Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Neuronal vacuolar degeneration of Angora goats

A scrapie-like neuronopathy is described in young Angora goats in Australia (where scrapie is not present), and is presumed to be genetically determined. Animals become ataxic at about 3 months of age, and progress to severe paresis. No significant gross lesions are present, but there is spectacular vacuolation of large neurons in the red nucleus and other brainstem nuclei, and in the spinal motor neurons. Some Wallerian changes are present in the brain stem, spinal cord and peripheral nerves.

Focal spongiform encephalopathy of dogs

A disease was originally described in **Bull Mastiffs** as familial cerebellar ataxia with hydrocephalus, but the main pathologic feature is spongy vacuolation of several gray matter nuclei. Clinical signs emerge between 6 and 9 weeks of age, and include ataxia and visual impairment, and a number of other variable deficits. An autosomal recessive genetic defect has been proposed.

Macroscopically, there is moderate to severe dilation of the ventricular system. Microscopically, bilaterally symmetrical spongy vacuolation and gliosis are evident in all three deep cerebellar nuclei, the posterior colliculi and, to a lesser extent, the lateral vestibular nuclei. The vacuolation is accompanied by axonal spheroids, but nerve cell bodies appear normal. Some of the vacuoles appear to involve myelin sheaths, but the lesions are essentially confined to the gray matter, and the cytologic basis of the vacuolation is not precisely defined.

Similar vacuolating lesions of these gray matter areas have been described in **Saluki** dogs.

Spongiform encephalopathy of unknown etiology and characterized histologically by neuronal vacuolation is recognized in **Rottweiler** dogs. The condition usually starts at 8 weeks of age and is characterized clinically by progressive laryngeal paralysis, tetraparesis, and cerebellar ataxia. Vacuolated neurons are prevalent in the cerebellar roof nuclei, nuclei of the extrapyramidal system, dorsal nerve root ganglia, myenteric plexus, and other ganglia of the autonomic nervous system.

A hereditary polioencephalomyelopathy of **Australian Cattle Dogs** is characterized histologically by neuronal, neuropilar, and astrocytic vacuolation, particularly in the ventral horn of the spinal cord, cerebellar, and brain stem nuclei. An autosomal recessive trait affecting the astrocytic mitochondria is suspected.

Alaskan Husky dogs can develop a hereditary familial encephalopathy (*Alaskan Husky encephalopathy*) similar to Leigh syndrome in humans and to the multifocal symmetrical myelinolytic encephalopathy of Simmental calves described above. Clinical signs usually start before 1 year of age and include seizures, ataxia, blindness, and behavioral abnormalities. Lesions are more prevalent in the basal nuclei, thalamus, midbrain, pons, and medulla oblongata, and include bilateral symmetrical malacia, status spongiosus, gemistocytic astrocytosis with marked intracytoplasmic vacuolation, gliosis, vascular hyperplasia, and mild infiltration of mixed inflammatory cells, with relative neuronal sparing. Similar but milder lesions occur in the cerebellar ventral vermis and the base of cerebral sulci. Neuronal sparing and marked astrocytic vacuolation suggests a role for astrocytes in the pathogenesis of this condition.

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INFLAMMATION IN THE CENTRAL NERVOUS SYSTEM

Brain and infection

Organs defend against invading infectious organisms either by innate or adaptive immunity. Innate immunity is composed of resident components, e.g., pulmonary alveolar macrophages, or recruited components, e.g., neutrophils. Unlike parenchymatous organs, the brain depends solely on resident innate immunity to recognize and clear pathogens. In other words, under normal nondisease conditions, the brain does not rely either on adaptive immunity or the recruited components of innate immunity for defense. Innate immunity in the brain is diverse and composed of structural units, e.g., blood–brain barrier (BBB), plus cellular and chemical components.

The structural units that separate vulnerable brain cells from the blood stream are the **blood–brain barrier (BBB)** and the **blood–cerebrospinal fluid barrier (BCSFB)**, which is present at the choroid plexuses. The BBB is made up of endothelial cells lining the blood capillaries, pericytes embedded in the capillary basement membranes, and the foot processes of astrocytes. The endothelial cells of the BBB differ from other body endothelial cells, first by having significantly fewer endocytotic vesicles, thereby limiting the amount of transcellular flux, and second, they are connected by both *adherens junction* (e.g., cadherin) and *tight junction proteins*; the latter significantly reduce paracellular flux. Also, BBB endothelial cells are rich in several transport systems that selectively transport essential nutrients to the brain or harmful material back into the blood (efflux transport proteins). One of the most important efflux proteins is *P-glycoprotein*. Inhibition of P-glycoprotein increases the tissue invasiveness of *Listeria monocytogenes*. In addition to these protective properties of the BBB, the CSF side of the BCSFB is also rich in tight junctions, which restricts movement to the CSF. *The ability of organisms to breach these barriers determines their neurotropism*. Neurotropic viruses and bacteria have developed several strategies to breach or to cross these barriers. For example, several neurotropic viruses bypass the BBB and invade the brain via axons (e.g., *Rabies virus*); intracellular bacteria (e.g., *Mycobacterium bovis*) invade the brain as Trojan horses, hidden in infected leukocytes; and finally some bacteria have a direct cytotoxic effect on the endothelial cells of the BBB (e.g., *Histophilus somni*).

The cellular part of the brain's innate immunity is composed of perivascular **dendritic cells, microglia**, and **astrocytes**. These cells

are rich in *pattern recognition receptors*, which bind directly and nonspecifically to *pathogen-associated molecular patterns*. For example, all three cell types are rich in *macrophage mannose receptor*, which is a lectin receptor that recognizes "nonself" sugars on the cell wall of gram-negative and gram-positive bacteria, parasites, and yeasts. Microglia cells also express several *tool-like receptors*, e.g., TLR 2 and 6, which have a major role as bridges between innate and adaptive immunity. Activated microglia express several receptors important for phagocytosis, e.g., CR3 and CR4; recognition of pathogens is followed by phagocytosis, largely by microglial cells and to a lesser extent by astrocytes. Finally, glial cells release several *cytokines* and *antimicrobial peptides*, for example, interleukin-1β, tumor necrosis factor-α, and the antimicrobial peptide *cathelicidin*. Inflammation of the brain starts once an infectious agent overcomes the resident innate immunity and recruiting begins of different components of adaptive immunity (leukocytes and humoral immunity), which are more specific and more effective but also more destructive.

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Inflammation in the central nervous system

Inflammation of the brain is **encephalitis**, of the spinal cord **myelitis**, of the ependyma **ependymitis**, of the choroid plexus **choroiditis**, and of the meninges **meningitis**, qualified as **leptomeningitis** when it involves the pia-arachnoid and as **pachymeningitis** when it involves the dura. This is the area of neuropathology that is of most veterinary importance because it embraces many of the transmissible highly fatal infections of animals, because even the sporadic infections are common, and because there is always a pressing need for the pathologist to separate the inflammations into general or specific etiological categories. Most of the specific infectious diseases to be described in this chapter are caused by agents that demonstrate a remarkable or specific neurotropism. These are, however, only a segment of the list of agents that commonly, occasionally, or rarely involve the CNS (Table 3.1); neurologic lesions are also discussed with systemic infections elsewhere in these volumes.

Inflammatory processes in the CNS are basically the same as those in other tissues, but they derive some specific features from the special responsiveness and anatomic arrangements of the CNS. It is important to recognize the criteria of inflammation in the CNS and then to presume from that, as far as is possible, the nature of the infecting organisms because opportunities to intervene clinically are brief and the time frame for clinical intervention is less than required for definitive microbiological diagnosis.

The problem is not only one of why and how the CNS, of known high vulnerability to infection, is so frequently spared in systemic diseases; it is also one of why and how it is infected hematogenously. There is presently no better knowledge of why four out of five cases of Glasser's disease will have meningitis than why one of five will not, even though in the one case the pathologic syndrome is otherwise fully developed.

