *(34,60,66,99,138,139)*. In approx 10% of the cases, neurological signs are the first presentation of the disease *(34,60,66,139)*. HIV-1-associated CNS complications vary with ethnicity *(140)* and geography *(40,47,141,142)*. The different findings likely reflect afflictions common to

Table 1
Survey of the More Common Neuropathological Changes Seen in the Brains of Patients Infected With HIV-1

Changes primarily attributable to HIV-1
 1. HIV-1 encephalitis (HIVE)
 2. HIV-1 leukoencephalopathy (HIVL)
 3. HIV-1 myelitis
 4. Lymphocytic meningitis (LM), meningeal lymphocytic infiltration (MLI), and perivascular lymphocytic infiltration (PLI)

Changes probably attributable to HIV-1
 1. Vacuolar myelopathy (VM)
 2. Vacuolar leukoencephalopathy (VL)

Opportunistic infections and neoplasias
 1. Viral Infections
    • Cytomegalovirus infection (CMV)
    • Progressive multifocal leukoencephalopathy (PML)
    • Others including herpes simplex 1, herpes simplex 2, herpes zoster, HTLV-1
 2. Parasitic infections
    • Protozoa: *Toxoplasma gondii*, Acanthamoeba, Leptomyxid amoeba, *Tryponosoma cruzi*
    • Metazoa: Strongyloides
 3. Fungal infections
    • *Aspergillus fumigatus*
    • Candida albicans
    • Cryptococcus neoformans
    • Others including histoplasma, phycomyces, coccidioides, blastomyces, acremonium, cladosporium
 4. Bacterial infections
    • Pyogenic: *Escherichia coli*, Listeria, Staphylococcus, Salmonella
    • Mycobacterial: *Mycobacterium tuberculosis*, *Mycobacterium avium intracellulare*
    • Spirochetal: *Treponema pallidum*
    • Filamentous: Nocardia
    • Miscellaneous: Whipple's disease
 5. Neoplasia
    • Lymphoma (primary and secondary)
    • Kaposi sarcoma

Table 2
*Neuropathological Changes Observed in the Peripheral Nervous System
and Skeletal Muscles of Patients Infected With HIV-1*

Peripheral nervous system
1. Acute inflammatory demyelinating (poly) (radiculo) neuropathy
2. Chronic inflammatory demyelinating (poly) (radiculo) neuropathy
3. Axonal neuropathy
4. Ganglionitis, ganglioradiculitis, (poly) (radiculo) neuritis
5. Necrotizing vasculitis, vasculitic neuropathy

Skeletal muscle
1. (Poly-)myositis
2. Necrotizing myopathy
3. Nemaline rod myopathy
4. Vesicular myopathy, mitochondrial myopathy
5. Necrotizing vasculitis

developing countries—a high prevalence of opportunistic infections and a high mortality rate. These conditions rarely lead to the development of complications such as lymphoma, which usually occurs later in the natural course of the HIV-1 infection. Death caused by systemic opportunistic infections may punctuate the course of HIV-1 encephalitis and prevent its full-blown morphological expression. However, larger autopsy studies of patients infected with HIV-1 over the course of longer time periods suggest that, despite the beneficial effects of modern antiretroviral combination therapy, involvement of the brain in AIDS subjects continues to be a frequent autopsy finding *(16,143–145)*.

3. GROSS ANATOMICAL CHANGES

It is important to emphasize the diffuse nature of the alterations that are likely to be present on gross examination. HIV-1 is rarely the cause of focal macroscopical lesions, even in heavily infected patients *(71)*. Therefore, systematic sampling of specimens for histological examination is required. If focal lesions are present, they are almost always caused by opportunistic infections, hemorrhages, or neoplasms.

Using imaging techniques (computed tomography, magnetic resonance imaging), it was claimed that brain atrophy is viewed in patients with HIV-1 infection and that this atrophy is already apparent in early stages of the infec-

tion *(146–148)*. Using autopsy brains and applying morphometrical techniques, one can assess whether signs of atrophy occur, which parts of the brain are affected, and to which extent these regions are affected.

The brain weight can be used as a rough indicator for atrophic changes occurring in the brain. Data on the weight of brains infected with HIV-1 are rarely published. The brain weight of 165 brains from HIV-1-positive patients and 155 age- and gender-matched controls was analyzed (Weis et al., unpublished data). No significant difference between controls and AIDS brains existed: the average brain weight of controls was 1434.94 g and that of HIV-1-positive patients was 1406.22 g. The degree of brain edema was rated using a three-point scale (0 = no brain edema; 1 = moderate brain edema; 2 = severe brain edema). There was no significant difference between the brains of controls and patients with AIDS. Furthermore, we used a three-point rating scale for assessing the widening of the ventricles (0 = no widening of lateral ventricles; 1 = moderate widening of lateral ventricles; 2 = marked widening of lateral ventricles). The widening of the lateral ventricles in the brains of patients with AIDS reached the level of statistical significance ($p = 0.04$; Weis et al., unpublished data).

Gelman and Guinto *(146)* measured cerebrospinal fluid (CSF) spaces in 64 consecutively autopsied patients with AIDS, which were compared with age-matched non-AIDS subjects (1992). Of the patients with AIDS, 37 (58%) had a CSF space index greater than 2 standard deviations above the mean of the age-matched control subjects. CSF spaces were expanded most in the frontal and temporal lobes; ventricular spaces were expanded more than the sulcal spaces. Patients with atrophy were much more likely to have HIV-1-associated histopathological changes in their brains, but the relationships were too weak to establish the microscopical cause of the atrophy.

Oster et al. *(147)* obtained stereological estimates of mean volumes, surface areas, and cortical thicknesses on formalin-fixed brains from 19 men with AIDS and 19 controls. In AIDS, the mean volume of the neocortex was reduced by 11%, and that of the central brain nuclei by 18%. Mean ventricular volume was increased by 55%. Mean neocortical thickness was reduced by 12%. The mean volume of the white matter was reduced by 13%. The findings in six clinically demented AIDS patients were not statistically different from the rest of the group.

The volumes of 20 cortical and 17 subcortical brain structures were estimated using Cavalieri's principle by Weis et al. *(149)*. Furthermore, the surface area and the mean cortical thickness of all cortical structures were measured. No significant changes were found in the cerebral cortex of patients

infected with HIV-1 as compared with age- and gender-matched controls. Only a significant reduction in volume was found in the internal capsule. The lack of significant changes in the brains of patients infected with HIV-1 might be attributed to the selection of the sample, which was composed of brains with the neuropathological diagnosis of HIV-1 encephalitis but that showed no remarkable gross anatomical changes.

Subbiah et al. *(148)* also used unbiased, stereological methods on post-mortem brain specimens to estimate volumes of different brain regions in patients prospectively diagnosed with and without HIV-associated dementia. A significant reduction in the mean neocortical volume (15%) was observed in the group with AIDS when compared with the seronegative controls, and this difference was accentuated when comparing only the group with HIV-associated dementia to the seronegatives (neocortex: 18%).

4. CHANGES PRIMARILY ATTRIBUTABLE TO HIV-1

4.1. HIV-1 Encephalitis

HIV-1 encephalitis (HIVE) is characterized by multiple disseminated inflammatory foci composed of microglia, macrophages, and multinucleated giant cells (MGCs). The foci are predominantly located perivascularly in the cortex, deep gray matter, and the white matter. The MGCs serve as the hallmark for HIVE, representing an HIV-1-specific cytopathic effect and are derived from HIV-1-mediated fusion of infected microglia and macrophages (Fig. 1A *[31,71,103,150]*). In their absence, the presence of HIV antigen or HIV nucleic acids has to be demonstrated either by immunohistochemistry (Fig. 1B) or by *in situ* hybridization, respectively *(31)*. MGCs contain as many as 20 round or elongated, basophilic nuclei that usually are arranged at the periphery of the cell. There is no strong correlation between HIVE and the clinical stages of the HAD *(71)*. The cytoplasm of MGCs is eosinophilic and appears densely stained in the center and vacuolated at the periphery. The cells are of monocyte/histiocyte lineage and include microglia and macrophages, as shown by immunohistochemical studies *(32,37,150,151)*. The nucleic acids of HIV proteins are located within their cytoplasm *(116)*. Electron microscopic analysis reveals retroviral particles either free in the cytoplasm or in cytoplasmic cisternae *(32)*. Microglia/macrophages and MGCs are capable of HIV synthesis and, thus, constitute the major reservoir and vehicle for the spread of the virus *(71,77,109,118,152)*.

