Infections

General aspects of the pathology of infectious agents, including pathogenetic mechanisms involving the CNS, are discussed in Chapter 8. To briefly recapitulate here, there are four principal routes by which infectious microbes enter the nervous system. Hematogenous spread is the most common means of entry; infectious agents ordinarily enter through the arterial circulation, but retrograde venous spread can occur through anastomotic connections between veins of the face and cerebral circulation. Direct implantation of microorganisms is almost invariably traumatic; rarely, it is iatrogenic, as when microbes are introduced with a lumbar puncture needle, or is associated with congenital malformations (such as meningomyelocele). Local extension occurs secondary to an established infection in an air sinus, most often the mastoid or frontal; an infected tooth; or a surgical site in the cranium or spine causing osteomyelitis, bone erosion, and propagation of the infection into the CNS. The fourth pathway is through the peripheral nervous system into the CNS, as occurs with certain viruses, such as rabies and herpes zoster. Damage to nervous tissue may be the consequence of direct injury of neurons or glia by the infectious agent or may occur indirectly through the elaboration of microbial toxins, destructive effects of the inflammatory response, or the result of immune-mediated mechanisms.

ACUTE MENINGITIS

Meningitis refers to an inflammatory process of the leptomeninges and CSF within the subarachnoid space. Meningoencephalitis refers to inflammation of the meninges and brain parenchyma. Meningitis is usually caused by an infection, but chemical meningitis may also occur in response to a nonbacterial irritant introduced into the subarachnoid space. Infiltration of the subarachnoid space by carcinoma is referred to as meningeal carcinomatosis (sometimes called carcinomatous meningitis) and by lymphoma as meningeal lymphomatosis. Infectious meningitis is broadly classified into acute pyogenic (usually bacterial meningitis), aseptic (usually acute viral meningitis), and chronic (usually tuberculous, spirochetal, or cryptococcal) on the basis of the characteristics of inflammatory exudate on CSF examination and the clinical evolution of the illness.

Acute Pyogenic (Bacterial) Meningitis

The microorganisms that cause acute pyogenic meningitis vary with the age of the patient. In neonates, the organisms include Escherichia coli and the group B streptococci; at the other extreme of life, Streptococcus pneumoniae and Listeria monocytogenes are more common. Among adolescents and in young adults, Neisseria meningitidis is the most common pathogen, with clusters of cases representing frequent public health concerns. The introduction of immunization against Haemophilus influenzae has markedly reduced the incidence of meningitis associated with this organism in the developed world; the population that was previously at highest risk (infants) now has a much lower risk of meningitis, with S. pneumoniae being the most prevalent organism.

Patients typically show systemic signs of infection superimposed on clinical evidence of meningeal irritation and neurologic impairment, including headache, photophobia, irritability, clouding of consciousness, and neck stiffness. A spinal tap yields cloudy or frankly purulent CSF, under
increased pressure, with as many as 90,000 neutrophils/mm$^3$, a raised protein level, and a markedly reduced glucose content. Bacteria may be seen on a smear or can be cultured, sometimes a few hours before the neutrophils appear. Untreated, pyogenic meningitis can be fatal. The Waterhouse-Friderichsen syndrome results from meningitis-associated septicemia with hemorrhagic infarction of the adrenal glands and cutaneous petechiae. It is particularly common with meningococcal and pneumococcal meningitis. Effective antimicrobial agents markedly reduce mortality associated with meningitis. In the immunosuppressed patient, purulent meningitis may be caused by other agents, such as *Klebsiella* or an anaerobic organism, and may have an atypical course and uncharacteristic CSF findings, all of which make the diagnosis more difficult.

Morphology.

The normally clear CSF is cloudy and sometimes frankly purulent. In acute meningitis, an exudate is evident within the leptomeninges over the surface of the brain (Fig. 28-21). The meningeal vessels are engorged and stand out prominently. The location of the exudate varies; in *H. influenzae* meningitis, for example, it is usually basal, whereas in pneumococcal meningitis, it is often densest over the cerebral convexities near the sagittal sinus. From the areas of greatest accumulation, tracts of pus can be followed along blood vessels on the surface of the brain. When the meningitis is fulminant, the inflammation may extend to the ventricles, producing ventriculitis.

**Figure 28-21** Pyogenic meningitis. A thick layer of suppurative exudate covers the brain stem and cerebellum and thickens the leptomeninges. *(From Golden JA, Louis DN: Images in clinical medicine: Acute bacterial meningitis. N Engl J Med 333:364, 1994.)*

On microscopic examination, neutrophils fill the entire subarachnoid space in severely affected areas and are found predominantly around the leptomeningeal blood vessels in less severe cases. In untreated meningitis, Gram stain reveals varying numbers of the causative organism, although they are frequently not demonstrable in treated cases. In fulminant meningitis, the inflammatory
cells infiltrate the walls of the leptomeningeal veins with potential extension of the inflammatory infiltrate into the substance of the brain (focal cerebritis). Phlebitis may also lead to venous occlusion and hemorrhagic infarction of the underlying brain.