Infections that, in other organs or tissues, may be inconsequential and even asymptomatic frequently cause death or permanent disability when they involve the nervous system. There are several contributing factors, the most important of which is the *indispensability of most portions of the CNS*. The nervous tissue cannot reconstitute itself, but it may, if the lesion develops slowly, manage a considerable degree of functional compensation. Vascular responses may be more of an impediment than a help in the reaction to inflammation, because they lead consistently to edema and brain swelling that spreads the consequences of the inflammation far from the active focus. Vascular proliferation and fibrous tissue encapsulation may develop only when the inflammatory reaction involves the meninges and the larger blood vessels because these are the only source of reticulin and collagenous tissue. Investigation continues into how viruses spread in nervous tissue; bacteria and fungi can spread rapidly and extensively in the fluid of the ventricular system and meninges. Spread of infection from the ventricular fluid to the periventricular veins occurs readily across the ependyma, and spread from the meninges to the brain, or vice versa, can occur via the Virchow–Robin spaces. The special drainage of CSF is such that exudate rich in fibrin and cells is drained very poorly.

The structure of nervous tissue and meninges limits the anatomical types of inflammation that may occur. **Fibrinous inflammation** is confined to the meninges and larger perivascular spaces. Fibrin is usually indicative of a bacterial infection, but there are exceptions. Fibrinopurulent, largely fibrinous, exudate is caused by the mycoplasmas; fibrinous exudation is typical of the meningeal reaction in malignant catarrhal fever of cattle, and it is occasionally observed in organomercurial poisoning of swine and cattle. **Hemorrhagic inflammation** is not common except as examples of symptomatic purpura in infections such as porcine erysipelas and infectious canine hepatitis and in the infarcts of embolic infections. Hemorrhage is characteristic of helminthic infections, but these lesions are perhaps better regarded as traumatic malacias. **Suppurative or granulomatous inflammation** is the usual response to bacterial or mycotic infections. Viral infections are characterized by **nonsuppurative inflammation**, which is described in more detail later; it is typically composed of neuronal degeneration, perivascular cuffing by mononuclear cells, and focal or diffuse glial proliferations.

Applying these broad criteria, there is seldom much difficulty in deciding on the class of the infecting agent. *There is occasionally some difficulty in distinguishing between the reactions to degeneration and to viral infections*. While suppuration does not occur in either of these processes, early infiltration of neutrophils occurs in acute degenerations, such as the malacias, and a few neutrophils can be found migrating in affected gray matter in the first stages of many cases of viral encephalomyelitis. Acute demyelinating processes are associated with, and probably stimulate, perivascular cuffing. The cuffs tend to be quite distinct from those in viral infections by being relatively very thick (up to ten or more cells thick) and to be composed of pure populations of lymphocytes. *If there are proliferated adventitial cells with plasma cells or other leukocytes mixed in the cuffs of lymphocytes, then the cuffs are likely to be a response to infection.* Only three diseases in animals are caused by viruses and characterized by demyelination and these, namely canine distemper, leukoencephalomyelitis of goats, and visna of sheep, have their own distinguishing characteristics. A possible fourth is so-called "old dog encephalitis." Glial responsiveness occurs in a variety of degenerative and viral lesions, but *glial nodules are characteristic only of an infectious process*, usually viral but occasionally rickettsial or bacterial.

Bacterial and pyogenic infections of the nervous system

Epidural/subdural abscess and empyema

The brain and spinal cord are protected against direct penetration of infection by the skeletal encasement and by the dura mater; the dura is almost impermeable to inflammatory processes. However, infection of the epidural space or the bony encasement with pyogenic bacteria and occasionally fungi can occur and may lead to localized *abscessation* or to the collection of suppurative material in the epidural or subdural space without forming a discrete abscess (*epidural or subdural empyema*). Infection may be hematogenous from *distant sites of infection* (e.g., septic valvular endocarditis, lung abscess), *direct extension* (e.g., osteomyelitis, middle ear and tympanic bullae, eye, paranasal sinuses, ethmoid cells), *trauma* (e.g., bite wounds especially in cats), or by *direct incidental injection* (e.g., contaminated spinal needle). Most cranial epidural abscesses arise by direct extension from one of the paranasal sinuses. Spread from the middle ear and through the cribriform plate is usually directly to the leptomeninges and brain. Occasionally, epidural suppuration is observed to have tracked from a retropharyngeal or nodal abscess through cranial foramina. Epidural suppuration about the base of the brain usually does not become encapsulated.

Tail biting in pigs, docking of lambs, and tail fracture in cats are common etiologies for spinal epidural abscesses that develop either secondary to local venous bacterial invasion or by direct extension from septic osteomyelitis. In cattle, spinal epidural abscesses are usually secondary to osteomyelitis of the vertebral bodies, are more prevalent at the lumbosacral area, and are usually caused by *Arcanobacterium pyogenes* or *Fusobacterium necrophorum*. Migrating grass awns can cause osteomyelitis and epidural abscess in the thoracolumbar regions in dogs. Common bacterial etiologies for epidural abscess or empyema in dogs and cats include *Streptococcus*, *Staphylococcus*, *Brucella*, *Pasteurella*, *Bacteroides*, and *Fusobacterium*, and in horses include *Actinobacillus* and *Streptococcus*.

Clinical signs vary according to the area affected, and can range from mild pain and restlessness to blindness and ataxia. Epidural abscessation at the lumbosacral area in ruminants may lead to circling, which can be confused with encephalitic listeriosis. Spinal epidural abscesses usually cause compression malacia of the cord, if the osteomyelitis from which they originate does not first lead to pathologic fracture with displacement.

Subdural abscessation is seldom observed, but can result from local penetration, perhaps most frequently from the paranasal sinuses. Extension can occur from epidural abscesses or, because subdural suppuration is prone to cause local phlebitis, it may give rise to epidural suppuration. Subdural infection is liable to spread widely via the veins or after penetrating the outer layer of the arachnoid. Spread is also permitted by the slowness with which leptomeningeal fibrous tissue develops to encapsulate the reaction.

Leptomeningitis

Leptomeningitis can be classified according to *etiology* (e.g., bacterial, mycotic), according to *duration* (e.g., acute, chronic), and according to the *type of exudates* (e.g., fibrinous, purulent). Classification by type of exudate is very useful, not only because it indicates the expected histologic lesions, but also clinically because it indicates the possible etiology. *Purulent meningitis* is by far the most common meningitis in domestic animals, especially neonates. *Serocellular meningitis* is described later with viral inflammation. *Hemorrhagic meningitis* occurs in septicemic anthrax and very seldom in other septicemias. Purely *fibrinous meningitis* occurs in malignant catarrhal fever, chlamydiosis, and seldom in anything else. *Mycoplasma bovis* is a rare cause of fibrinous meningitis in calves. *Granulomatous meningitis* occurs in systemic infections of this type, such as tuberculosis and cryptococcosis. The nonsuppurative inflammations of the leptomeninges are described with the diseases of which they may be part. They are mentioned here to draw attention to the wide variety of infectious agents that may localize in and produce inflammation of the leptomeninges. We have also mentioned or discussed purulent leptomeningitis with the many specific diseases of which it can be part, but dwell on the purulent process here because it is common, lacks specificity, and is suitable for a "type" description.

Purulent leptomeningitis may arise by direct extension from an adjacent structure. Extension from an epidural abscess or inflammation may result in diffuse leptomeningitis but, in most of the few cases of this origin, the leptomeningitis is local and overshadowed by the brain abscess that usually forms. Leptomeningitis may arise by local extension from a brain abscess, either by direct permeation or by spread in the Virchow–Robin spaces. Such an origin is observed frequently in listeriosis and in association with very large cerebral abscesses, but most cerebral abscesses, which are usually small, track inwards to the white matter rather than out to the meninges. The reverse sequence in which meningitis spreads to the brain and cord is not unusual in granulomatous infections but is distinctly unusual in suppurative infections, and when it occurs it consists of invasion of the surface of the brain by neutrophils (Fig. 3.100A) rather than of abscessation.