Despite the introduction of highly active anti-retroviral therapy (HAART) with a greater life expectancy of infected individuals, epidemiological data
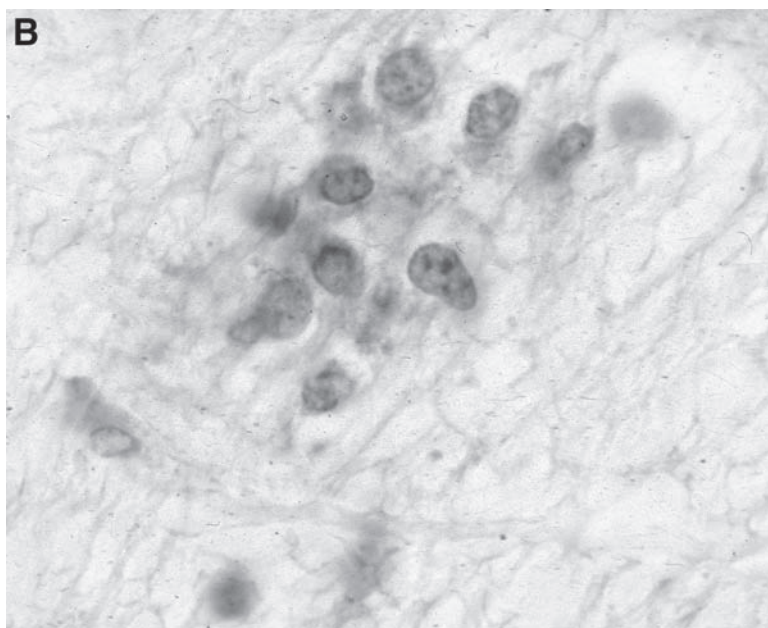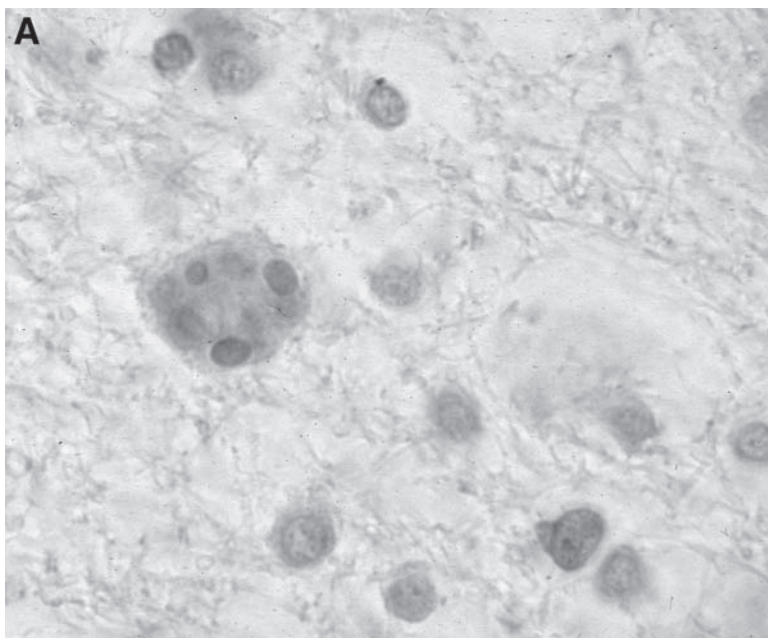
Fig. 1. (A), Multinucleated giant cell (cresyl violet). **(B),** HIV-1 antigen shown in a small gliomesenchymal nodule (immunohistochemistry for p24).

suggest that the prevalence of HIVE is on the rise *(153–155)*. Additionally, a new variant of HIVE has emerged in the era of HAART as a severe leukoencephalopathy with significant perivascular infiltration of macrophages and lymphocytes, which is assumed to be the result of an exaggerated response from a newly reconstituted immune system *(155)*. Synonyms previously used to describe HIVE include giant-cell encephalitis, multifocal giant-cell encephalitis, multinucleated cell encephalitis, and subacute encephalitis.

4.2. HIV-1 Leukoencephalopathy

HIV-1 leukoencephalopathy (HIVL) is characterized by diffuse damage to the white matter with myelin loss, reactive astrogliosis, macrophages, and MGCs. Only few, if any, inflammatory infiltrates are seen. In the absence of MGCs, the presence of HIV-1 antigen or HIV nucleic acids has to be demonstrated either by immunohistochemistry or by *in situ* hybridization *(31)*. Axonal damage can be demonstrated with immunohistochemistry for β-amyloid precursor protein *(156,157)*. *Progressive diffuse leukoencephalopathy* is another phrase previously used in describing HIVL.

HIVE and HIVL usually occur in the later stages of the AIDS infection. The differentiation between HIVE and HIVL can be confusing because in both cases the histological features have been described as MGCs in a focus with reactive astrocytes, microglia, and lymphocytes occurring in the white matter for HIVL and in both gray and white matter for HIVE. On the basis of our experience, the term HIVE should be used to describe the above-mentioned changes occurring in the gray matter only and HIVL to changes occurring in the white matter only. However, in most of the cases, myelin pallor usually is found around the gliomesenchymal nodule containing the MGCs. Furthermore, the analysis of 300 autopsy cases in our laboratory (Weis et al., unpublished observation) shows that the above-described changes (gliomesenchymal nodule with MGC) are found mainly in the cortex and deep gray matter but less frequently in the white matter, hence, necessitating a clear-cut delineation between HIVE and HIVL. Thus, the term HIVE should be reserved for changes in the gray matter and HIVL for changes in the white matter. If both gray and white matter are involved, the term HIVE/L should be used.

4.3. Lymphocytic Meningitis, Meningeal Lymphocytic Infiltrates, and Perivascular Lymphocytic Infiltration

Lymphocytic meningitis (LM) is characterized by a significant number of lymphocytic infiltrates in the leptomeninges (Fig. 2A). No opportunistic

pathogens are present in the meninges *(31)*. LM should be distinguished from meningeal lymphocytic infiltrates (MLI), which show lymphocytes in lesser quantity infiltrating the leptomeninges than LM (Fig. 2B). Perivascular lymphocytic infiltration (PLI) is characterized by a significant number of lymphocytic infiltrates in the perivascular spaces of the brain tissue (Fig. 2C). No opportunistic pathogens are present in the perivascular brain tissue *(31)*.

The relation of MLI and PLI to the HIV-1 infection is not yet clearly established, but it seems that lymphocytic infiltrates in the leptomeninges and in the perivascular spaces of the brain tissue constitute changes occurring in the early stages of the HIV-1 infection (*see* Section14).

5. CHANGES PROBABLY ATTRIBUTABLE TO HIV-1

Vacuolar myelopathy (VM) and vacuolar leukoencephalopathy (VL) are changes that are probably attributable to HIV-1 *(31)*. However, it is not yet clear whether these changes are caused by a direct effect of HIV-1 or constitute secondary changes.

5.1. Vacuolar Myelopathy

VM is characterized by numerous vacuolar myelin swellings and macrophages in multiple areas of the spinal cord *(31,71,158–163)*. VM predominantly involves the dorsolateral spinal tracts (Fig. 3A,B). Some macrophages may be found in the vacuoles. The axon is at first unaffected, but it is damaged in the later stages of the disease *(71,164)*.

The changes of VM might not be specific for HIV-1 because they can occur in the absence of HIV-1. However, in several studies HIV-1 has been shown to be present in spinal cord tissue showing VM using immunohistochemistry or *in situ* hybridization *(38,163,165)*. Thus, a direct relationship between the presence of HIV-1 and the changes of VM can be drawn.

HIV-1 may rarely produce a MGC myelitis analogous to HIVE *(71,161,163)*. Opportunistic infections and lymphomas of the spinal cord are uncommon *(161,163)*.

5.2. Vacuolar Leukoencephalopathy

VL is characterized by numerous vacuolar myelin swellings in the central white matter. Some macrophages may be found in the vacuoles. VL is a rare condition *(166)*.
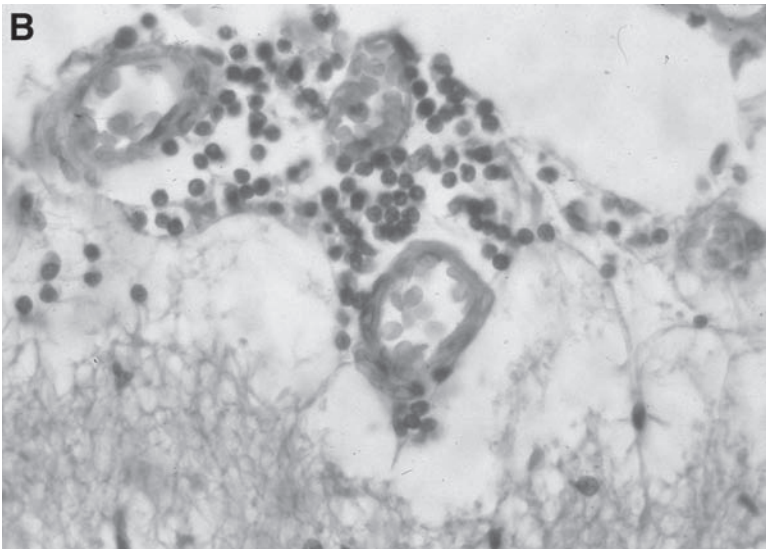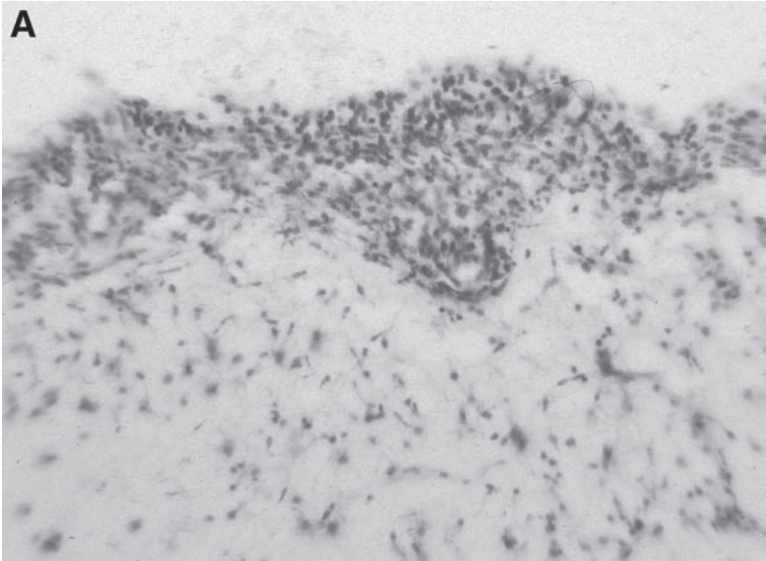
Fig. 2. (A), Lymphocytic meningitis (cresyl violet stain). **(B),** Meningeal lymphocytic infiltrates (Hematoxylin and eosin stain). **(C),** Perivascular lymphocytic infiltrates (Cresyl violet stain).