Leptomeningeal fibrosis and consequent hydrocephalus may follow pyogenic meningitis, although if it is treated early, there may be little remaining evidence of the infection. In some infections, particularly in pneumococcal meningitis, large quantities of the capsular polysaccharide of the organism produce a particularly gelatinous exudate that encourages arachnoid fibrosis, chronic adhesive arachnoiditis.

**Acute Aseptic (Viral) Meningitis**

Aseptic meningitis is a misnomer, but it is a clinical term referring to the absence of recognizable organisms in an illness with meningeal irritation, fever, and alterations of consciousness of relatively acute onset. The disease is generally of viral, and rarely of bacterial or other etiology. The clinical course is less fulminant than that of pyogenic meningitis, and the CSF findings also differ between the two conditions. In aseptic meningitis, there is a lymphocytic pleocytosis, the protein elevation is only moderate, and the sugar content is nearly always normal. The viral aseptic meningitides are usually self-limiting and are treated symptomatically. In approximately 70% of cases, a pathogen can be identified, most commonly an enterovirus. Echovirus, coxsackievirus, and nonparalytic poliomyelitis are responsible for up to 80% of these cases.

A true noninfectious process has been associated with some classes of medications, including NSAIDs and antibiotics; this entity has been termed drug-induced aseptic meningitis. An aseptic meningitis-like picture may also develop subsequent to rupture of an epidermoid cyst into the subarachnoid space or the introduction of a chemical irritant ("chemical" meningitis). In these cases, the CSF is sterile, there is pleocytosis with neutrophils and a raised protein level, but the sugar content is usually normal.

**Morphology.**

There are no distinctive macroscopic characteristics except for brain swelling, seen in some instances. Pathologic material is limited, however, because recovery of patients is the rule. On microscopic examination, there is either no abnormality or a mild to moderate infiltration of the leptomeninges with lymphocytes.

**ACUTE FOCAL SUPPURATIVE INFECTIONS**

**Brain Abscess**

Brain abscesses may arise by direct implantation of organisms, local extension from adjacent foci (mastoiditis, paranasal sinusitis), or hematogenous spread (usually from a primary site in the heart, lungs, or distal bones or after tooth extraction). Predisposing conditions include acute bacterial endocarditis, which tends to produce multiple abscesses; cyanotic congenital heart disease, in which there is a right-to-left shunt and loss of pulmonary filtration of organisms; and chronic pulmonary sepsis, as can be seen with bronchiectasis. Streptococci and staphylococci are the most common offending organisms identified in nonimmunosuppressed populations.
Cerebral abscesses are destructive lesions, and patients almost invariably present clinically with progressive focal deficits in addition to the general signs of raised intracranial pressure. The CSF is under increased pressure; the white cell count and protein level are raised but the sugar content is normal. A systemic or local source of infection may be apparent, or a small systemic focus may have ceased to be symptomatic. The increased intracranial pressure and progressive herniation can be fatal, and abscess rupture can lead to ventriculitis, meningitis, and venous sinus thrombosis. With surgery and antibiotics, the otherwise high mortality rate can be reduced to less than 10%.

Morphology.

On macroscopic examination, abscesses are discrete lesions with central liquefactive necrosis, a surrounding fibrous capsule, and edema (Fig. 28-22). The most common brain regions that are affected, in descending order of frequency, are the frontal lobe, the parietal lobe, and the cerebellum. On microscopic examination, there is exuberant granulation tissue with neovascularization around the necrosis that is responsible for the marked vasogenic edema. The collagen of the capsule is produced by fibroblasts derived from the walls of blood vessels. Outside the fibrous capsule is a zone of reactive gliosis with numerous gemistocytic astrocytes.

![Figure 28-22](image)

**Figure 28-22** Frontal abscesses (arrows).

Subdural Empyema

Bacterial or occasionally fungal infection of the skull bones or air sinuses can spread to the subdural space and produce a subdural empyema. The underlying arachnoid and subarachnoid spaces are usually unaffected, but a large subdural empyema may produce a mass effect. Further, a thrombophlebitis may develop in the bridging veins that cross the subdural space, resulting in venous occlusion and infarction of the brain. With treatment, including surgical drainage, resolution of the empyema occurs from the dural side, and if it is complete, a thickened dura may be the only residual finding. Symptoms include those referable to the source of the infection. In addition, most patients are febrile, with headache and neck stiffness, and, if untreated, may develop focal neurologic signs, lethargy, and coma. The CSF profile is similar to that seen in brain abscesses, because both are parameningeal infectious processes. If diagnosis and treatment are prompt, complete recovery is usual.
Extradural Abscess

Extradural abscess, commonly associated with osteomyelitis, often arises from an adjacent focus of infection, such as sinusitis or a surgical procedure. When the process occurs in the spinal epidural space, it may cause spinal cord compression and constitute a neurosurgical emergency.

CHRONIC BACTERIAL MENINGOENCEPHALITIS

Tuberculosis

Patients with tuberculous meningitis usually have symptoms of headache, malaise, mental confusion, and vomiting. There is only a moderate CSF pleocytosis made up of mononuclear cells or a mixture of polymorphonuclear and mononuclear cells; the protein level is elevated, often strikingly so; and the glucose content typically is moderately reduced or normal.

Morphology.