Both purulent meningitis and cerebral abscesses are usually of hematogenous origin, but they are seldom concurrent, and one usually finds meningitis alone or abscessation alone. There are occasional exceptions including thromboembolic lesions and leptomeningitis complicated by choroiditis. Septic emboli are prone to localize in the brain but may localize in meningeal vessels (Fig. 3.100B). Although those in meningeal vessels may lead to diffuse suppurative meningitis, they are usually quickly walled off and prevented from spreading (Fig. 3.100C,D). In the other exception, that of choroiditis concurrent with leptomeningitis, encephalitis or cerebral abscesses may develop because choroiditis leads to exudation into the cerebrospinal fluid and the ependyma is virtually no barrier to infection. Even this combination of pathologic processes is unusual and, when choroiditis is complicated by ependymitis and suppurative encephalitis (Fig. 3.100E), there is usually little or no meningitis. Whether encephalitis develops by spread of meningitis may be largely a question of time, but it is not unusual for animals with purulent meningitis to survive for a week, and sometimes much longer. There is ample time for the inflammation to spread throughout the cranial and spinal meninges – and to the brain if it were going to do so – but it seldom does, and *there is seldom anatomic justification for the common diagnosis of suppurative meningoencephalitis.*

In the section on inflammatory diseases of joints and synovial structures, attention is drawn to the frequent concurrence of polyarthritis with choroiditis and leptomeningitis in fibrinopurulent infections. Erysipelas, in which arthritis is a typical lesion, is an

Table 3.1 Infectious agents/diseases inducing inflammatory changes in the nervous system

Species	Canine	Feline	Porcine	Bovine	Equine	Ovine/Caprine	Camelid	Remarks on brain lesions
a. Viral disease/agent								
Akabane virus	N	N	N	Y	N	S	SC	
Bovine herpesvirus 1	N	N	N	Y	N	N	N	
Bovine herpesvirus 5	N	N	N	Y	N	N	N	
Borna disease virus	Y	Y	N	Y	Y	Y	S	
Bovine paramyxovirus (unclassified)	N	N	N	S	N	N	N	
Canine adenovirus 2	S	N	N	N	N	N	N	Multiple hemorrhages particularly in brain stem/caudate nuclei.
Canine distemper virus	Y	N	N	N	N	N	N	
Canid herpesvirus 1	Y	N	N	N	N	N	N	Necrotizing meningoencephalitis which is most severe in cerebrum and brain stem.
Canine parvovirus 2	S	N	N	N	N	N	N	Vasculitis-induced lesions.
Classical swine fever virus	N	N	Y	N	N	N	N	Vasculitis-induced lesions.
Equine encephalitis viruses (EEEV, WEEV, VEEV)	SC/S	N	S	SC	Y	SC	?	
Equid herpesvirus 1 and EHV-4	N	N	N	N	Y	N	N	EHV 4 rarely causes encephalitis.
Equid herpesvirus 9	?	?	?	?	?	?	?	Natural disease only reported in deer.
Encephalomyocarditis virus	?	?	Y	S	S	?	S	Infection in some species (e.g., bovine) may be limited to myocarditis.
Equine infectious anemia virus	N	N	N	N	S	N	N	Multifocal to diffuse encephalomyelitis is a rare manifestation of EIAV infection; may also cause lymphohistiocytic periventricular leukoencephalitis.
Feline immunodeficiency virus	N	S	N	N	N	N	N	Nonsuppurative encephalomyelitis in some naturally infected cats; secondary *Toxoplasma* or *Feline infectious peritonitis virus* infections.
Feline leukemia virus	N	S	N	N	N	N	N	Non-inflammatory degenerative myelopathy.
Feline infectious peritonitis virus	N	Y	N	N	N	N	N	Fibrinopyogranulomatous periventriculitis, meningitis, and perivasculitis; chronic leukoencephalitis; segmental myelitis; choroiditis.
Hemagglutinating encephalomyelitis virus (HEV)	N	N	Y	N	N	N	N	
Highlands J virus	N	N	N	N	S	N	N	
Japanese encephalitis virus	SC	N	Y	SC	SC	SC	?	
La Crosse virus	S	N	N	N	N	N	?	

Species	Canine	Feline	Porcine	Bovine	Equine	Ovine/Caprine	Camelid	Remarks on brain lesions
Lentivirus encephalomyelitis	N	N	N	N	N	Y	N	
Louping ill virus	Y	?	Y	Y	Y	Y	Y	
Malignant catarrhal fever	N	N	S	Y	N	SC	?	
Nipah virus	Y	Y	Y	S	Y	Y	?	
Porcine arterivirus	N	N	Y	N	N	N	?	
Porcine circovirus-2	N	N	Y	N	N	N	?	
Porcine paramyxovirus (unclassified)	N	N	S	N	N	N	N	
Porcine rubulavirus	N	N	S	N	N	N	N	
Pseudorabies virus	Y	Y	Y	Y	S	Y	?	
Rabies virus	Y	Y	S	Y	Y	S	Y	
Porcine teschovirus (Teschen disease)	N	N	Y	N	N	N	N	
Tick-borne encephalitis virus	Y	?	?	?	?	?	?	
West Nile virus	Y	Y	SC	SC	Y	S	Y	
b. Protozoal diseases								
Acanthamoeba encephalitis	S	?	?	?	?	S	?	
Babesiosis	S	S	S	Y	S	Y	Y	Sludging of parasitized RBCs in blood capillaries.
Neospora caninum	Y	N	N	Y*	S	S	Y	* in bovine encephalitis, is only observed in aborted fetuses or very young calves infected in utero.
Neospora hughesi	N	N	N	N	Y	N	N	
Sarcocystis canis	S	N	N	N	N	N	N	
Sarcocystis neurona	N	S	N	N	Y	N	N	
Theileriosis	S	N	N	Y	S	Y	Y	
Toxoplasmosis	Y	Y	Y	SC/S	SC	Y	Y	
c. Bacterial diseases								
Listeria monocytogenes	S	S	S	Y	Y	Y	Y	
Histophilus somni	N	N	N	Y	N	Y	?	
d. Chlamydial and rickettsial diseases								
Chlamydophila pecorum	?	?	?	S	?	?	?	

Y The species is susceptible to natural infection and overt disease is reported regularly.
S The species is susceptible to natural infection but overt disease is reported only sporadically.
SC The species is susceptible to natural infection but the disease occurs subclinically without neurologic signs.
N The species is not susceptible to natural infection.
? No refereed papers about species susceptibility to natural infection.