Fig. 2. *(continued)*

6. VIRAL INFECTIONS IN THE COURSE OF HIV-1 INFECTION

6.1. Cytomegalovirus Infection

In general, there are no gross anatomical changes in the brains of patients with AIDS who have cytomegalovirus (CMV) infection *(167–171)*. In some cases, a necrotizing ependymitis with small areas of necrosis lining the ventricles is seen *(172)*. Histologically, microglial nodules are seen scattered throughout the nervous system. Within these microglial nodules, large cells containing inclusion bodies are found (Fig. 4A). The microglial nodules located in the gray and white matter usually are not surrounded by a necrotic area, whereas along the periventricular spaces, CMV-containing cells are found within the necrotic areas. Figure 4B shows the immunohistochemical staining of an inclusion body. Diagnostic difficulties encountered are described in Sec-
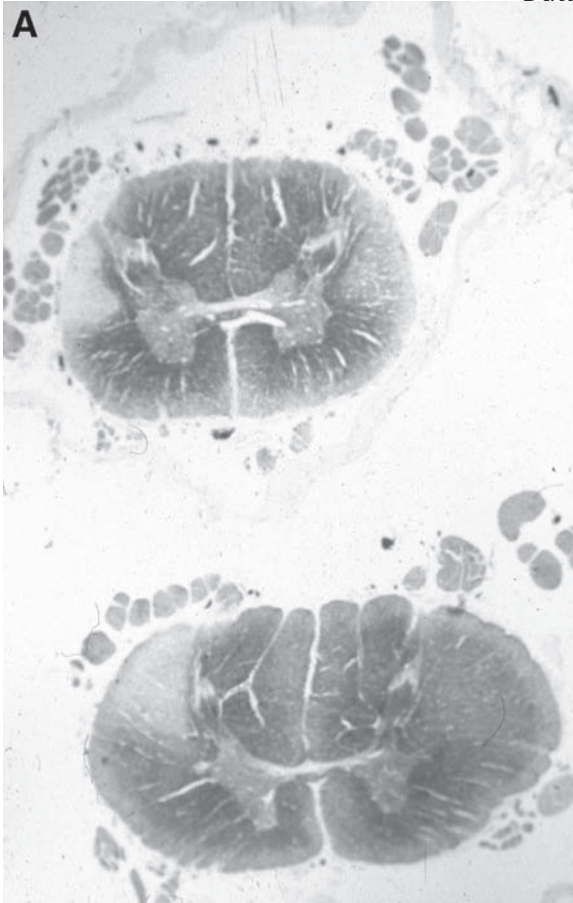
Fig. 3. Spinal cord showing vacuolar myelopathy of the dorsal tracts. **(A),** Woelcke's myelin stain; **(B),** Hematoxylin and eosin stain.

tion 12. The effects of CMV on the peripheral nervous system are reviewed elsewhere *(173,174).*

6.2. Progressive Multifocal Leukoencephalopathy

The causative agent in progressive multifocal leukoencephalopathy (PML) is papovavirus. Grossly, multiple areas of discoloration of the white matter are quite characteristic of PML (Fig. 5). Sometimes, the white matter may appear softened and mottled. Histologically, the diagnostic features for the presence of PML are *(a)* multiple foci of demyelination seen in the white matter consisting of loss of myelin sheaths; *(b)* enlarged, bizarre astrocytes; and
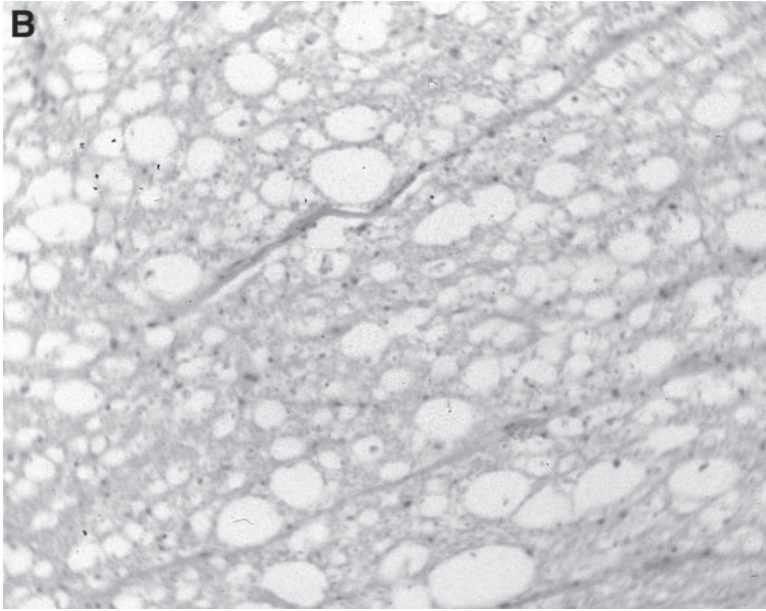
Fig. 3. *(continued)*

(c) intranuclear inclusions found within large swollen oligodendrocytes, the latter being the hallmark of PML *(175–178)*.

7. PARASITIC INFECTIONS

7.1. Toxoplasma gondii

Macroscopically, lesions appear as zones of necrosis with an area of hyperemia and/or small hemorrhages surrounded by a poorly defined area of edema (Fig. 6A). Microscopically, large zones of necrosis are found in the brain tissue. Chronic inflammatory cell response may be seen in the area of necrosis, which might be intense and sometimes gives the appearance of a lymphoma. The infiltrates are composed of lymphocytes, plasma cells, and histiocytes. The necrotic lesions are surrounded by reactive astrocytes, activated microglia, and inflammatory cells. Toxoplasma may be found in two forms: encysted organisms (Fig. 6B) and tachyzoites found in small or larger collections diffusely distributed near the junctional area between necrosis and brain tissue *(179,180)*. Toxoplasmosis restricted to the CNS can be pathogenetically classified as reactivation of a latent infection, whereas acute, systemic toxoplasmosis involving other organs is seen in patients who prob-
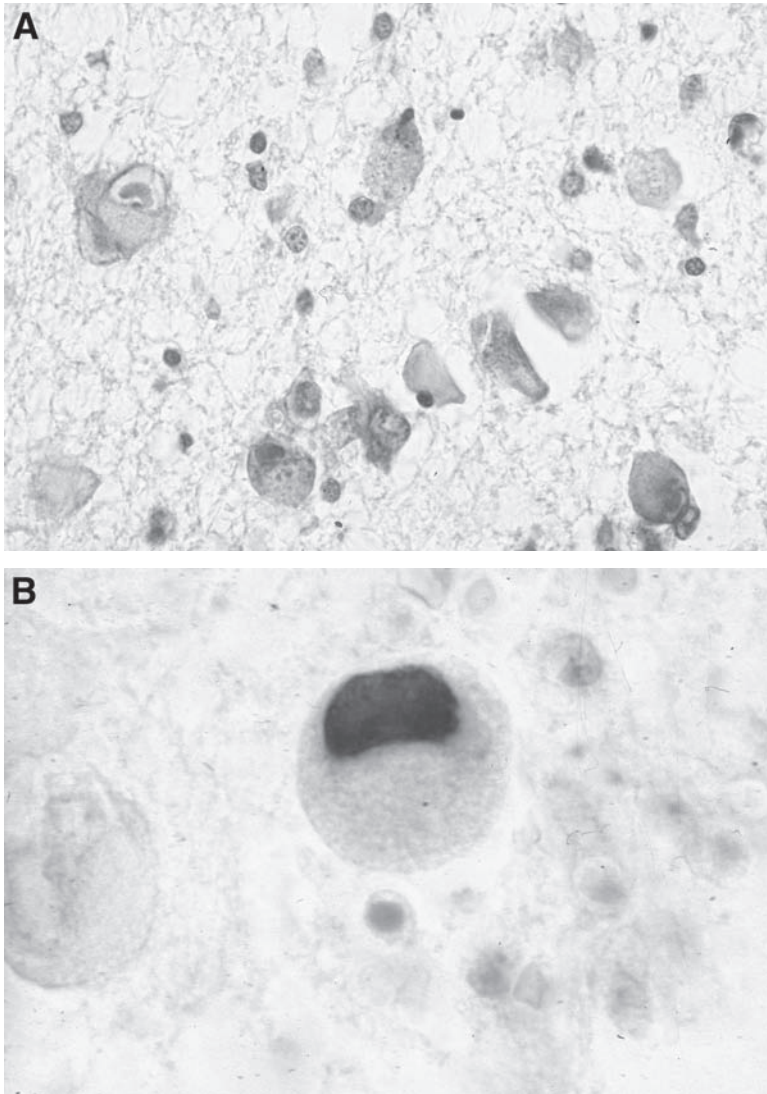
Fig. 4. Cytomegalovirus (CMV) infection. **(A),** Cells with inclusion bodies (Nissl stain). **(B),** Cytomegalic cell with inclusion body (immunohistochemistry for CMV).

ably acquired the infection during HIV-induced immunosuppression *(181)*. Diffuse, necrotizing toxoplasma encephalitis with widespread, confluent areas of necrosis was observed primarily during the early period of the AIDS epidemic and restricted to patients who did not receive chemotherapy. In subse-
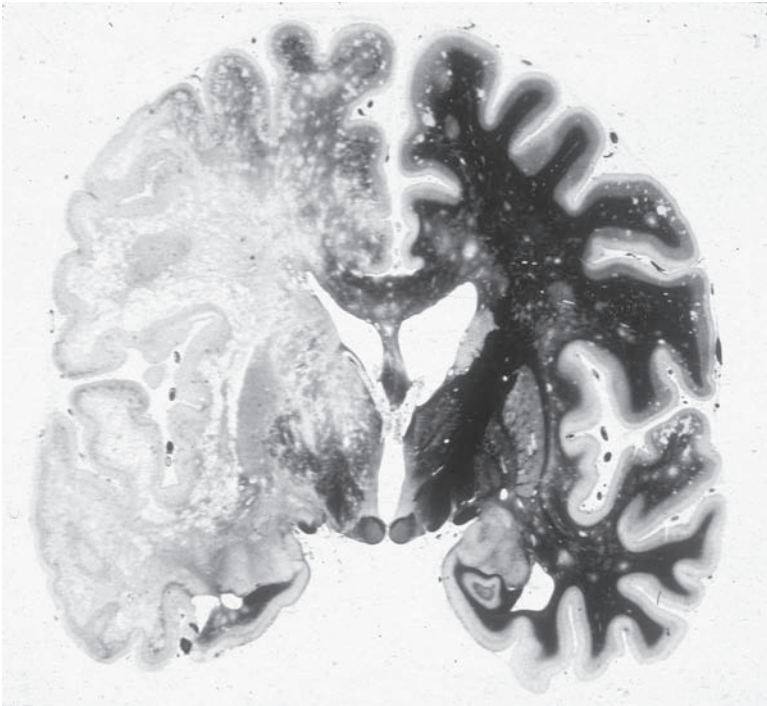
Fig. 5. Progressive multifocal leukoencephalopathy (Woelcke's myelin stain).

quent years, chronic, burnt-out lesions were observed. These are mainly composed of lipid-laden macrophages and immunocytochemistry for *Toxoplasma gondii* usually fails to detect the parasite *(181)*.