On macroscopic examination, the subarachnoid space contains a gelatinous or fibrinous exudate, most often at the base of the brain, obliterating the cisterns and encasing cranial nerves. There may be discrete, white granules scattered over the leptomeninges. The most common pattern of involvement is a diffuse meningoencephalitis. On microscopic examination, there are mixtures of lymphocytes, plasma cells, and macrophages. Florid cases show well-formed granulomas, often with caseous necrosis and giant cells. Arteries running through the subarachnoid space may show obliteratorive endarteritis with inflammatory infiltrates in their walls and marked intimal thickening. Organisms can often be seen with acid-fast stains. The infectious process may spread to the choroid plexuses and ependymal surface, traveling through the CSF. In cases of long-standing duration, a dense, fibrous adhesive arachnoiditis may develop, most conspicuous around the base of the brain.

Another manifestation of the disease is the development of a single (or often multiple) well-circumscribed intraparenchymal mass (tuberculoma), which may be associated with meningitis. A tuberculoma may be up to several centimeters in diameter, causing significant mass effect. On microscopic examination, there is usually a central core of caseous necrosis surrounded by a typical tuberculous granulomatous reaction; calcification may occur in inactive lesions.

Clinical Features.

The most serious complications of chronic tuberculous meningitis are arachnoid fibrosis, which may produce hydrocephalus, and oblitterative endarteritis, which may produce arterial occlusion and infarction of underlying brain. Because the process involves the spinal cord subarachnoid space, spinal roots may also be affected.

Infection by *Mycobacterium tuberculosis* in patients with acquired immunodeficiency syndrome (AIDS) is often similar to that in non-AIDS patients, but there may be less host reaction. HIV-positive patients are also at risk for infection by *M. avium-intracellularare*, usually in the setting of disseminated infection. When this occurs, the lesions may consist of confluent sheets of macrophages filled with organisms, and minimal granulomatous reaction.
Neurosyphilis

Neurosyphilis is the tertiary stage of syphilis and occurs in only about 10% of patients with untreated infection. The major forms are meningovascular neurosyphilis, paretic neurosyphilis, and tabes dorsalis.

Patients with HIV infection are at increased risk for neurosyphilis, and the rate of progression and severity of the disease appear to be accelerated, presumably related to the impaired cell-mediated immunity. CNS involvement by *T. pallidum* in this setting may be manifested as asymptomatic infection, acute syphilitic meningitis, meningovascular syphilis, and, rarely, direct parenchymal invasion of the brain.

Morphology.

**Meningovascular neurosyphilis** is a chronic meningitis involving the base of the brain and, variably, also the cerebral convexities and the spinal leptomeninges. In addition, there may be an associated oblitative endarteritis (Heubner arteritis) accompanied by a distinctive perivascular inflammatory reaction rich in plasma cells and lymphocytes. Cerebral gummas (plasma cell-rich mass lesions) may also occur in relation to meninges and extending into the cerebral hemispheres, diencephalon, or spinal cord.

**Paretic neurosyphilis** is caused by invasion of the brain by *Treponema pallidum* and is clinically manifested as insidious but progressive loss of mental and physical functions with mood alterations (including delusions of grandeur), terminating in severe dementia (*general paresis of the insane*). On microscopic examination, inflammatory lesions are associated with parenchymal damage in the cerebral cortex (particularly the frontal lobe but also affecting other areas of the isocortex) characterized by loss of neurons with proliferations of microglia (rod cells), gliosis, and iron deposits demonstrable with the Prussian blue stain (perivascularly and in the neuropil, presumably from damage to the microcirculation). The spirochetes can be, at times, demonstrated in tissue sections. There is often an associated hydrocephalus with damage to the ependymal lining and proliferation of subependymal glia, called *granular ependymitis*.

**Tabes dorsalis** is the result of damage by the spirochete to the sensory nerves in the dorsal roots, which produces impaired joint position sense and resultant ataxia (locomotor ataxia); loss of pain sensation, leading to skin and joint damage (Charcot joints); other sensory disturbances, particularly the characteristic "lightning pains"; and absence of deep tendon reflexes. On microscopic examination, there is loss of both axons and myelin in the dorsal roots, with pallor and atrophy in the dorsal columns of the spinal cord. Organisms are not demonstrable in the cord lesions.

Although these three forms of expression of neurosyphilis have been described separately, patients often show incomplete or mixed pictures, notably the combination of tabes dorsalis and general paresis (taboparesis).

Neuroborreliosis (Lyme Disease)
Lyme disease is caused by the spirochete *Borrelia burgdorferi*, transmitted by various species of *Ixodes* tick; involvement of the nervous system is referred to as neuroborreliosis. Neurologic symptoms are highly variable and include aseptic meningitis, facial nerve palsies, mild encephalopathy, and polyneuropathies. The rare cases that have come to autopsy have shown a focal proliferation of microglial cells in the brain as well as scattered organisms (identified by Dieterle stain) in the extracellular spaces. Other findings include granulomas and vasculitis.