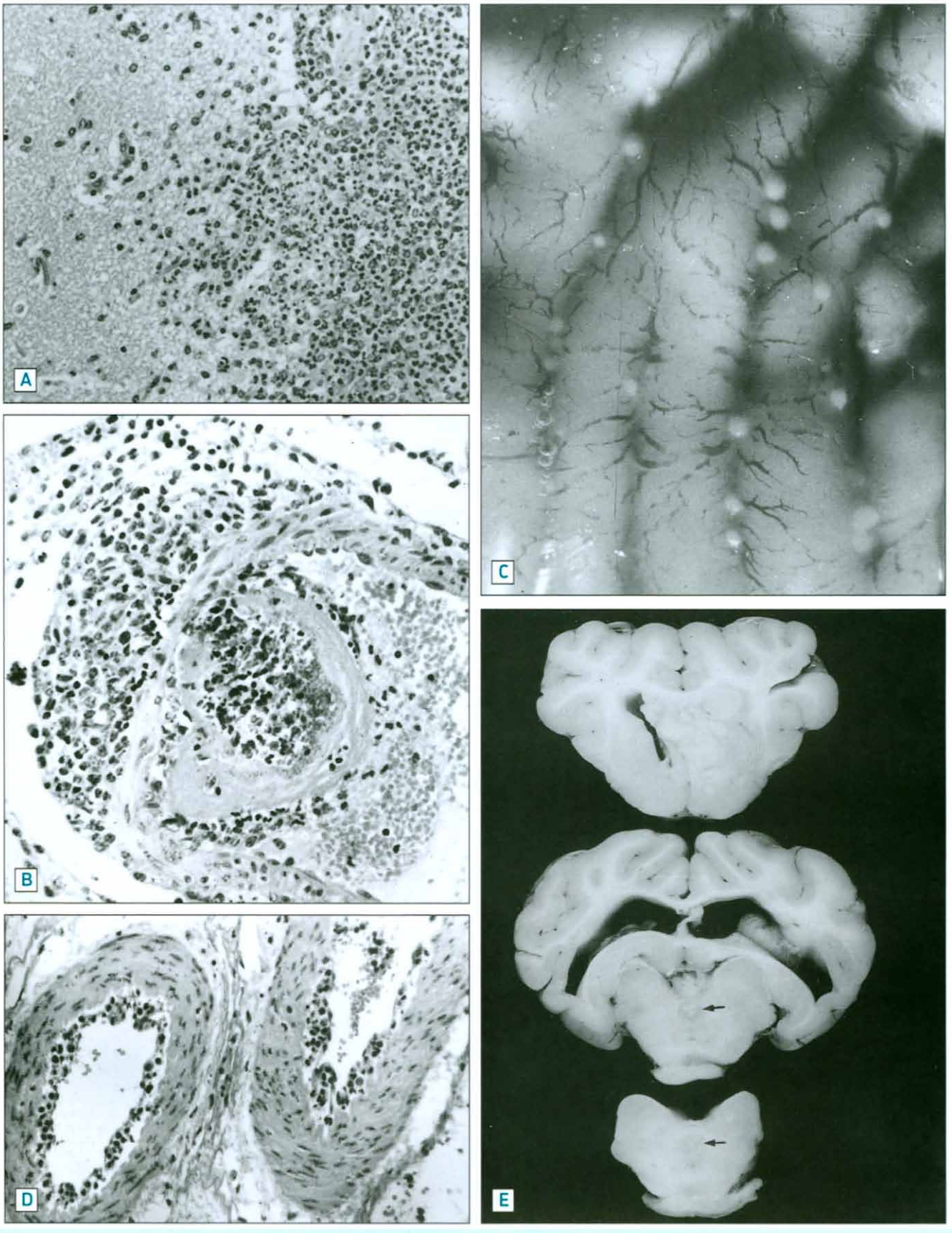

Figure 3.100 A. Suppurative meningitis with extension into cerebellar cortex. **B. Embolic meningeal arteritis** from streptococcal endocarditis in a pig. **C.** Miliary **meningeal abscesses** in a calf due to *Arcanobacterium pyogenes*. **D. Meningeal arteritis** with leukocytes beneath endothelium in coliform meningitis in a calf. **E.** Frontal sections to show periventricular abscess, early hydrocephalus, and occlusive ependymitis of aqueduct (arrows) secondary to **streptococcal choroiditis** in a pig.

exception in that it may produce septicemic and embolic lesions in the brain but it does not cause suppurative meningitis. Several bacteria, such as streptococci and *E. coli*, cause bacteremia and suppurative meningitis in neonates resulting in an important clinical entity, especially in ruminants and pigs, called **neonatal bacterial suppurative meningitis** (NBSM). Streptococcal NBSM in calves, lambs, and piglets (but not in foals), frequently has a combination of polyarthritis, purulent leptomeningitis, choroiditis and, in calves only, endophthalmitis (Fig. 3.101A, B). In pigs, *Streptococcus suis* types 1 and 2 (see Vol. 1, Bones and joints) cause NBSM that is usually accompanied by polyserositis; *S. suis* meningitis is suppurative in the acute stage, and lymphoplasmacytic in pigs that survive. *Streptococcus pneumoniae* usually produces fulminating septicemia in calves characterized only by very acute splenitis but, if the course of this infection is less fulminating than usual, polyarthritis and meningitis can be found. *E. coli*, another cause of NBSM of protracted course, commonly causes well-developed meningitis and polyarthritis in neonatal calves and lambs, but even in fulminating infections the mild changes of early inflammation can be found in these structures. On the other hand, both coliform and streptococcal infections in calves and piglets may avoid the joints and meninges and localize instead in the choroid plexuses and spread from there to the ventricles and brain, or localize in the brain alone. The coliforms and streptococci behave differently in calves with respect to the eyes; a combination of synovial, meningeal, and intraocular localizations is almost invariably of streptococcal origin (and the lesions can be well developed within 12 hours of birth, or even at birth according to farmers); the coliforms can, but only seldom do, cause endophthalmitis.

Mannheimia haemolytica and *P. multocida* are usually regarded only as causes of fibrinous pneumonia and hemorrhagic septicemia, but they are responsible for localized infections in other locations, including the meninges, in ruminants. When polyarthritis is present in septicemic or pulmonary pasteurellosis, *fibrinosuppurative leptomeningitis* can also be anticipated. Isolated cases and limited outbreaks of pasteurellosis that is entirely meningeal are observed in cattle and sheep, usually young ones. The course is asymptomatic until meningitis develops.

Once infectious agents gain access to the leptomeninges there is little resistance to spread in the meningeal spaces, and the inflammatory process becomes more or less diffuse in most cases. When the inflammatory process, excepting some that are granulomatous, remains localized, it is probable that only the inflammatory reaction, and not the infection, reaches the meningeal spaces. Cerebrospinal fluid is an excellent culture medium for many sorts of bacteria and these spread rapidly in the fluid, assisted to some slight extent by normal flow so that, although meningitis may appear grossly to have a limited distribution, its true distribution can be determined only microscopically.

The apparent gross distribution of meningitis varies somewhat with the cause. Thus in listeriosis, the process is confined largely or entirely to the meninges covering the medulla oblongata and upper cord, and in Glasser's disease and in malignant catarrhal fever the exudate is concentrated over the cerebellum and occipital poles of the cerebrum. In pyogenic meningitis, the basal meninges show the most obvious changes.

In the first day or so of suppurative meningitis before exudation is clearly recognizable, the meninges may be faintly opaque and hyperemic (Fig. 3.101C). After a few days, the appearance of the brain and cord is typical. The basal cisterns that accumulate the most exudate are filled with creamy pus or with gray-yellow fibrinopurulent exudate. The extreme exudation in these cisterns is due in part to their large size but in part also to sedimentation of particulate exudate. The exudate is in the arachnoid spaces and there is little if any on the outer surface of this membrane (Fig. 3.101D). The arachnoid appears stretched. *It is easy to overlook even copious exudates because their color is not very different from that of the brain.* A useful clue is that even the largest basilar vessels and the trunk of the oculomotor nerve are partially or completely buried and obscured by exudate and the filling-in of basal sinuses and grooves obliterates the normal topography. Over the hemispheres the exudate is usually confined to the fissures, where the arachnoid space is wide, and spares the surfaces of the gyri, where the arachnoid space is narrow. There is seldom frank pus over the hemispheres except in cases of unusually long survival.

The severe degree of exudation described above is what is usually seen in animals. In very acute or early cases, the exudation may be considerably less, and detectable only as congestion and cloudiness of the basal meninges extending towards the convexity of the hemispheres as fine gray sleeves about the arteries and veins. On careful inspection by naked eye, almost every case of purulent meningitis can be detected but the microscope may be necessary to confirm some cases.

The brain is swollen in every acute case of pyogenic meningitis, and the swelling is frequently severe enough to cause displacement with coning of the cerebellum. The pathogenesis of the edema and swelling is not known. The edema affects the white matter. It is possible that obstruction of the meningeal orifices of Virchow–Robin spaces by exudate and stasis of flow of meningeal fluid may contribute to the edema. The brain itself is normal except for softness and swelling and the rare cortical infarcts in the cerebrum or cerebellum.

Choroiditis commonly complicates leptomeningitis. It is usually quite obvious when it affects the plexuses of the fourth ventricles, but that affecting the plexuses of the lateral ventricle is not apparent until the ventricles are opened, although it may be expected if cloudy fluid escapes from the third ventricle when the infundibular process is opened. The CSF is cloudy, flakes of exudate overlie the plexuses and float in the fluid, and smeary sediments of pus lie on the walls of the ventricles (Fig. 3.101B). The exudate may be impacted in the aqueduct, occluding it and leading to ependymitis. Internal hydrocephalus then develops rapidly.

Microscopically, purulent meningitis does not differ in its character from pyogenic inflammation in other loose tissues, such as the lung. A few mononuclear cells are mixed with a very large number of neutrophils in the arachnoid spaces (Fig. 3.101E). The amount of fibrin in the exudate varies. There may be some infiltration for a short distance along the Virchow–Robin spaces about veins (Fig. 3.102). The pia mater as a rule remains intact, and it is only in exceptional cases that some microbial activity is observed in the adjacent parenchyma, or the pia is eroded to allow neutrophils to invade the surface of the brain. When the choroid plexuses are involved, they are swollen and infiltrated with leukocytes, many of them mononuclear. The plexus epithelium is eroded and covered by fibrin and cells. The ependyma is also eroded, there is edema of subependymal tissues, and the surrounding veins are infiltrated.