8. FUNGAL INFECTIONS

8.1. **Aspergillus fumigatus**

Macroscopically, necrotizing lesions in various regions of the brain might be seen in patients with Aspergillus infection. Aspergillus mainly involves large vessels. Thus, the lesions are usually associated with hemorrhage and hemorrhagic infarctions in large areas of the brain, but can be less pronounced. Microscopically, the vessel walls are invaded by septaled, branching hyphae. Thrombosis of the vessels and invasion of the tissue by the organisms are associated with necrosis *(64,76)*.
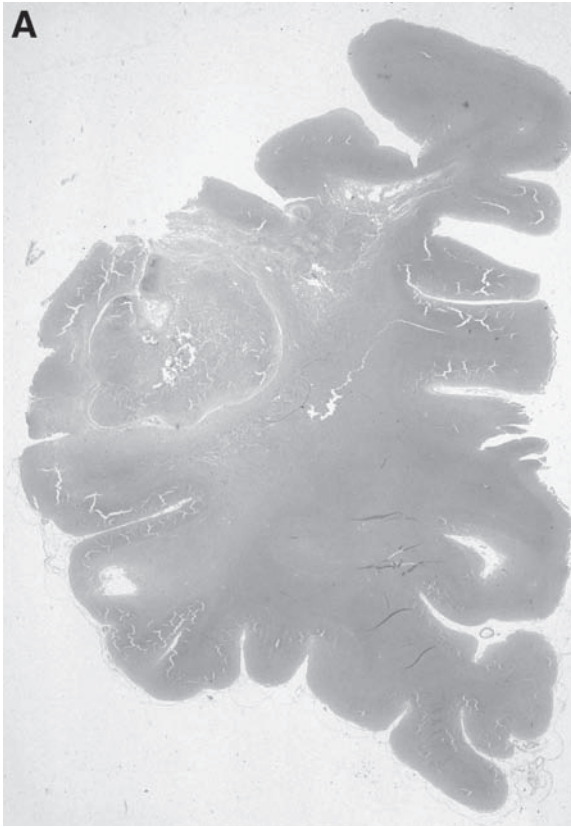
Fig. 6. *Toxoplasma gondii* infection. **(A),** Large area of necrosis in the frontal lobe (hematoxylin and eosin stain); **(B),** Encysted organisms in a gliomesenchymal nodule (cresyl violet stain).

8.2. **Candida albicans**

Nonspecific changes are found in the brain at gross anatomical examination. Occasionally, a mild to moderate edema with yellow softening of the brain tissue is noted. Histologically, multifocal microabscesses might be found containing polymorphonuclear, monocytic, and microglial cells sometimes surrounded by necrosis *(139).*

8.3. **Cryptococcus neoformans**

Macroscopically, the appearance of the brain lesions attributable to cryptococcus are diverse *(11,182).* Sometimes, no changes can be discerned, or
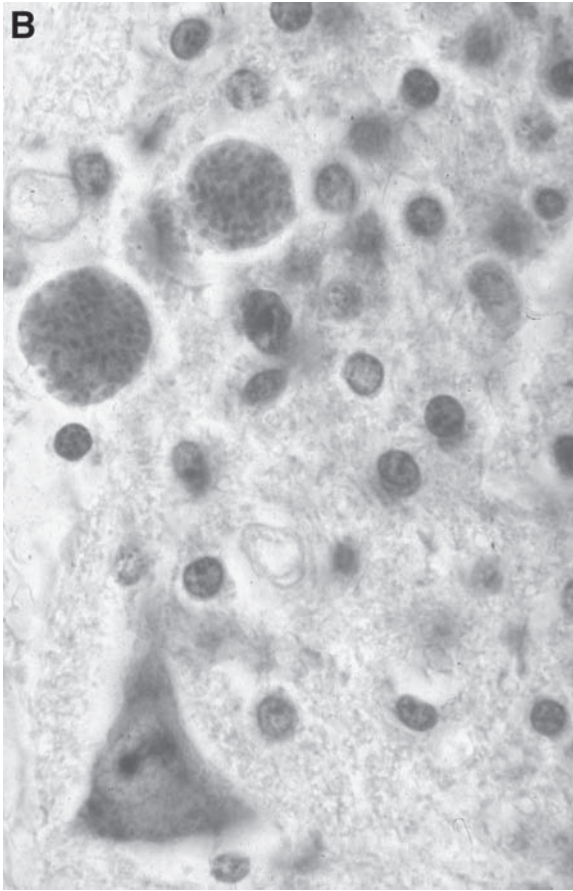
Fig. 6. *(continued)*

only small or large foci of gelatinous material may be seen either in the lep-
tomeninges or within the brain parenchyma (Fig. 7). These gelatinous areas
are histologically composed of thick mucin-positive capsules that contain the
cryptococcus spores. There may be minimal inflammatory response in the
neighborhood of the capsules *(182)*.

Furthermore, a spectrum of various opportunistic diseases, for example,
varizella-zoster virus *(183,184)*, herpes simplex virus *(185)*, neurosyphilis
(186), tuberculosis *(40,187)*, rabies *(188)*, nocardiosis *(189)*, and coccidioido-
mycosis *(190)* has been described in patients infected with HIV-1, but these
are rare conditions.
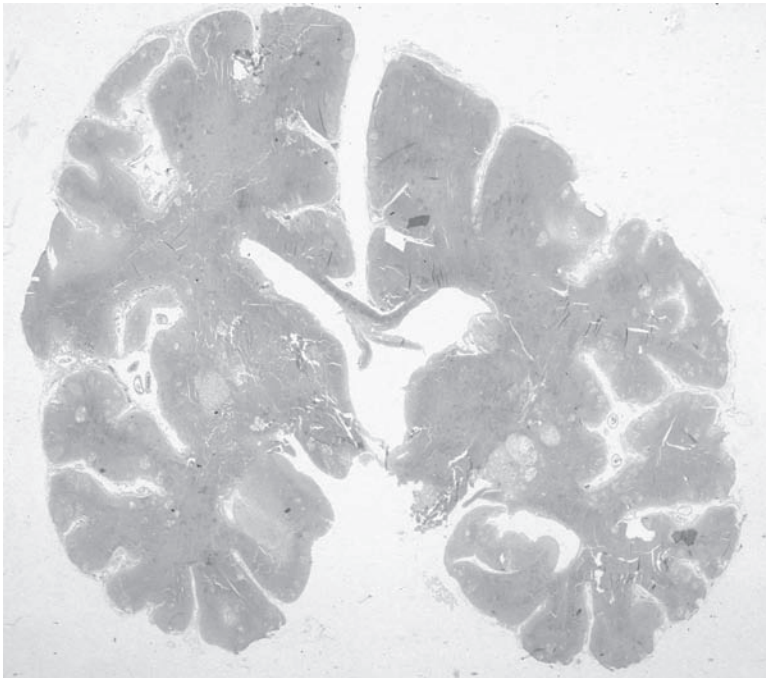
Fig. 7. Cryptococcus neoformans infection (Alcian blue stain).

9. NEOPLASIA IN THE COURSE OF HIV-1 INFECTION

9.1. Lymphomas

Lymphomas may occur as primary or secondary lesions; primary lymphoma is most commonly seen in AIDS brains *(191,192)*. Multifocal mass lesions that may be partially necrotic, partially hemorrhagic can be macroscopically localized anywhere in the brain. The tumors are composed of a high number of large, pleomorphic malignant cells with cleaved and folded nuclei and a varying amount of cytoplasm (Fig. 8). Most of the lymphomas are non-Hodgkin's B-cell tumors *(193–196)*. The infiltration of the tumor consists either of single cells or of cells that diffusely infiltrate the adjacent tissue. Diffuse infiltration of the vessel walls can be noted.

Brain tumors (excluding lymphomas) occurring in patients infected with HIV-1 have only occasionally been described *(197)* but must be considered in the differential diagnosis of an intracranial space-occupying lesion in this population.
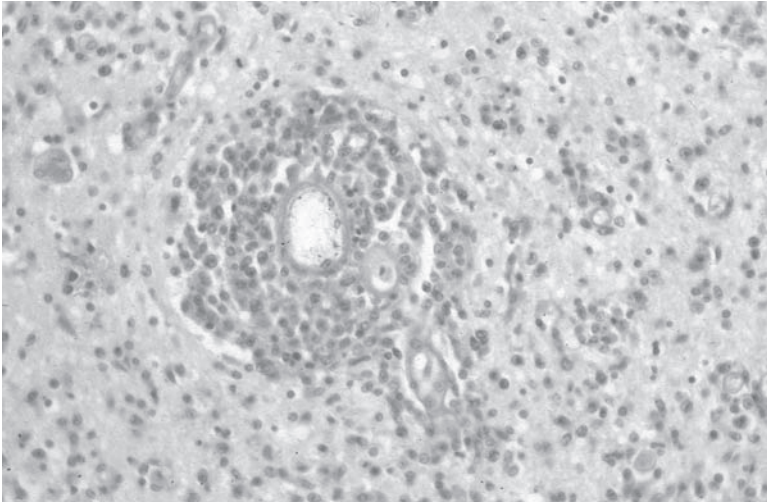
Fig. 8. Polymorphic non-Hodgkin's B-cell lymphoma (hematoxylin and eosin stain).

9.2. Kaposi Sarcoma

Intracerebral Kaposi sarcoma, which is frequently present in peripheral organs, has only been found in rare cases *(198)*.