**VIRAL MENINGOENCEPHALITIS**

*Viral encephalitis* is a parenchymal infection of the brain almost invariably associated with meningeal inflammation (*meningoencephalitis*) and sometimes with simultaneous involvement of the spinal cord (*encephalomyelitis*). The most characteristic histologic features of viral encephalitis are perivascular and parenchymal mononuclear cell infiltrates (lymphocytes, plasma cells, and macrophages), glial cell reactions (including the formation of microglial nodules), and neuronophagia (Fig. 28-23). Direct indications of viral infection are the presence of viral inclusion bodies and, most important, the identification of viral pathogens by ultrastructural, immunocytochemical, and molecular methods.

![Figure 28-23](image)

Characteristic findings of viral meningitis include perivascular cuffs of lymphocytes (*A*) and microglial nodules (*B*).

The phenomenon of nervous system *tropism* that characterizes some viral encephalitides is particularly noteworthy; there are pathogenic viruses that infect specific cell types (such as oligodendrocytes), while others preferentially involve particular areas of the brain (such as medial temporal lobes or the limbic system). The capacity of some viruses for *latency* is especially important in neurologic disease (see the discussion of herpes zoster later in this chapter). Systemic viral infections in the absence of direct evidence of viral penetration into the CNS may be followed by an *immune-mediated disease*, such as perivenous demyelination (see later, acute disseminated encephalomyelitis). Intrauterine viral infection may cause *congenital malformations*, as occurs with rubella. A slowly progressive degenerative disease syndrome may follow many years after a viral
illness; an example is postencephalitic parkinsonism after the viral influenza epidemic that occurred during and after the First World War. 

Arthropod-Borne Viral Encephalitis

Arboviruses are an important cause of epidemic encephalitis, especially in tropical regions of the world, and they are capable of causing serious morbidity and high mortality. In the Western hemisphere, the most important types are Eastern and Western equine, Venezuelan, St. Louis, and La Crosse; elsewhere in the world, pathogenic arboviruses include Japanese B (Far East), Murray Valley (Australia and New Guinea), and tick-borne (Russia and Eastern Europe). In the United States, West Nile virus has recently emerged as a pathogen, with associated public health concerns. All have animal hosts and mosquito vectors, except for the tick-borne type. Clinically, affected patients develop generalized neurologic deficits, such as seizures, confusion, delirium, and stupor or coma, and often focal signs, such as reflex asymmetry and ocular palsies. The CSF is usually colorless but with a slightly elevated pressure and, initially, a neutrophilic pleocytosis that rapidly converts to lymphocytes; the protein level is elevated, but sugar content is normal.

Morphology.

The encephalitides caused by various arboviruses differ in epidemiology and prognosis, but the histopathologic picture is similar among them, except for variations in the severity and extent of the lesions within the CNS. Characteristically, there is a lymphocytic meningoencephalitis (sometimes with neutrophils) with a tendency for inflammatory cells to accumulate perivascularly. Multiple foci of necrosis of gray and white matter are found; in particular, there is evidence of single-cell neuronal necrosis with phagocytosis of the debris (neuronophagia). Viral antigens can be detected in neurons by immunoperoxidase staining. In severe cases, there may be a necrotizing vasculitis with associated focal hemorrhages. Some cases have predominantly cortical involvement, whereas in others, the basal ganglia bear the brunt of the disease, as can be demonstrated with neuroradiographic studies.

Herpes Simplex Virus Type 1 (HSV-1)

HSV-1 produces an encephalitis that occurs in any age group but is most common in children and young adults. Only about 10% of the patients have a history of prior herpes. The most commonly observed clinical presenting symptoms in herpes encephalitis are alterations in mood, memory, and behavior. PCR-based methods for virus detection in CSF samples have increased the ease of diagnosis and the recognition of a subset of patients with less severe disease.

Antiviral agents now provide effective treatment in many cases, with a significant reduction in the mortality rate. In some individuals, HSV-1 encephalitis follows a subacute course with clinical manifestations (weakness, lethargy, ataxia, seizures) that evolve during a more protracted period (4 to 6 weeks).

Morphology.
This encephalitis starts in, and most severely involves, the inferior and medial regions of the temporal lobes and the orbital gyri of the frontal lobes (Fig. 28-24). The infection is necrotizing and often hemorrhagic in the most severely affected regions. Perivascular inflammatory infiltrates are usually present, and Cowdry type A intranuclear viral inclusion bodies may be found in both neurons and glia. In patients with slowly evolving HSV-1 encephalitis, there is more diffuse involvement of the brain.

**Figure 28-24**  
A, Herpes encephalitis showing extensive destruction of inferior frontal and anterior temporal lobes. B, Necrotizing inflammatory process characterizes the acute herpes encephalitis.  
(Courtesy of Dr. T.W. Smith, University of Massachusetts Medical School, Worcester, MA.)

**Herpes Simplex Virus Type 2 (HSV-2)**

HSV-2 also infects the nervous system and usually manifests in adults as a meningitis. A generalized and usually severe encephalitis develops in as many as 50% of neonates born by vaginal delivery to women with active primary HSV genital infections. The dependence on route of delivery indicates that the infection is acquired during passage through the birth canal rather than transplacentally. HSV-1 causes a similar encephalitis in neonates. In AIDS patients, HSV-2 may cause an acute, hemorrhagic, necrotizing encephalitis.