Internal hydrocephalus is a sequel to ependymitis and occlusion of the aqueduct, as a result of which the lateral and third ventricles are

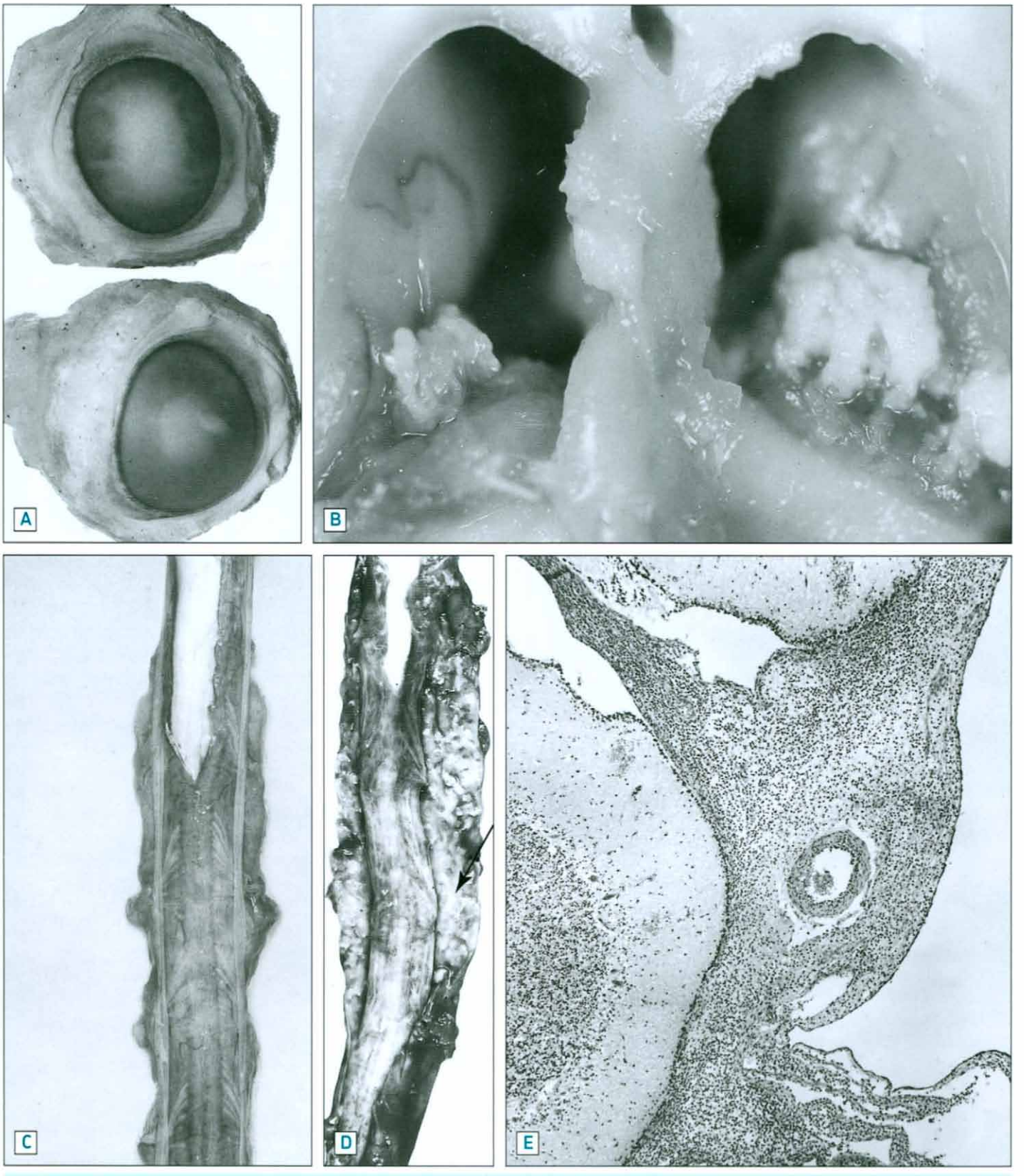

Figure 3.101 A. Hypopyon in streptococcal endophthalmitis in a calf. **B.** Horizontal slice through lateral ventricles to show **streptococcal choroiditis** and acquired hydrocephalus. **C. Spinal leptomeningitis** in a calf, due to *Escherichia coli*. (The dura is incised and reflected full length, the congested leptomeninges are incised at top.) **D. Spinal meningitis** in a dog; dura reflected to expose exudate (arrow). **E. Fibrinopurulent exudate** in leptomeninges in a pig, due to *Haemophilus parasuis*.

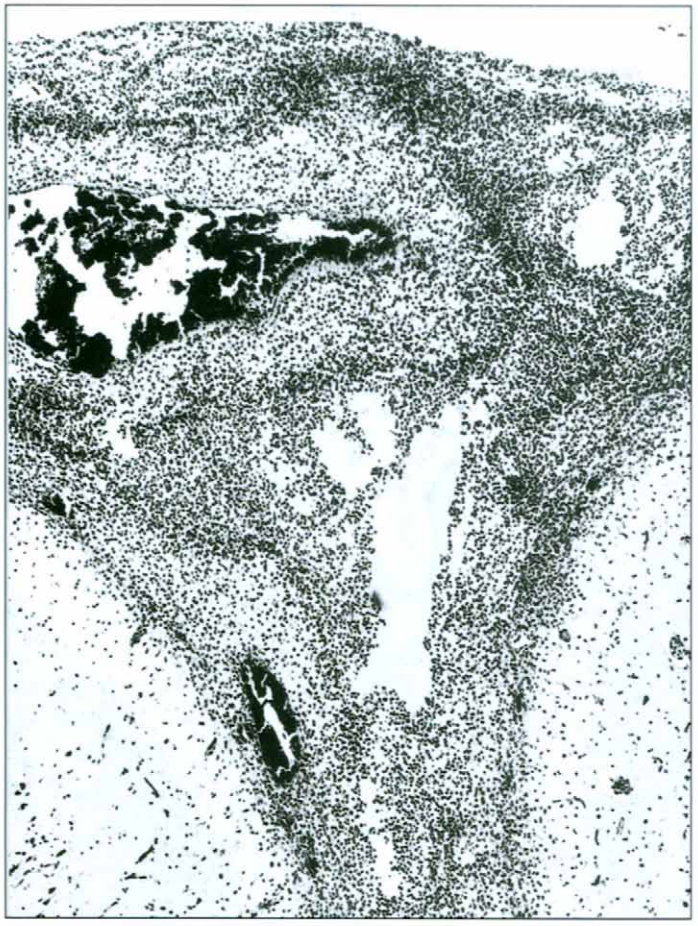

Figure 3.102 Purulent meningitis caused by *Haemophilus* spp. in a pig.