10. FREQUENCY AND TOPOGRAPHICAL DISTRIBUTION OF NEUROPATHOLOGICAL CHANGES

10.1. Frequency of Neuropathological Changes

The frequency of neuropathological changes seen in the brains of patients infected with HIV-1 by different research groups is shown in Table 3 (Weis et al., unpublished data and refs. *6,8,14,16,29,32,33,35,37–43,47–49,51,52,55, 57,60,61,63–65,69,70,74–76,80,139,141,143,151,194,199–202*).

Table 3 shows a high variation in the frequency of the different neuropathological entities varying among the different research groups. These differences in the frequency and the occurrence of the various neuropathological changes might be caused by several factors that are given in the next section.

10.1.1. Sample Size

Sample size was quite small in the early reports. In recent reports the sample size ranges between 150 and 200 cases. However, although the variability might be reduced by large sample sizes, there still exist intercontinen-

Table 3

Comparison of the Reported Frequencies of Neuropathological Changes
in Brains of Patients Infected With HIV-1 (in %)

City/Country	Year	*n*	HIVE	HIVL	CMV	PML	TOXO	LYM	Reference
Miami	1984	52	5.7	nip	3.8	3.8	30.7	1.9	*41*
NYCor	1984	40	nip	nip	37.5	2.5	12.5	7.5	*65*
New Jersey	1985	8	0.0	nip	12.5	12.5	50.0	0.0	*74*
UCSF	1985	128	27.3	nip	nip	1.6	14.1	8.6	*139*
UCLA	1986	89	*a*	nip	15.7	6.7	6.7	4.5	*29*
NYCor	1986	70	28.1	nip	24.3	nip	nip	nip	*42*
NYCor	1986	153	28.2	nip	26.1	2.0	10.5	5.9	*43*
Sao Paulo	1986	22	nip	nip	0.0	0.0	18.2	9.1	*141*
Bronx	1987	53	9.4	nip	11.3	nip	9.4	5.6	*37*
Boston	1987	30	90.0	nip	6.6	3.3	16.6	6.6	*151*
USC	1987	100	nip	nip	17.0	nip	5.0	13.0	*69*
AU/I	1987	100	26.0[b]	25.0[b]	18.0	5.0	17.0	6.0	*32*
Frankfurt	1987	28	60.7	nip	17.8	3.6	28.6	7.1	*199*
France	1988	40	37.5	nip	20.0	5.0	47.5	2.5	*55*
CH	1989	135	15.5	nip	10.4	6.6	25.9	6.6	*39*
Mu/I	1989	51	50.9[c]	nip	5.8	7.8	19.6	5.8	*35*
Denmark	1989	43	nip	nip	18.6	2.3	9.3	6.9	*57*
Oxf/Lon-hem	1989	11	9.1	nip	0.0	0.0	0.0	nip	*80*
Ox/Lon-nonhem		31	25.8	nip	9.7	9.7	22.6	nip	*80*
London	1989	26	23.0	nip	7.6	nip	7.6	11.5	*60*
Genoa (I)	1989	22	22.7	nip	13.6	18.2	31.8	13.6	*52*
UCLA	1989	158	10.1	nip	17.1	5.1	7.6	3.2	*75*
Japan	1991	15	26.6	nip	20.0	6.6	13.3	13.3	*51*
New York	1991	111	nip	nip	nip	nip	nip	13.5	*194*
Texas	1991	141	19.8	nip	16.3	2.8	3.5	6.4	*33*
Bronx	1991	221	25.8	nip	12.7	5.4	13.1	5.4	*38*
Sao Paulo	1992	252	10.7	nip	7.9	0.8	34.1	4.0	*47*
Vancouver	1992	39	43.5	nip	23.1	2.6	17.9	28.2	*48*
Milan	1993	202	27.7[d]	19.8	nip	nip	nip	nip	*200*
Untreated		120	29.2	27.5	nip	nip	nip	nip	*200*
Zidovudine-treated		82	25.6	8.5	nip	nip	nip	nip	*200*
USC	1993	400	35.7[e]	8.0[e]	7.7	nip	8.2	5.7	*70*
Düsseldorf	1993	70	17.1	2.8	8.5	2.8	21.4	8.6	*64*
Berlin	1995	200	33.5[f]	nip	13.0	8.0	34.0	14.0	*61*
Drug abusers		37	59.5	nip	8.0	16.0	43.0	11.0	*61*

Table 3
(continued)

City/Country	Year	*n*	HIVE	HIVL	CMV	PML	TOXO	LYM	Reference
Homo/bisexuals		150	28.0	nip	13.0	7.0	35.0	16.0	*61*
Hamburg	1996	28	10.7	nip	3.6	nip	3.6	nip	*8*
New York[g]	1996	471	10.6	nip	2.7	1.9	4.7	3.8	*6*
Asymptomatic		123	0.0	nip	0.0	0.0	0.0	0.0	*6*
Early stages		127	16.5	nip	0.0	0.0	0.0	0.0	*6*
Full-blown AIDS		221	13.1	nip	5.9	4.1	10.0	8.1	*6*
UK	1997[h]	349							
Homo/bisexual		238	21.4	–	20.2	6.7	8.8	13.9	*49*
Injecting drug users		53							
Blood recipient		40	17.5	–	12.5	2.5	5.0	5.0	*49*
Heterosexual		18							
Poland	1997	100	22.0	7.0	23.0	11.0	16.0	10.0	*63*
India	1998	85	0.0	–	7.0	–	13.0	–	*40*
Poland	1998	172	nip	nip	22.7	9.3	16.3	nip	*76*
International	1998	1087	26.4[i]	–	16.4	5.3	16.0	11.1	*14*
Baltimore		293	24.6	–	18.7	3.4	7.5	10.2	*14*
Newark		115	13.0	–	5.2	1.7	13.0	2.6	*14*
Edinburgh		81	44.4	–	13.6	3.7	8.6	16.0	*14*
London		283	22.3	–	18.4	4.9	9.5	11.3	*14*
Paris		243	30.0	–	16.5	10.7	38.7	13.6	*14*
Budapest		72	38.9	–	19.4	4.2	12.5	13.9	*14*
UCSD	2000	390	26.3	nip	22.3	2.9	2.5	8.4	*143*
Austria	2000	450	8.4	4.4	16.9	6.7	19.1	8.0	*16*
1984–1992		190	11.5	2.6	17.4	5.7	24.0	6.3	*16*
1993–1995		162	5.6	6.2	20.0	8.7	20.4	11.2	*16*
1996–1999		98	8.0	5.0	11.0	5.0	8.0	6.0	*16*
pre-HAART, <1996[j]		352	8.5	4.3	18.5	7.1	22.2	8.5	*16*
UCSD	2003	151	38.4	nip	16.5	5.9	2.6	13.2	*201*
Before 1995		62	25.8	nip	16.1	6.4	6.4	19.3	*201*
After 1995		89	43.8	nip	16.8	5.6	0.0	8.9	*201*
France	2003	23	17.4	nip	8.7	17.4	13.0	13.0	*202*
Munich		300	11.1	3.2	13.0	0.8	13.0	7.1	*Weis unpublished*

Table 3
(continued)

[a]Authors report microglial nodules present in 62.9% of the cases without further specification.

[b]13% of the cases with HIVE only, 12% of cases with HIVL only and 13% of cases with HIVE + HIVL.

[c]Subacute microglial encephalitis with and without multinucleated giant cells.

[d]The combination of HIVE + HIVL gave the following results: 6.4% of the total sample, 8.3% in the untreated group, and 3.6% of the zidovudine treated group.

[e]Nodular encephalitis defined as gliomesenchymal cell or microglial nodules and diffuse leukoencephalopathy defined as white matter pallor, demyelination, spongiform change, macrophages, and astrogliosis. Note that there is no specific mention of multinucleated giant cells.

[f]HIV-related encephalopathy defined as vacuolization or spongy changes and astrocytosis in subcortical white matter and, occasionally, in gray matter. Note that there is no specific mention of multinucleated giant cells. MGCs were seen in 17.5% of the cases.

[g]A total of 221 persons from this study were used in a paper published by Kure et al. (*38*).

[h]HIVE and HIVL given together as HIVE/L.

[i]Diagnoses were given as HIVE/L.

[j]This category was created by the authors of the present paper.

nip, no information provided; NYCor, New York Cornell University; UCSF, University of California, San Francisco; UCLA, University of California, Los Angeles; USC, University of Southern California; AU, Austria; I, Italy; CH, Switzerland; Mu, Munich; Oxf/Lon, Oxford/London; UCSD, University of California, San Diego.

tal differences (e.g., United States, European countries), differences between countries (e.g., Switzerland, Austria, Italy, Germany) and differences between various regions within one country.

10.1.2. Composition of the Sample

The composition of the sample according to age (only adults), race (blacks, Caucasians), ethnic origin (Haitians, Hispanics), and risk group (drug addicts, hemophiliacs, homosexuals) might have an influence on the observed differences in the frequency of changes. However, there exists, until now, no paper dealing systematically with this problem.