**Varicella-Zoster Virus (Herpes Zoster)**

Primary varicella infection presents as one of the childhood exanthems (chickenpox), ordinarily without any evidence of neurologic involvement. Reactivation in adults (commonly called "shingles") usually manifests as a painful, vesicular skin eruption in a single or limited dermatomal distribution.

Herpes zoster reactivation is usually a self-limited process, but there may be a persistent postherpetic neuralgia syndrome in up to 10% of patients. Overt CNS involvement with herpes zoster is much rarer but can be more severe. Herpes zoster has been associated with a
granulomatous arteritis; immunocytochemical and electron microscopic evidence of viral involvement has been obtained in a few of these cases. In immunosuppressed patients, herpes zoster may cause an acute encephalitis with numerous sharply circumscribed lesions characterized by demyelination followed by necrosis. Inclusion bodies can be found in glia and neurons. Varicella-zoster virus infection accounts for about 12% of all systemic herpesvirus infections in patients with AIDS.

Cytomegalovirus

This infection of the nervous system occurs in fetuses and immunosuppressed individuals. The outcome of infection in utero is periventricular necrosis that produces severe brain destruction followed later by microcephaly with periventricular calcification. Cytomegalovirus (CMV) is the most common opportunistic viral pathogen in patients with AIDS, affecting the CNS in 15% to 20% of cases.

Morphology.

In the immunosuppressed individual, the most common pattern of involvement is that of a subacute encephalitis, which may be associated with CMV inclusion-bearing cells (see Fig. 8-13). Although any type of cell within the CNS (neurons, glia, ependyma, endothelium) can be infected by CMV, there is a tendency for the virus to localize in the paraventricular subependymal regions of the brain. This results in a severe hemorrhagic necrotizing ventriculoencephalitis and a choroid plexitis. The virus can also attack the lower spinal cord and roots, producing a painful radiculoneuritis. Prominent cytomegalic cells with intranuclear and intracytoplasmic inclusions can be readily identified by conventional light microscopy, immunocytochemistry, and in situ hybridization. These latter two techniques have also shown that normal-appearing, noncytomegalic cells at the edges of the lesions may contain virus.

Poliomyelitis

Poliovirus is a member of the picorna group of enteroviruses. While paralytic poliomyelitis has been effectively eradicated by vaccination in many parts of the world, there are still many regions where it remains a problem. In nonimmunized individuals, poliovirus infection causes a subclinical or mild gastroenteritis. In a small fraction of the vulnerable population, however, it secondarily invades the nervous system.

Morphology.

Acute cases show mononuclear cell perivascular cuffs and neuronophagia of the anterior horn motor neurons of the spinal cord. In situ reverse transcriptase-polymerase chain reaction has shown poliovirus RNA in anterior horn cell motor neurons. The inflammatory reaction is usually confined to the anterior horns but may extend into the posterior horns, and the damage is occasionally severe enough to produce cavitation. The motor cranial nuclei are sometimes involved. Postmortem examination in long-term survivors of symptomatic poliomyelitis shows loss of neurons and long-standing gliosis in the affected anterior horns of the spinal cord, some residual
inflammation, atrophy of the anterior (motor) spinal roots, and neurogenic atrophy of denervated muscle. 

Clinical Features.

CNS infection manifests initially with meningeal irritation and a CSF picture of aseptic meningitis. The disease may progress no further or advance to involve the spinal cord. When the disease affects the spinal cord with loss of motor neurons, it produces a flaccid paralysis with muscle wasting and hyporeflexia in the corresponding region of the body—the permanent neurologic residue of poliomyelitis. In the acute disease, death can occur from paralysis of the respiratory muscles, and a myocarditis sometimes complicates the clinical course. Permanent cranial nerve (bulbar) weakness is rare, as is any evidence of encephalitis, but severe respiratory compromise is an important cause of long-term morbidity.

A late neurologic syndrome can develop in patients affected by poliomyelitis who had been stable during intervening years (postpolio syndrome). This syndrome, which typically develops 25 to 35 years after the resolution of the initial illness, is characterized by progressive weakness associated with decreased muscle mass and pain, and has an unclear pathogenesis.

Rabies

Rabies is a severe encephalitis transmitted to humans by the bite of a rabid animal, a dog or various wild animals that form natural reservoirs. Exposure to bats, even without a known bite, has also been identified as a risk factor for developing infection, although transmission appears to be limited to certain bat species.

Morphology.

On macroscopic examination, the brain shows intense edema and vascular congestion. On microscopic examination, there is widespread neuronal degeneration and an inflammatory reaction that is most severe in the rhombencephalon (midbrain, and floor of the fourth ventricle, particularly in the medulla). The basal ganglia, spinal cord, and dorsal root ganglia may also be involved. Negri bodies, the pathognomonic microscopic finding, are cytoplasmic, round to oval, eosinophilic inclusions that can be found in pyramidal neurons of the hippocampus and Purkinje cells of the cerebellum, sites usually devoid of inflammation (Fig. 28-25). The presence of rabies virus can be detected within Negri bodies by ultrastructural and immunohistochemical examination.
Clinical Features.