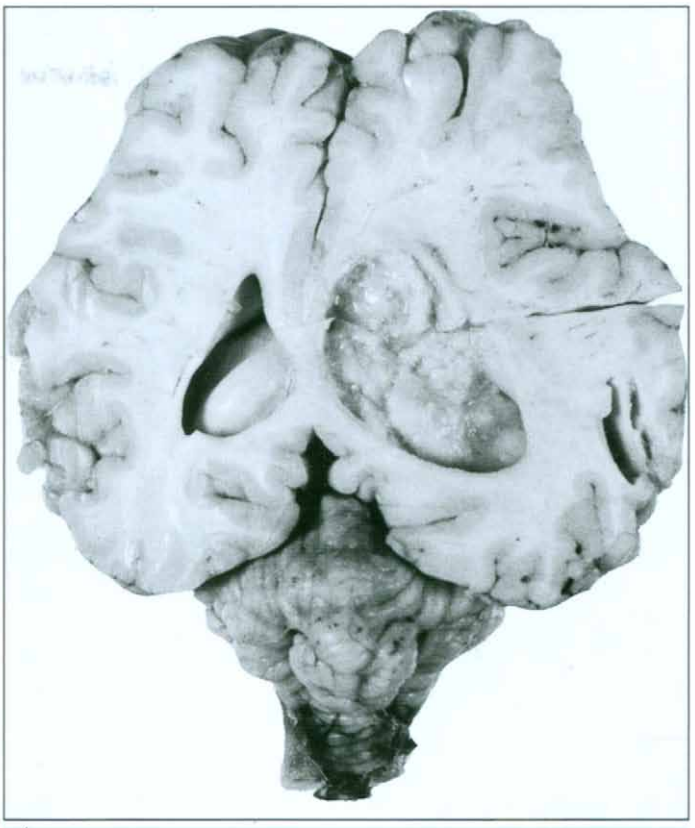

Figure 3.103 Necrobacillary abscess arising in **choroiditis** in an ox: swelling of hemisphere and caudal displacement with coning of cerebellum.

dilated (Fig. 3.103). This condition is a complication of choroiditis, but hydrocephalus may also be a sequel without choroiditis being present. The medullary foramina are frequently occluded as a result of inflammation in the tela choroidea so that CSF cannot escape from the ventricular system to the arachnoid spaces; the hydrocephalus is noncommunicating. Obstruction to the flow of fluid in the arachnoid spaces may occur as a result of brain swelling with impaction in the tentorial incisure, heavy deposits of exudate in the arachnoid space, or as a result of meningeal adhesions and thickenings in chronic inflammations. The hydrocephalus of this pathogenesis is communicating.

Chronic pyogenic leptomeningitis is rarely observed in animals. The process may sterilize itself or be sterilized by antimicrobials, but much of the injury is established in the early stages of the process and, once the diagnosis is evident clinically, *death is the expected outcome*. The early injury is exaggerated by the persistence of exudate even after the infection is controlled because there is no free drainage from the meningeal spaces. Healing occurs only after there has been considerable destruction of the meningeal framework with repair by fibrous tissue. Meningeal adhesions may produce cystic loculations in the arachnoid space, and obliterate the medullary foramen or basal arachnoid space and cause lingering death from hydrocephalus.

In a purulent process, *leptomeningeal vasculitis commonly occurs*. The expected sequelae of venous or ischemic infarcts are seldom observed even in those few cases with vasculitis in which thrombi can be found. This apparent discrepancy is probably due to the rate at which the vascular obstructions develop and on the type and size of vessel. Cases in which suppurative thrombophlebitis of the sagittal or transverse sinuses, or both, can be readily observed may not have venous infarcts in the brain. Thrombosis in the afferent circulation usually involves the smallest of meningeal vessels and usually develops at a rate that allows collateral circulation to develop. Inflammation of larger arteries (Fig. 3.100D) in which the endothelium is dissected from the intima by leukocytes has not been observed to lead to thrombosis.

Septicemic lesions, septic embolism, and cerebral abscess

The brain responds in septic or endotoxemic shock by releasing or controlling the release of several proinflammatory and anti-inflammatory cytokines; this major biochemical role is not always associated with a morphologic change in the CNS. *The CNS is injured to some extent in every episode of septicemia or sustained bacteremia.* The simplest and most common type of injury is inflicted on the venules, especially those of the cerebral white matter and to a lesser extent those of the cerebellar white matter. Injury of this type is not of much significance. There is sludging of leukocytes and probably of erythrocytes in these vessels, associated usually with degenerative and reactive changes in the endothelium. In the symptomatic purpuras, it is frequently possible to find the site of diapedesis in the brain, but not in other organs. Associated with endothelial injury

there is often leakage of plasma into the perivascular space and, given time, adventitial proliferation and infiltration of a few lymphocytes or other leukocytes into the Virchow–Robin spaces. Commonly, the injury is more severe, the vessel wall is totally necrotic in its cross-section, and in these lesions a few bacteria may be demonstrable (Fig. 3.104).

Septic embolism in the CNS may be a complication of active endocarditis; the bacteria are usually gram-positive. The bacteria implicated most commonly are *Erysipelothrix rhusiopathiae* in pigs, streptococci in all species, and *Arcanobacterium pyogenes* in cattle.

The toxigenicity and pathogenicity of many infections by gram-negative bacteria in septicemic phase seem to depend largely on the number of organisms present, as has been demonstrated in sheep for septicemic pasteurellosis caused by *Mannheimia haemolytica*. In septicemic pasteurellosis of sheep, in infection of foals by *Actinobacillus equuli*, in infections of sheep and cattle by *Histophilus somni*, and in some coliform infections of calves, the blood literally swarms with bacteria because common to these infections is massive and widespread bacterial embolism. These are the principal infections in which bacterial embolism occurs in the CNS without there being a demonstrable primary focus such as endocarditis, pneumonia, or an abscess. The problem of cerebral embolism in these infections is not solely one of quantitative factors determined by the height of the bacteremia; qualitative factors of unknown nature are also involved.

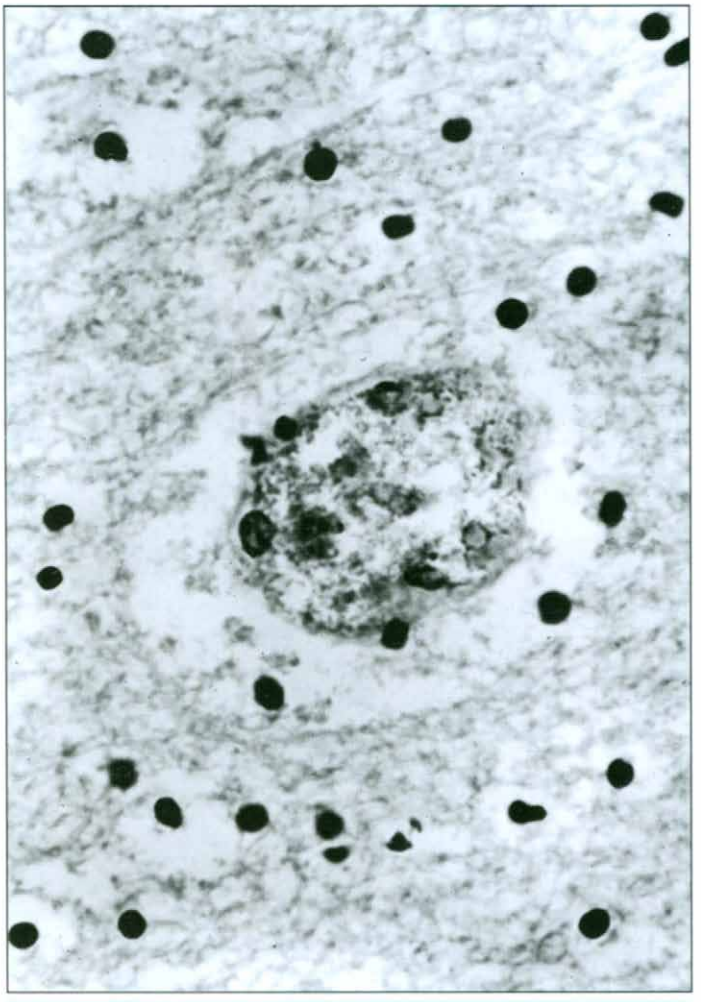

Figure 3.104 Necrosis of cerebral venule in *Escherichia coli* septicemia in a calf.

Septic thromboemboli and **bacterial emboli** lodge in the small cerebral vessels but, whereas thromboemboli tend to lodge particularly in small arterioles, bacterial emboli lodge in capillaries and venules. Consequences depend on the vessels involved, although the consequences are not particularly significant because abscessation occurs in either location. *Arterial emboli frequently cause ischemic infarcts, and venous and capillary emboli cause hemorrhagic infarcts.* The venular lesions also extend rapidly to involve large veins, whereas local spread in arteries does not occur.

Cerebral abscesses may arise in embolism, by direct implantation in wounds, or by direct invasion of the brain from an adjacent structure. Leptomeningitis rarely leads to abscessation, whereas choroiditis commonly leads to periventricular abscess. Abscesses in the spinal cord are seldom sought or observed; they may be hematogenous via arteries or veins (Fig. 3.105), and rarely do they enter through the dura.