10.1.3. Source of the Brains Analyzed

In our experience, differences result if brains are derived from Institutes of Pathology or from Institutes of Forensic Medicine. Brains derived from Institutes of Pathology show changes mainly seen in the late stages of the disease. Brains derived from Institutes of Forensic Medicine (composed mainly of brains from autopsied persons who committed suicide or had lethal accidents or died from other non-natural causes) mainly show changes seen in the

Table 4
Frequency of Lesions Encountered in the Late Stages of HIV-1 Infection
as Related to Their Topographical Localization in the Brain

Region	HIVE	HIVL	CMV	PML	TOX	CRY	ASP	LYM
Frontal	8.3	2.9	3.4	1.0	8.3	1.9	0.0	5.8
Parietal	3.2	1.6	3.2	1.1	7.4	2.1	0.0	1.6
Temporal	4.7	0.5	6.7	1.0	6.2	1.6	0.5	3.6
Occipital	2.0	1.5	3.9	1.0	7.1	1.5	0.5	4.1
Basal ganglia	5.7	–	7.8	–	8.8	1.6	0.5	4.7
Thalamus	4.9	–	7.4	–	2.5	1.8	0.0	3.1
Cerebellum	3.0	0.0	7.1	0.0	6.6	2.0	0.5	3.0
Mesencephalon	3.7	0.0	3.7	0.5	3.7	1.6	0.5	4.3
Pons	2.6	0.0	5.7	0.0	3.1	1.5	0.0	5.2
Medulla oblongata	2.6	0.0	6.7	0.0	3.1	1.5	0.5	4.1

HIVE, HIV-1 encephalitis; HIVL, HIV-1 leukoencephalopathy; CMV, cytomegalovirus encephalitis; PML, progressive multifocal leukoencephalopathy; TOX, *Toxoplasma gondii* encephalitis; CRY, *Cryptococcus encephalitis*; ASP, *Aspergillus fumigatus* encephalitis; LYM, lymphoma.

early stages of the disease. However, data regarding the time of seroconversion as well as the presence of clinical and neurological signs are often lacking.

10.1.4. Bias in Sampling

The number of patients infected with HIV-1 who undergo an autopsy after death might also have a considerable influence. Most of the time, clinicians are interested to see only the brains from interesting clinical cases to be analyzed by a pathologist/neuropathologist and insist for an autopsy, whereas "uninteresting cases" might not undergo autopsy.

10.1.5. Diagnostic Criteria

The diagnostic criteria may play a fundamental role. The use of immunohistochemistry or *in situ* hybridization to render the diagnosis of HIV encephalitis is not performed in all laboratories dealing with brains infected with HIV-1, thus limiting the reliability of this diagnosis.

10.2. Topographical Distribution of Neuropathological Changes

The topographical localization of the various neuropathological changes has not been described systematically until now. Table 4 shows the results of
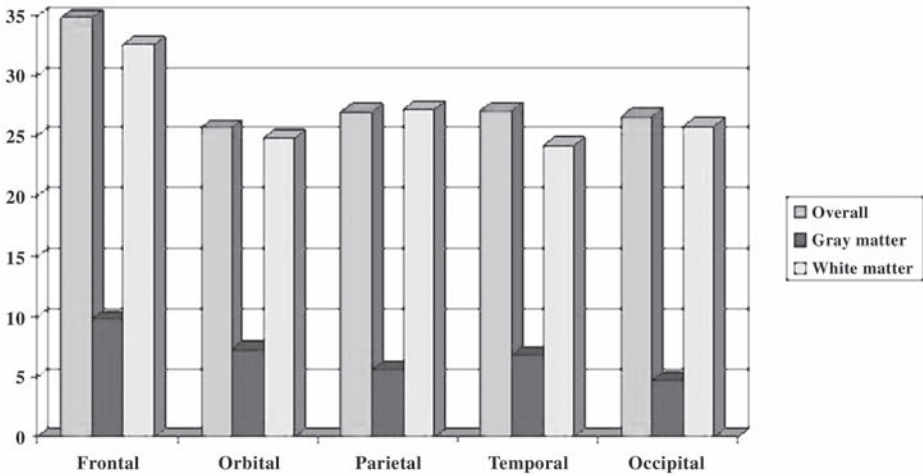
Fig. 9. Frequencies expressed as percent of cases of p24-immunopositive cells in various cortical regions.

a study in our laboratory of 300 cases. No consistent pattern for the distribution of the various neuropathological changes can be discerned (Weis et al., unpublished data).

11. IMMUNOHISTOCHEMICAL DEMONSTRATION OF HIV-1: FREQUENCY AND TOPOGRAPHY

The incidence and distribution of HIV-1 antigen, as shown immunohistochemically with an antibody against the glycoprotein p24, is shown in Fig. 9 (Weis et al., unpublished data). Data derived from other systematic analyses are, thus far, lacking.

12. DIAGNOSTIC DIFFICULTIES: UNSPECIFIED NODULAR ENCEPHALITIS

In many of the brains of patients infected with HIV-1, the only histological finding is the presence of gliomesenchymal nodules (GMNs; Fig. 10). GMNs, which are composed of microglia, macrophages, and reactive astrocytes, are found in the gray and white matter. The diagnostic problem is a result of the fact that there are neither MGCs present in the nodules nor large cells containing inclusion bodies. The differential diagnosis for GMNs includes HIV-1 encephalopathy/leukoencephalopathy, CMV encephalitis or *Toxoplasma*
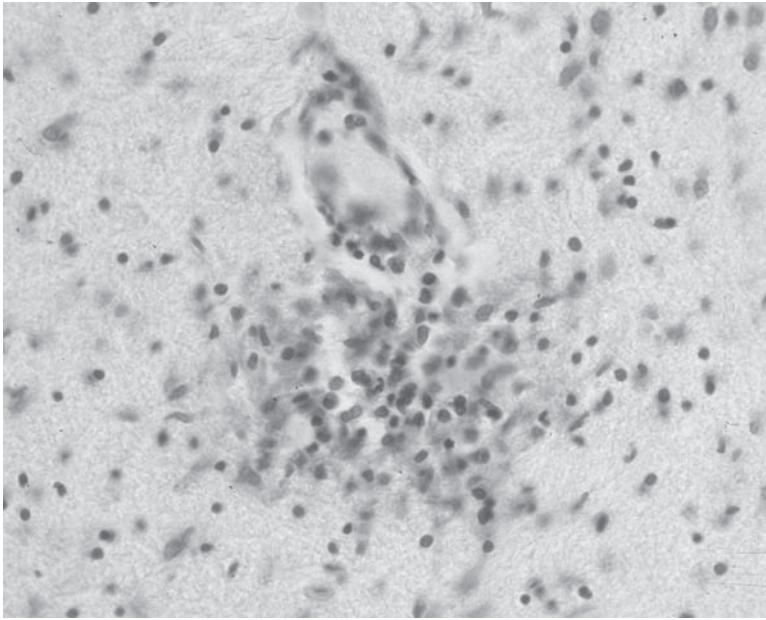
Fig. 10. Unspecified nodular encephalitis (cresyl violet stain).

gondii encephalitis. As proposed by Budka et al. *(32)*, these nodules are very suspicious to contain CMV when further serial sectioning is performed. In our experience, immunohistochemistry for CMV is of limited value. As described by Schmidbauer et al. (*169*), improvement may be provided by *in situ* hybridization, which might yield a positive result in cases with negative immunohistochemistry. In most of the cases, there is no immunohistochemical staining for gp41 or p24. Thus, the term "unspecified nodular encephalitis" is used in the diagnosis of these cases. Complete clarification is sometimes not possible.

13. NEUROPATHOLOGICAL CHANGES IN CHILDREN INFECTED WITH HIV-1

Children born to mothers who are infected with HIV-1 also are infected by the virus 10 to 39% of the time *(203)*. These children develop symptoms before the age of 2 years. Approximately 30% of children infected with HIV-1 develop opportunistic infection or HIV-1 encephalopathy within the first year of life. Brain growth is impaired, leading to intellectual deficiency. The macroscopial analysis frequently shows brains that are too small for the child's age, either as microcephaly and/or brain atrophy *(203,204)*. The most com-

mon finding in the brains of children infected with HIV-1 is mineralization/
calcification of predominantly small vessels in the basal ganglia found in 95%
of the cases *(203,206)*. Myelin pallor and gliosis are noted changes of the
white matter and occur in 78% of the cases *(203,205)*. Inflammatory infil-
trates and/or MGCs are seen in 62% of children infected with HIV-1 *(203,205)*.
HIV-1 infection in fetal brains usually is below the limits of detection of
immunocytochemistry, but HIV-1 detection is usually successful with poly-
merase chain reaction (PCR *[38]*). In contrast to adults, opportunistic infec-
tions are comparatively uncommon in the pediatric population *(203)*. For
details, the reader is referred to some articles and textbooks *(38,203,205–217)*.

14. Neuropathological Changes in Early Stages of HIV-1 Infection

Gray et al. described early brain changes in 11 HIV-1 seropositive, non-
AIDS cases in comparison with 11 HIV-1 seronegative heroin addicts *(218)*.
Cerebral vasculitis was significantly more frequent and marked in HIV serop-
ositive cases and was often associated with lymphocytic meningitis. Granular
ependymitis, myelin pallor with reactive astrocytosis, and microglial prolif-
eration also were more frequent and more severe in HIV seropositive cases.
Immunohistochemistry for HIV antigens was negative. Later, these authors
interpreted their results as being related to the occurrence of a usually
asymptomatic and transient immunopathological reaction coinciding with early
HIV infection of the nervous system *(219)*. This immunological process
includes an inflammatory T-cell reaction with vasculitis and leptomeningitis
and immune activation of brain parenchyma with an increased number of
microglial cells, upregulation of major histocompatibility complex class II
antigens, and local production of cytokines *(220,221)*. Some co-authors of the
Gray et al. *(220)* review articles reported separately their findings on 36 brains
of asymptomatic individuals *(222)*. They detected HIV-1 DNA in 17 cases
(47%), astrogliosis in 34 cases (94%), microgliosis in 31 cases (86%), and
meningitis in 11 cases (31%). One has to stress that astrogliosis and microgliosis
were only rated, but no quantitative data were provided. Furthermore, the
authors demonstrated highly expressed cytokines (tumor necrosis factor-α,
interleukin [IL]-1, -4, -6). They used these findings to explain neuropatho-
logic changes and neuronal damage confirmed by the demonstration of
apoptotic neurons by *in situ* end labeling *(222)*. Interestingly, it was stated in
the review article by this group *(220)* that neuronal death is only observed in
the late stages of the HIV-1 infection. The same group also reported having
detected HIV-1 DNA by PCR in all HIV-1-positive asymptomatic cases and

by *in situ* PCR in astrocytes and endothelial cells, in addition to microglial cells, in 6 of 18 HIV-1-asymptomatic patients *(223)*. The validity of the studies reporting the presence of HIV-1 in various cell types other than macrophages was questioned recently *(224)*.