Since the virus enters the CNS by ascending along the peripheral nerves from the wound site, the incubation period (commonly between 1 and 3 months) depends on the distance between the wound and the brain. The disease manifests initially with nonspecific symptoms of malaise, headache, and fever, but the conjunction of these symptoms with local paresthesias around the wound is diagnostic. As the infection advances, the patient exhibits extraordinary CNS excitability; the slightest touch is painful, with violent motor responses progressing to convulsions. Contracture of the pharyngeal musculature on swallowing produces foaming at the mouth, which may create an aversion to swallowing even water (hydrophobia). There is meningismus and, as the disease progresses, flaccid paralysis. Periods of alternating mania and stupor progress to coma and death from respiratory center failure.

Human Immunodeficiency Virus

As many as 60% of patients with AIDS develop neurologic dysfunction during the course of their illness; in some, it dominates the clinical picture until death. (See Chapter 6 for a discussion of the epidemiology and pathogenesis of AIDS.) In the first 15 years or so after recognition of the disease, neuropathologic changes were demonstrated at postmortem examination in as many as 80% to 90% of cases. In recent years, with the introduction of highly active antiretroviral therapy, these figures have dropped dramatically. The changes described include direct or indirect effects of HIV, opportunistic infection, and primary CNS lymphoma (Chapter 14).

HIV aseptic meningitis occurs within 1 to 2 weeks of seroconversion in about 10% of patients; antibodies to HIV can be demonstrated, and the virus can be isolated from the CSF. The few neuropathologic studies of the early and acute phases of symptomatic or asymptomatic HIV invasion of the nervous system have shown a mild lymphocytic meningitis, perivascular inflammation, and some myelin loss in the hemispheres.
HIV Meningoencephalitis (Subacute Encephalitis)

Patients affected with this remarkable neurologic disorder can manifest clinically with dementia referred to as AIDS-dementia complex (ADC). The dementia begins insidiously, with mental slowing, memory loss, and mood disturbances, such as apathy and depression. Motor abnormalities, ataxia, bladder and bowel incontinence, and seizures can also be present. Radiologic imaging of the brain may be normal or may show some diffuse cortical atrophy, focal abnormalities of the cerebral white matter, and ventricular dilation.

Morphology.

The brains of individuals with HIV encephalitis with or without dementia show comparable findings. On macroscopic examination, the meninges are clear, and there is some ventricular dilation with sulcal widening but normal cortical thickness. The process is best characterized microscopically as a chronic inflammatory reaction with widely distributed infiltrates of microglial nodules, sometimes with associated foci of tissue necrosis and reactive gliosis (Fig. 28-26). The microglial nodules are also found in the vicinity of small blood vessels, which show abnormally prominent endothelial cells and perivascular foamy or pigment-laden macrophages. These changes occur especially in the subcortical white matter, diencephalon, and brainstem. An important component of the microglial nodule is the macrophage-derived multinucleated giant cell. In some cases, there is also a disorder of white matter characterized by multifocal or diffuse areas of myelin pallor with associated axonal swellings and gliosis.

Figure 28-26  HIV encephalitis. Note the microglial nodule and multinucleated giant cells.

HIV can be detected in CD4-positive mononuclear and multinucleated macrophages and microglia by immunoperoxidase and molecular methods. HIV infection has been reported in retinal and cerebral endothelial cells and astrocytes in some studies. It appears likely that neurons and oligodendrocytes are not directly infected by HIV, and damage to these cells occurs indirectly through the release of toxic cytokines and alterations of the blood-brain barrier. The pathogenesis of the dementing illness has not been fully elucidated (see the discussion in Chapter 6).
**Vacuolar Myelopathy**

This disorder of the spinal cord is found in 20% to 30% of patients with AIDS in the United States, less often in Europe. The histopathologic findings resemble those of subacute combined degeneration, though serum levels of vitamin B₁₂ are normal. The pathogenesis of the lesions is unknown; it does not appear to be caused directly by HIV, and virus is not present within the lesions.

Of related interest is the condition known as *tropical spastic paraparesis* or HTLV-1-associated myelopathy (HAM), which occurs in several countries in the Caribbean, along the Indian Ocean, in Japan, and in South America. Some cases show a severe lymphocytic meningomyelitis unlike that seen in vacuolar myelopathy. Virologic studies and polymerase chain reaction data have implicated another retrovirus: human T-cell lymphotrophic virus 1 (HTLV-1).

**AIDS-Associated Myopathy and Peripheral Neuropathy**

Inflammatory myopathy has been the most often described skeletal muscle disorder in patients with HIV infection. The disease is characterized by the subacute onset of proximal weakness, sometimes pain, and elevated levels of serum creatine kinase. The histologic findings include muscle fiber necrosis and phagocytosis, interstitial infiltration with HIV-positive macrophages, and, in a few cases, cytoplasmic bodies and nemaline rods. An acute, toxic, reversible myopathy with “ragged red” fibers and myoglobulinuria may also develop in patients treated with zidovudine (AZT).

The most commonly reported clinical syndromes of peripheral neuropathy include acute and chronic inflammatory demyelinating polyneuropathy, distal symmetric polyneuropathy, polyradiculopathy, mononeuritis multiplex, and, rarely, sensory neuropathy due to ganglioneuritis. The histopathologic findings that are observed in most of these cases include segmental demyelination, axonal degeneration, and epineurial and endoneurial mononuclear cell inflammation.