Abscesses of hematogenous origin may occur anywhere in the brain, but there are two areas of remarkable predilection – the hypothalamus, and the cerebral cortex at the junction of gray and white matter (Fig. 3.106A, B). *Listeria monocytogenes* is an exception because it always demonstrates an affinity for the reticular formation in the brain stem. There may be only one abscess in the brain, or they may be multiple, especially when due to bacterial embolism. Multiple abscesses of septic thromboembolic origin tend often to be localized in one area of the brain. Some care is necessary in specifying the origin of multiple adjacent foci of suppuration because the *production of satellites*, each of which may be larger than the primary, is a natural attribute of brain abscesses.

Abscesses arising by direct invasion of the brain may develop in any location. There are two common sites of invasion, namely the *cribriform plate and inner ear*, and two somewhat less common, namely the *hypophyseal fossa and the paranasal sinuses*. Hypothalamic abscesses

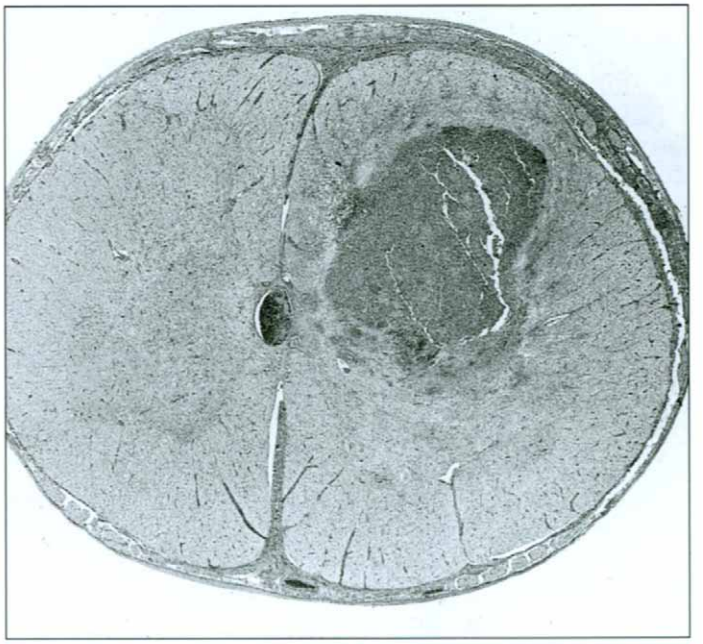

Figure 3.105 Meningitis, tracking abscess in dorsal horn, and ependymitis, complicating docking wound in a lamb.

are observed occasionally in cattle and dogs. At least some of those in dogs are caused by minute foreign bodies migrating with phlebitis through the orbital fissure or foramen rotundum and carrying actinomycetes. The importance of the cribriform plate and internal ear in the development of cerebral abscess is due to the frequency with which infections occur in those locations, that in neither site is there an actual or potential epidural space to protect the brain, and because nerves and vessels enter and leave through both.

Frontal abscesses of sinus origin occur occasionally in cattle as a complication of dehorning wounds, but abscesses in this site occur most commonly in sheep in which sinusitis, especially in the ethmoid cells, develops as a suppurative complication of myiasis (*Oestrus ovis*). *Arcanobacterium pyogenes* is the organism usually present. The olfactory bulb is destroyed and the first ventricle is opened, infection then spreading to the substance of the hemisphere (Fig. 3.107). There is little tendency to spread into the meninges from the point of entry or to invade the cortical gray matter, although both layers are usually secondarily involved by expansion of the abscess later.

Abscesses commonly develop at about the *cerebellopontine angle* as complications of suppurative otitis media. These are usually problems of pharyngitis, infection spreading via the Eustachian tube to the middle ear and from there to the brain, either by erosion of the bulla or extension along natural foramina.

Cerebellopontine abscesses are rarely, if ever, observed in horses in spite of the frequency of pharyngitis in this species. This exemption of horses may be due to the diversion of exudates from the Eustachian tube to the guttural pouches. Otogenic cerebral infections are very

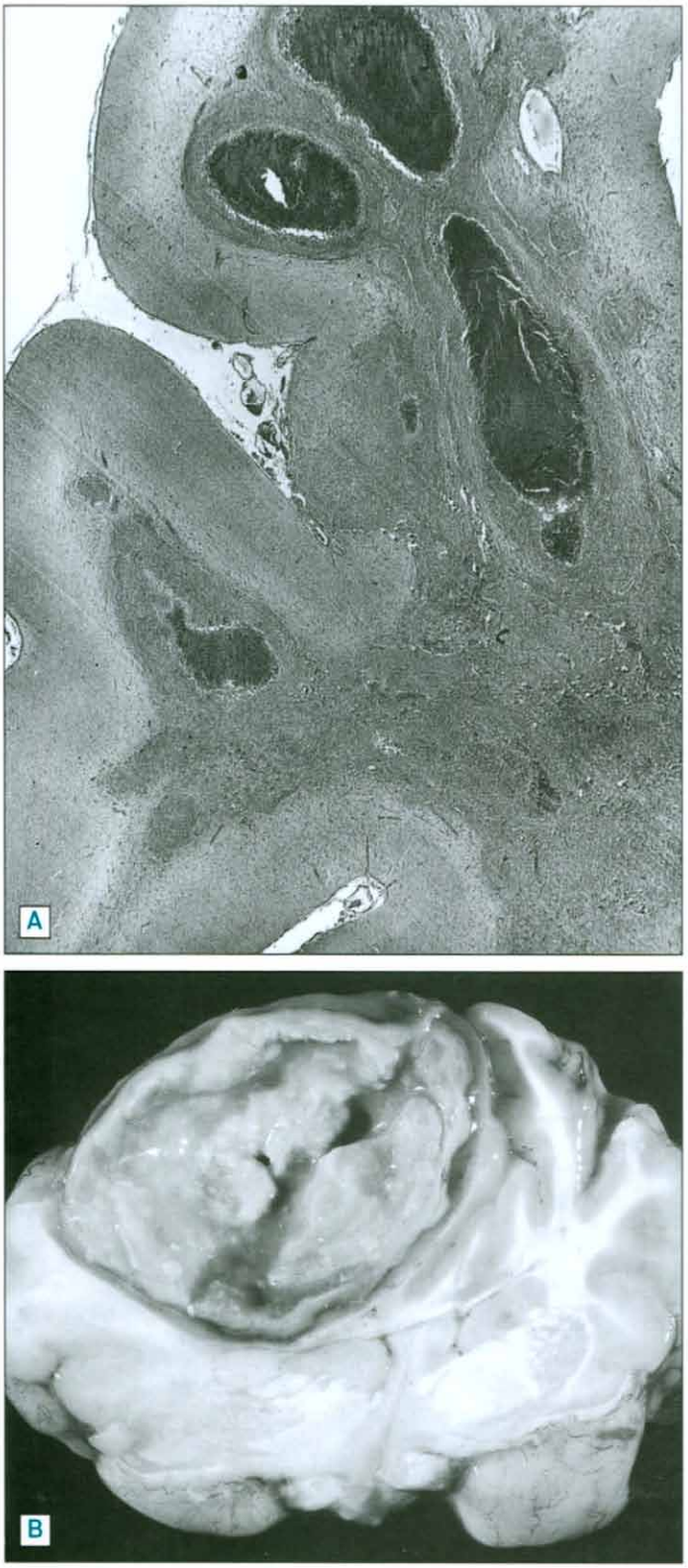

Figure 3.106 A. Hematogenous **abscesses** in cerebrum in a pig. **B. Abscess** distorting left cerebral hemisphere in a goat. *Pasteurella multocida* and *Fusobacterium necrophorum*.