In an ongoing study of 44 males in our laboratory representing early stages of HIV-1 infection, PLIs or MLIs were found in 70% of the cases. PLI alone was observed in 61% of the cases, MLI alone in 43% of the cases, and the combination of PLI and MLI in 34% of the cases (Weis et al., unpublished data). Sometimes, the extent of lymphocytic infiltrates in the meninges is more than normal but not enough to render a diagnosis of LM. Therefore, we apply the term MLI to describe these changes. Both changes, PLI and MLI, may occur together or separately in the brains of patients with HIV-1 at the early stages of infection. The histopathological changes of vasculitis and leptomeningitis, as reported by Gray et al. *(218–220)*, are rarely seen in the late stages of full-blown AIDS. In our study of 300 cases, we could never identify these changes either in the pre-AIDS stages or the late stages of the infection. Our data are in accordance with findings published by Kibayashi et al. in 1996 on 123 asymptomatic carriers and 127 persons with the early stages of AIDS *(6)*. They found lymphocytic infiltration of the meninges in 24.4% and of the perivascular spaces in 28.5% of the asymptomatic carriers, whereas these respective changes were seen in 11.8% and 11% of the early stage patients.

15. NEUROPATHOLOGICAL CHANGES IN THE HAART ERA

In 1995/1996, HAARTs that combine nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PIs) were introduced in the treatment of patients infected with HIV-1. NRTIs specifically inhibit the viral reverse transcriptase enzyme necessary for DNA chain elongation of the virus. The non-nucleoside reverse transcriptase inhibitors (NNRTI) are similar to the NRTIs in their mechanism of action; however, their effects on reverse transcriptase are by noncompetitive means. The PIs prevent the production of active virus by interfering with the cleavage of proteins necessary for viral assembly *(225)*.

The frequency of HIV-1-related CNS diseases has been reduced by these combinations of antiviral agents, in part through the reduction of both viral load in the blood and continuous penetration of virus into the brain *(226)*, although this therapy will probably not be sufficient to completely abolish any neurological risk. HIV-1-related dementia also depends on the intensity of glial cell activation in the CNS, which induces reactivation of latent infection in these cells, and on the secretion of soluble inflammatory mediators

acting on nearby neurons. During the HAART era, patients who test positive for HIV live longer *(144)*. The median survival after AIDS increased from 19.6 months for those patients diagnosed with AIDS in 1993–1995 to 39.6 months for those diagnosed in 1996–2000 in an Australian patient group *(227)*. The proportion of deaths that followed an HIV-related disease decreased by 23% annually; in contrast, there was a 32% yearly increase in the proportion of deaths caused by known causes other than HIV-related or suicides *(144)*. The higher prevalences of cirrhosis and arteriosclerosis suggest that entities not targeted by antiretroviral reconstitution of immunity will play an increasingly important role in HIV-related mortality in the future *(140)*.

Maschke et al. *(228)* compared the incidence and prevalence in two groups of 563 patients seen between 1995–1996 and 1997–1998. Significantly, more patients received HAART in 1997/1998 and the mean CD4$^+$ cell count was significantly higher in this group. The prevalence of HIV-associated dementia and HIV-associated polyneuropathy were significantly lower in 1997–1998, and the incidence of toxoplasma encephalitis decreased from 5.7% in 1995–1996 to 2.2% in 1997–1998. In a prospective, single-center study of all consecutive patients infected with HIV who presented with focal brain lesions observed between January 1991 and December 1998 ($n = 281$), Ammassari et al. *(229)* reported the following results: during the HAART period, patients were less likely to be male, contracted HIV more often through heterosexual exposure, had fewer previous AIDS-defining events, received anti-toxoplasma prophylaxis less frequently, and had a CD4$^+$ lymphocyte count 2.5 times higher. They found a relevant decline of primary CNS lymphoma, whereas the frequency of toxoplasma encephalitis decreased during the pre-HAART period and was stable afterward. A slight increase was observed over time for PML. Focal white-matter lesions without mass effect or contrast enhancement became the focal brain lesions observed most frequently. In an Australian patient group of 4351 AIDS cases, the proportion of patients with ADC increased from 5.2% in 1993–1995 to 6.8% in 1996–2000. The median survival after ADC increased from 11.9 months in 1993–1995 to 48.2 in 1996–2000. Most striking was the increase in survival among those patients with ADC and a CD4 cell count below 100×10^6 cells/L at diagnosis (5.1 months in 1993–1995 to 38.5 months in 1996–2000 *[227]*).

Larger cohort autopsy studies of HIV-infected patients over longer time periods suggest that, despite the beneficial effects of modern anti-retroviral combination therapy, involvement of the brain in AIDS subjects continues to be a frequent autopsy finding *(16,55,143,153,154,230)*.

Vago et al. *(230)* recently reviewed 1597 consecutive autopsies of HIV-1-positive patients performed between 1984 and 2000 and divided into four

Year infections	*n*	Therapy	HIVE/L	Opportunistic
1984–1987	119	None	53.8	40.3
1988–1994	1116	Mono	32.2	46.8
1995–1996	256	Dual	17.9	42.6
1997–2000	106	Triple	15.1	42.5

From ref. *230.*

time periods on the basis of the therapeutic regimens available: 1984–1987: no therapy; 1988–1994: monotherapy (zidovudine); 1995–1996: dual combination therapy with NRTIs; and 1997–2000: triple combination therapy, including two NRTIs and at least one PI or non-NRTI (*230*). They reported the results for HIV-related lesions (including HIVE and HIVL) and opportunistic infectious diseases (without specifying the causative agent) as shown in Table 5.

The results of other autopsy studies with more detailed information of neuropathological entities are listed in Table 6 *(16,55,143,202)*. The most consistent feature in it is its inconsistency of results. Thus, no consistent trend for the frequency of HIV-1-related changes is seen. In one study the frequency decreases, whereas in a second study it remains stable but increases dramatically in a third study. The frequency of CMV was reduced in two of three studies. PML and non-Hodgkin's lymphomas were increased in frequency in one study, whereas the frequency was unchanged in two studies. In all three studies, the frequency of toxoplasma encephalitis was significantly reduced.

Gray et al. speculated that the overall decrease in incidence of cerebral toxoplasmosis, CMV encephalitis, and HIVE was the result of successful treatment *(202)*. They also described a new variant of HIVE characterized by severe leukoencephalopathy with intense perivascular macrophage and lymphocytic infiltration, possibly the result of an exaggerated response from a newly reconstituted immune system. Furthermore, they detected chronic "burnt-out" forms of HIVE as well as varicella zoster virus encephalitis, toxoplasmosis, and PML, possibly associated with prolonged survival, in which neither inflammation nor organisms, could be detected.

In contrast, Langford et al. suggested that the increasing resistance of HIV strains to antiretrovirals led to the resurgence in the frequency of HIVE and HIVL *(201)*. HIVE and HIVL in AIDS patients failing HAART is charac-

Table 6

*Frequencies of Various Neuropathological Changes in the Pre-HAART Era
Compared With the HAART Era (in %; n = sample size)*

Author (year) (Reference)	*n*	HIVE	HIVL	CMV	PML	TOX	LYM
Gray et al. (1988)							
(55) pre-HAART	40	37.5	nip	20.0	5.0	47.5	2.5
Gray et al. (2003)							
(202)[a] HAART	23	17.4	nip	8.7	17.4	13.0	13.0
Jellinger et al. (2000)							
(16) pre-HAART	352	8.5	4.3	18.5	7.1	22.2	8.5
HAART	98	8.0	5.0	11.0	5.0	8.0	6.0
Langford et al. (2003)							
(201) pre-HAART	62	25.8	nip	16.1	6.4	6.4	19.3
HAART	89	43.8	nip	16.8	5.6	0.0	8.9

[a]Frequencies for the pre-HAART could not be calculated because of the lack of original data in this publication.

HIVE, HIV-1 encephalitis; HIVL, HIV-1 leukoencephalopathy; CMV, cytomegalovirus encephalitis; PML, progressive multifocal leukoencephalopathy; TOX, *Toxoplasma gondii* encephalitis; LYM, primary non-Hodgkin's lymphoma; nip, no information provided.

terized by massive infiltration of HIV-infected monocytes/macrophages into the brain and extensive white matter destruction. This condition might be attributable to interactions of anti-retrovirals with cerebrovascular endothelium, astroglial cells, and white matter of the brain. These interactions might lead to cerebral ischemia, increased BBB permeability and demyelination. The authors postulate that potential mechanisms of such interactions include alterations in host cell signaling that may result in trophic factor dysregulation and mitochondrial injury *(201)*.

Future studies have to address the above-mentioned points by systematic investigation of the various cell systems (e.g., neurons, astrocytes, microglia, oligodendrocytes) in much larger samples. Before reaching final conclusions about the changed pattern of neuropathological changes in the HAART era, one has also to prove that these reported divergent results are not due to a sampling error, for example, the most interesting cases undergo autopsy, whereas the less interesting cases are not autopsied.

Table 7
Incidence of Cerebral Infarcts and Cerebral Hemorrhages in Larger Autopsy
Series of Patients Infected With HIV-1

Authors (Year) (Reference)	Ischemic stroke	Intracranial hemorrhage
Anders et al. (1986) *(29)*	14.6% (13/89)	5,6% (5/89)
Berger et al. (1990) *(231)*	7.2 % (13/181)	nip
Budka et al. (1987) *(32)*	nip	11.0% (11/100)
Burns et al. (1991) *(33)*	7.8% (11/141)	5.7% (8/141)
Jellinger et al. (2000) *(16)*	5.6–6.3%	1.2–4.0%
Kieburtz et al. (1993) *(235)*	30% (14/70)	nip
Kure et al. (1991) *(38)*	19.5% (43/221)	5.4% (12/221)
Mizusawa et al. (1988) *(236)*	29% (24/83)	6% (5/83)
Moskowitz et al. (1984) *(41)*	3.9% (2/52)	8.0% (4/52)
Rhodes et al. (1993) *(70)*	9.0% (36/400)	5.8% (23/400)

nip, no information provided.