**AIDS in Children**

Neurologic disease was common in children with congenital AIDS, occurring in 15% to 30% of infants born to seropositive mothers; the incidence of the disease has decreased dramatically with the introduction of multidrug antiretroviral therapy. Clinical manifestations of neurologic dysfunction are evident by the first years of life and include microcephaly with mental retardation and motor developmental delay with spasticity of limbs. The most frequent morphologic abnormality is calcification of the large and small vessels and parenchyma within the basal ganglia and deep cerebral white matter. There is also loss of hemispheric myelin or delay in myelination; multinucleated giant cells and microglial nodules are also observed in many cases. HIV is present in brain tissue. Opportunistic infections of the CNS, including toxoplasmosis, CMV infection, progressive multifocal leukoencephalopathy, and cryptococcal meningitis, are relatively rare in infants and children with AIDS compared with adults.

**Progressive Multifocal Leukoencephalopathy**
Progressive multifocal leukoencephalopathy (PML) is a viral encephalitis caused by the JC polyomavirus; because the virus preferentially infects oligodendrocytes, demyelination is its principal pathologic effect. The disease occurs almost invariably in immunosuppressed individuals in various clinical settings, including chronic lymphoproliferative or myeloproliferative illnesses, immunosuppressive chemotherapy, granulomatous diseases, and AIDS. Although the incidence of PML appears to be decreasing in HIV-infected individuals with the advent of newer antiretroviral therapies, there may be direct interaction between HIV and JC viruses within cells.

No clinical disease has been associated with primary infection by the JC virus, but about 65% of normal people have serologic evidence of exposure to the virus by the age of 14 years. It is thought that PML results from the reactivation of virus as a result of immunosuppression. Clinically, patients develop focal and relentlessly progressive neurologic symptoms and signs, and both computed tomography (CT) and magnetic resonance imaging (MRI) scans show extensive, often multifocal lesions in the hemispheric or cerebellar white matter.

Morphology.

The lesions consist of patches of irregular, ill-defined destruction of the white matter ranging in size from millimeters to extensive involvement of an entire lobe of the brain (Fig. 28-27). The cerebrum, the brainstem, the cerebellum, and occasionally the spinal cord can be involved. On microscopic examination, the typical lesion consists of a patch of demyelination, most often in a subcortical location, in the center of which are scattered lipid-laden macrophages and a reduced number of axons. At the edge of the lesion are greatly enlarged oligodendrocyte nuclei whose chromatin is replaced by glassy amphophilic viral inclusion. These oligodendrocytes can be shown to contain viral antigens by immunohistochemistry (Fig. 28-27), viral genome by in situ hybridization, and viral nucleocapsids by electron microscopy. Within the lesions, there may be bizarre giant astrocytes with irregular, hyperchromatic, sometimes multiple nuclei. Reactive fibrillary astrocytes are scattered among the bizarre forms.
**Figure 28-27**  Progressive multifocal leukoencephalopathy.  

*A*, Section stained for myelin showing irregular, poorly defined areas of demyelination, which become confluent in places.  

*B*, Enlarged oligodendrocyte nuclei stained for viral antigens surround an area of early myelin loss.

**Subacute Sclerosing Panencephalitis**

Subacute sclerosing panencephalitis (SSPE) is a rare progressive clinical syndrome characterized by cognitive decline, spasticity of limbs, and seizures. It occurs in children or young adults, months or years after an initial, early-age acute infection with measles. This disease is thought to represent persistent, but nonproductive, infection of the CNS by an altered measles virus; changes in several viral genes have been associated with the disease. On microscopic examination, there are
widespread gliosis and myelin degeneration; viral inclusions, largely within the nuclei, of oligodendrocytes and neurons; variable inflammation of white and gray matter; and neurofibrillary tangles. [102] Ultrastructural study shows that the inclusions contain nucleocapsids characteristic of measles, and immunohistochemistry for measles virus antigen is positive. With widespread measles vaccination programs, the disease seems to have largely disappeared. However, there are still cases being reported around the world.

**FUNGAL MENINGOENCEPHALITIS**

As with the systemic deep mycoses, in industrialized nations, fungal disease of the CNS is encountered primarily in immunocompromised patients. The brain is usually involved only late in the disease, when there is widespread hematogenous dissemination of the fungus, most often *Candida albicans*, *Mucor*, *Aspergillus fumigatus*, and *Cryptococcus neoformans*. In endemic areas, pathogens such as *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis* may involve the CNS after a primary pulmonary or cutaneous infection; again, this often follows immunosuppression. [102]

There are three main patterns of fungal infection in the CNS: chronic meningitis, vasculitis, and parenchymal invasion. Vasculitis is most frequently seen with *Mucor* and *Aspergillus*, both of which have a marked predilection for invasion of blood vessel walls, but it occasionally occurs with other organisms, such as *Candida*. The resultant vascular thrombosis produces infarction that is often strikingly hemorrhagic and that subsequently becomes septic from ingrowth of the causative fungus.