16. CEREBROVASCULAR COMPLICATIONS

Several case reports and larger autopsy series described cerebrovascular complications in patients with HIV-1 infection *(16,29,32,33,38,41,47,70,231–237)*. Cerebrovascular disease has been reported to occur in about 10% of asymptomatic HIV-1 carriers, 7% of patients with early AIDS, and 5% of patients with fully developed AIDS *(6)*. Autopsy series of patients with AIDS have found a 4% to 30% prevalence of cerebral infarction and 1.2% to 11% of intracranial hemorrhage (Table 7). Cerebral infarcts were mostly caused by nonbacterial thrombotic endocarditis or concomitant opportunistic CNS infection, whereas intracerebral hemorrhages were usually associated with thrombocytopenia or primary CNS lymphoma. In a recent study it could be demonstrated that AIDS patients have an increased risk of stroke with an adjusted relative risk of 9.1 for ischemic stroke and 12.7 for intracerebral hemorrhage *(238)*. According to the authors, AIDS is strongly associated with both ischemic stroke and intracranial hemorrhage.

Besides these macromorphological changes, alterations of the BBB could be demonstrated by several research groups (*see* Section 17). Furthermore, an HIV-1-associated vasculopathy with small vessel thickening, rarefaction, perivascular pigment deposition, and vessel wall mineralization has been described in HIV-1-infected patients *(232,239)*, but a true cerebral vasculitis is exceptionally rare *(240)*.

17. PATHOGENETIC MECHANISMS

The pathogenetic mechanisms induced by the HIV-1 infection and leading to the multiple facets of brain damage are not yet clearly understood. A complete review of the proposed mechanisms is not within the scope of the present chapter; rather, we elected to briefly describe some of the most probable aspects.

17.1. Mode of Entrance of HIV-1 to the Brain

HIV-1 is believed to enter the CNS by being passively carried by T-lymphocytes and monocytes, that is, the "Trojan Horse" hypothesis *(77,241,242)*. Recent evidence suggests that cell-free HIV-1 particles may also penetrate brain microvascular endothelial cells *(243)*. After crossing the BBB into the CNS, macrophages spread productive HIV-1 infection to neighboring microglia *(77,89,105,118,244)*. The potential role of the CSF or the choroid plexus as a means for HIV-1 entry in the brain is still unclear *(245)*. At the time of primary HIV-1 infection, an acute aseptic meningitis or encephalitis indicates CNS invasion *(103)*. Opportunistic infectious agents or drugs of abuse disturbing the BBB may further attract more HIV-1 infected T-lymphocytes and macrophages into the brain. The point in time when the migration of HIV-1-infected lymphocytes into the brain takes place is not known. It has been shown that, at the time of seroconversion, HIV-1 can be detected in the CSF; this is the time when, clinically, a subacute meningitis develops, thus, suggesting that HIV-1 enters the CNS at a very early stage of the disease *(96,246)*.

17.2. Target Cells of HIV-1

Although it has been claimed that HIV-1 is neurotrophic, the few articles describing the localization of HIV-1 in nerve cells have been subsequently disproved *(59,71,89,247)*. Despite the detection of HIV-1 proteins in endothelial cells *(248)*, it is now generally believed that productive HIV-1 infection of the cerebral endothelium does not occur *(103,137,247)*. Furthermore, there is only infection at low level in a subset of astrocytes *(71,103,249)*. Bissel and Wiley *(224)* reviewed the evidence of productive and nonproductive infection for each cell type (neurons, astrocytes, oligodendrocytes, microglia/macrophages, endothelial cells) in the brains of patients with HIV with and without HIV encephalitis. They concluded that despite the voluminous literature and substantial experimental effort during the past two decades, evidence for productive infection of any brain cell other than macrophages is weak.

The cells in the brain identified to contain HIV-1 are the microglia, macrophages, and MGCs *(59,71,84,89,109,116–118,137,152,247,250,251)*.

Microglia and monocyte-derived macrophages are the only cells in the CNS that express both the CD4 and chemokine coreceptors (CCR5, CXCR4), the prerequisite for HIV-1 to enter a cell *(77,252,253)*. The HIV-1 glycoprotein-mediated syncytia formation, which results from fusion of microglia or brain macrophages, may be observed as multinucleated giant cells (*see* Subheading 4.1.). It has been demonstrated that perivascular macrophages are a major CNS cell population that is productively infected with HIV-1. Such productive infection occurs with an accumulation of macrophages in perivascular cuffs, an event that correlates with entry of HIV-1 to the CNS *(241)*. Brain macrophages and microglia serve as a reservoir for persistent viral infection, a vehicle for viral dissemination throughout the brain, and a major source of neurotoxic products that, when produced in abundance, affect neuronal function and finally lead to cell death *(89,105,118,155)*. How HIV-1 evades the immune function characteristic for these cells as a first line of defense is still unclear.

In vitro test system by cell culture enables one to infect neuronal, astroglial, and endothelial cell lines, but does not seem to be the appropriate medium to test the infectivity of cell groups. Moreover, these results contradict the in vivo situation of the human brain.

17.3. Mechanisms of Brain Lesions

HIV-1 infection of the CNS occurs early after infection in the periphery, from hours to days, but neurological symptoms and HIV-associated dementia often occur years later, concomitant with or after the development of AIDS. Because productive infection reemerges with the development of AIDS, it is suggested that virus that enter the CNS early after infection can become latent and then reemerge with AIDS or that productive infection, which results with the development of AIDS, occurs from reseeding new virus from the periphery *(241)*.

The development of brain lesions from opportunistic infections and lymphomas might be explained by the lack of a competent immunological defense system. The clinical signs and symptoms can be correlated with the site of the lesion as well as the brain structures involved.

In contrast, changes caused by direct or rather indirect effects of HIV-1 are more controversially discussed. Data based on systematic morphometrical analyses of the various constituents of the brain give new insight into the damage of the brain caused by HIV-1 *(147–149,254–256)*. Neuronal loss was shown by independent research groups to occur in the frontal, parietal, and temporal cortex *(50,257,258)*. Ketzler et al. (*257*), Weis et al. (*258*), and Weis (*256*) showed that this neuronal dropout occurs in brain regions that are free from any neuropathological changes. Others showed that neuronal damage in AIDS

was, at least, partly caused by apoptosis *(259–262)*. However, no correlation was found between the presence and severity of neuronal loss or of neuronal apoptosis and a history of cognitive disorders.

Weis et al. *(263)* showed an increase of glial fibrillary acidic protein-positive astrocytes, a decrease of glial fibrillary acidic protein-negative astrocytes, but no changes in the total number of astroglial cells. The reactive astrogliosis was not correlated with the loss of nerve cells, indicating that this reaction pattern is rather a response to toxic factors secreted into the brain tissue.

In addition, significant structural and functional abnormalities in the microvasculature have been identified, including serum protein leakage *(264–266)*, alterations in endothelial cells and basement membranes *(267–269)*, as well as disruption of tight junctions *(252,270–272)*, suggestive for BBB damage in the course of HIV-1 infection. These alterations are believed to be the result of a complex cascade of events and molecules involving HIV-1 proteins as well as products of monocytes, microglia, astrocytes, and activated brain endothelial cells *(155,244,246,252,273–277)*.

One might assume that the above-described changes might result from infection with HIV-1. However, it has been shown that neither neurons, nor astrocytes, nor endothelial cells are significantly infected with HIV-1 *(103)*. Therefore, these changes are more probably the result of indirect toxic factors that are produced either by infected MGCs or by activated microglia, or neurotoxic viral proteins *(77,84,89,107–109,116,275)*.

The number of activated microglia/macrophages is significantly increased in all brain regions *(278)*. This activation of microglia is not correlated with the presence of HIV-1 antigen in the brain tissue. This result might give a hint that, most probably, the activated microglia/macrophages, rather than MGCs, secrete toxic factors. However, this hypothesis remains to be proven. How a finite number of infected macrophages/microglia, localized in particular areas of the brain, can lead to widespread neuronal injury is summarized below.

The neurotoxicity associated with HIV-1 infection is mediated, in part, through cytokines and arachidonic acid metabolites, produced during cell-to-cell interactions between HIV-1 infected brain macrophages and astrocytes *(84,89,103,105,118,155,279–281)*. The relationship between viral proteins, CA^{2+} channels, NMDA receptors, chemokines, and cytokines on one hand and cell damage on the other is summarized elsewhere *(84,89,93,94,103,155,282–286)*.

Briefly, the pathobiological events underlying the neurodegenerative processes in HIV-1-associated dementia are believed to begin with productive infection of monocytes/macrophages by HIV-1. Peripheral activation causes

the differentiation of macrophages to produce a variety of immune products that lead to the upregulation of adhesion molecules on brain microvascular endothelial cells and the expression of cytokines on the monocyte-macrophage cell surface. After penetration of the BBB, the differentiated brain macrophages and microglia can be vehicles for viral dissemination throughout the brain and focal reservoirs for productive HIV-1 replication. The neurotoxic events in the brain are caused by neurotoxins produced by these cells, which are primed by HIV-1 and secondarily activated by factors such as immune stimuli or by T-cells trafficking through the nervous system. The primed and immune-activated brain macrophages/microglia secrete a variety of factors that affect neural and glial function and eventually lead to CNS inflammation. A proinflammatory cytokine response from blood-derived monocytes/macrophages, microglia, and astrocytes is amplified and leads finally to neurodegeneration. Immune neurotoxic factors may contribute to the breakdown of the BBB and affect the generation of chemokines, leading to transendothelial migration of monocytes into the brain perpetuating the inflammatory cascade. As a result of the neurotoxic activities of activated macrophages/microglia, astrocytes may suppress or increase macrophages/microglia secretory functions and toxicity, depending on the astrocytic functional status. Cytolytic T-lymphocytes serve to eliminate infected cells, but are lost in late-stage HIV-1 disease, allowing the virus-induced, neurodegenerative response to continue unabated *(84,89,105,118,155,244)*.

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