Parenchymal invasion, usually in the form of granulomas or abscesses, can occur with most of the fungi and often coexists with meningoitis. The most commonly encountered fungi invading the brain are *Candida* and *Cryptococcus*. *Candida* usually produces multiple microabscesses, with or without granuloma formation. Although most fungi invade the brain by hematogenous dissemination, direct extension may also occur, particularly with *Mucor*, most commonly in diabetics with ketoacidosis.

*Cryptococcal meningitis*, observed now with increasing frequency in association with AIDS, may be fulminant and fatal in as little as 2 weeks or indolent, evolving over months or years. The CSF may have few cells but a high concentration of protein. The mucoid encapsulated yeasts can be visualized in the CSF by India ink preparations and in tissue sections by PAS and mucicarmine as well as silver stains.

**Morphology.**

With cryptococcal infection, the brain shows a chronic meningoitis affecting the basal leptomeninges, which are opaque and thickened by reactive connective tissue and may obstruct the outflow of CSF from the foramina of Luschka and Magendie, giving rise to hydrocephalus. Sections of the brain disclose a gelatinous material within the subarachnoid space and small cysts within the parenchyma ("soap bubbles"), which are especially prominent in the basal ganglia in the distribution of the lenticulostriate arteries (Fig. 28-28A). Parenchymal lesions consist of aggregates of organisms within expanded perivascular (Virchow-Robin) spaces associated with
minimal or absent inflammation or gliosis (Fig. 28-28A). The meningeal infiltrates consist of chronic inflammatory cells and fibroblasts admixed with cryptococci. Well-formed granulomas are not seen ordinarily; in some cases, however, there is a marked chronic inflammatory and granulomatous reaction similar to that seen with *M. tuberculosis*.

**Figure 28-28** Cryptococcal infection. *A*, Whole brain section showing the numerous areas of tissue destruction associated with the spread of organisms in the perivascular spaces. *B*, At higher magnification, it is possible to see the cryptococci in the lesions.

**OTHER INFECTIOUS DISEASES OF THE NERVOUS SYSTEM**

Protozoal diseases (including malaria, toxoplasmosis, amebiasis, and trypanosomiasis), rickettsial infections (such as typhus and Rocky Mountain spotted fever), and metazoal diseases (especially cysticercosis and echinococcosis) may also involve the CNS and are discussed in Chapter 8.

*Cerebral toxoplasmosis* has assumed greater importance with the AIDS epidemic. Infection of the brain by *Toxoplasma gondii* is one of the most common causes of neurologic symptoms and morbidity in patients with AIDS. The average incidence of CNS infection in most clinical and autopsy series ranges from 4% to 30%. The clinical symptoms are subacute, evolving during a 1- or 2-week period, and may be both focal and diffuse. CT and MRI studies may show multiple ring-enhancing lesions; however, this radiographic appearance is not pathognomonic, since similar findings may be associated with CNS lymphoma, tuberculosis, and fungal infections.

Like CMV encephalitis, toxoplasmosis may also occur in the fetus. Primary maternal infection with toxoplasmosis, particularly if it occurs early in the pregnancy, may be followed by a cerebritis in the fetus, with the production of multifocal cerebral necrotizing lesions that may calcify, producing severe damage to the developing brain.
A rapidly fatal necrotizing encephalitis occurs with infection with *Naegleria* species, and a chronic granulomatous meningoencephalitis has been associated with infection with *Acanthamoeba*.[1] The amoebae may sometimes be difficult to distinguish from histiocytes (Fig. 28-30). Methenamine silver or PAS stains are helpful in visualizing the organisms, although definitive identification ultimately depends on combined immunofluorescence studies, morphology, culture, and molecular methods.

**Figure 28-30** Necrotizing amoebic meningoencephalitis involving the cerebellum (*organism highlighted by arrow*).

**Morphology.**

In toxoplasmosis of the CNS, the brain shows abscesses, frequently multiple, most involving the cerebral cortex (near the gray-white junction) and deep gray nuclei, less often the cerebellum and brainstem, and rarely the spinal cord (Fig. 28-29A). Acute lesions consist of central foci of necrosis with variable petechiae surrounded by acute and chronic inflammation, macrophage infiltration, and vascular proliferation. Both free tachyzoites (Fig. 28-29B) and encysted bradyzoites (Fig. 28-29C) may be found at the periphery of the necrotic foci. The organisms are usually seen on routine H & E or Giemsa stains, but they can be more easily recognized by immunocytochemical methods. The blood vessels in the vicinity of these lesions may show marked intimal proliferation or even frank vasculitis with fibrinoid necrosis and thrombosis. After treatment, the lesions consist of large, well-demarcated areas of coagulation necrosis surrounded by lipid-laden macrophages. Cysts and free tachyzoites can also be found adjacent to these lesions but may be considerably reduced in number or absent if therapy has been effective. Chronic lesions consist of small cystic spaces containing small numbers of lipid- and hemosiderin-laden macrophages with surrounding gliosis. Organisms are difficult to detect in these older lesions.
Figure 28-29  A, *Toxoplasma* abscesses in the putamen and thalamus. B, Free tachyzoites demonstrated by immunostaining. C, *Toxoplasma* pseudocyst with bradyzoites highlighted by immunostaining.