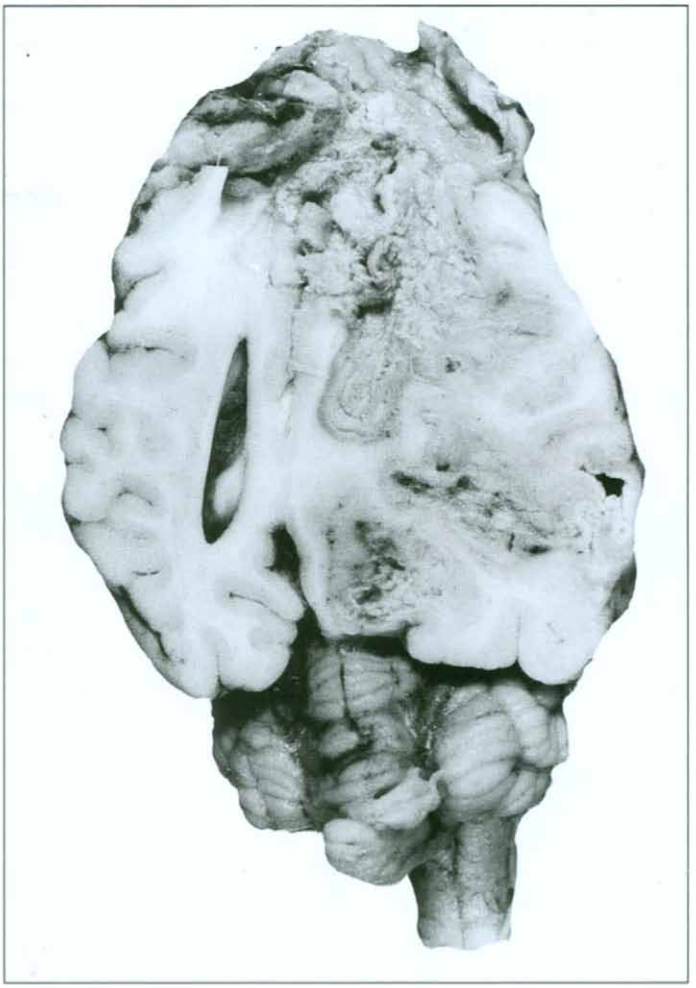

Figure 3.107 Arcanobacterial **abscess** arising from right ethmoid in a sheep.

seldom observed in dogs. Those observed have come via the auditory meatus rather than the Eustachian tube, and the cerebral reaction is nonspecifically granulomatous, usually without pus. Otitis media caused by *Pasteurella multocida* is fairly common as a complication of chronic cases of upper respiratory infection in cats and, when the infection extends to the cranial cavity, it produces diffuse purulent leptomeningitis and not, as expected, a cerebellopontine abscess. Most otogenic infections occur in sheep and swine; a few are observed in cattle, and in each species the outcome is an abscess of the brain.

Otic infections are commonly bilateral so that otogenic abscesses may be also. The usual organism in these abscesses is *Arcanobacterium pyogenes* alone or mixed with *Pseudomonas aeruginosa*, *Pasteurella multocida*, and mixed cocci. Affected pigs usually have several other chronic debilitating infections at the same time so that several animals in the herd may have otogenic abscesses. This pattern of infection in calves is uncommon and sporadic. In sheep on the other hand, the disease may be observed in limited outbreaks and there is an association with grazing on rough, dry, mature summer pastures. The reasons for this association are unknown.

Established abscesses are found much more commonly in the white matter than in the gray, in spite of the fact that they usually begin in the gray. There is no suitable explanation for this tendency to track into white matter, but once within white matter they do permeate along fiber tracts (Fig. 3.108). As a result of this activity, satellite abscesses are to be expected, sometimes chains of them. Connecting purulent tracts may be very thin and difficult to find.

An abscess may begin as an intense accumulation of neutrophils in and around a thrombosed vessel (Fig. 3.109A), or in a focus of septic encephalitis in which neutrophils lightly infiltrate a zone of early softening. The principal differences between a cerebral abscess and an abscess in some other location are the vulnerability of the surrounding nervous tissue to edema, which can destroy it, and the slowness with which encapsulation occurs (Fig. 3.109B). The meninges and larger blood vessels are the only sources of fibroblastic tissue for encapsulation.

In the *early stages*, the abscess cavity contains a liquefying center and the margins are irregular and poorly defined even microscopically. The surrounding brain tissue is edematous and infiltrated by neutrophils. The microglia and vessels are fairly resistant and reactive in a narrow peripheral zone, but the neurons and neuroglia degenerate. Most abscesses develop rather slowly and later become encapsulated. The capsule seems often to be formed more by condensation of vessels around an expanding focus than by proliferating fibroblastic tissue, but both contribute; the result is an irregular capsule thicker on the meningeal than on the ventricular aspect. Most capsules are very distinct and 1–3 mm wide. Their distinctness is due to the paucity of reticulin or collagen spreading out into the surrounding parenchyma or into the abscess cavity. In old abscesses with shrinkage, the core may separate from the capsule, and the capsule may separate extensively from the surrounding cerebral substance. The surrounding tissue is discolored yellow due to edema, the edematous zone often being much larger than the abscess itself. The *microscopic structure of the wall of a chronic abscess* does not differ much from case to case except in the thickness of the capsule. A narrow zone of histiocytes or gitter cells faces the neutrophilic debris. The next zone is a laminated layer of collagenous fibers between which are rows of gitter cells laden with debris. The outer zone is vascular, the vessels being large and usually nonreactive. The surrounding nervous tissue is severely edematous, with degeneration of myelin and fibers. Astrocytes are swollen and reactive about encapsulated abscesses, but it takes a long time for their fibrils to begin to intertwine with capsular reticulin. The veins are heavily cuffed by lymphocytes.

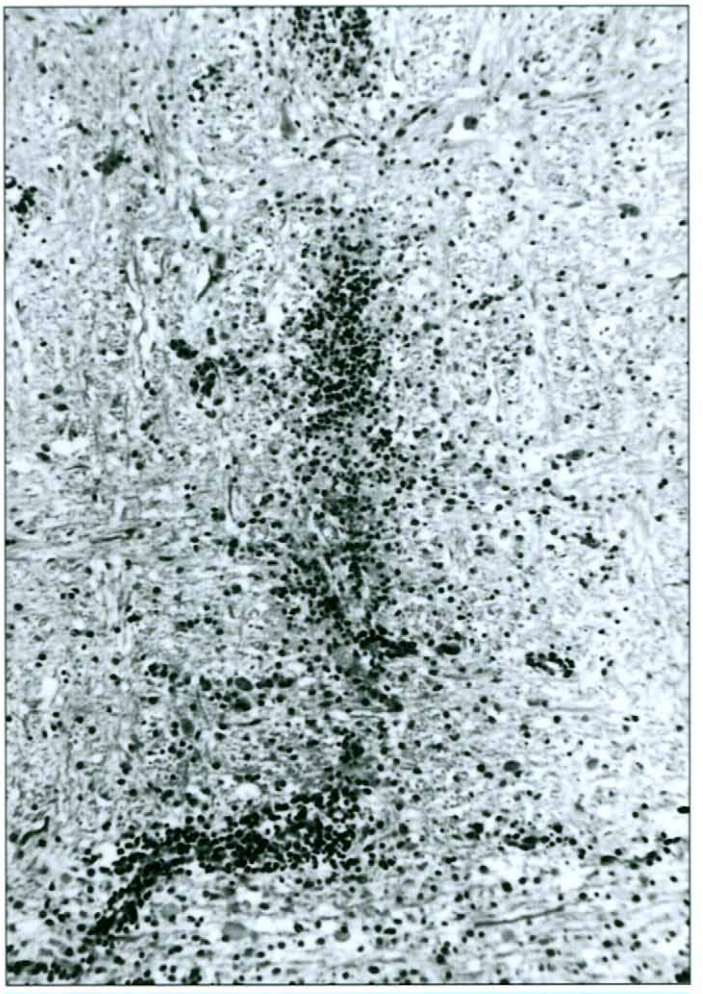

Figure 3.108 Spreading tract in suppurative (streptococcal) encephalitis in a pig.

When abscesses are multiple, death is the outcome after a short course. When they are isolated, they may permit prolonged survival. The course is usually short with medullary abscess, even when small, because it, or more usually the edema it provokes, interferes with vital centers. Abscesses in the hypothalamus or cerebrum may track through the white matter to the ventricles to produce pyencephaly that is quickly fatal (Fig. 3.110A, B, C, D). Large abscesses ultimately expand to the meninges to produce adhesive meningitis. Many abscesses act as space-occupying lesions by virtue of their size or the edema they provoke or both. The consequences of space occupation depend on the site and size of the lesion.

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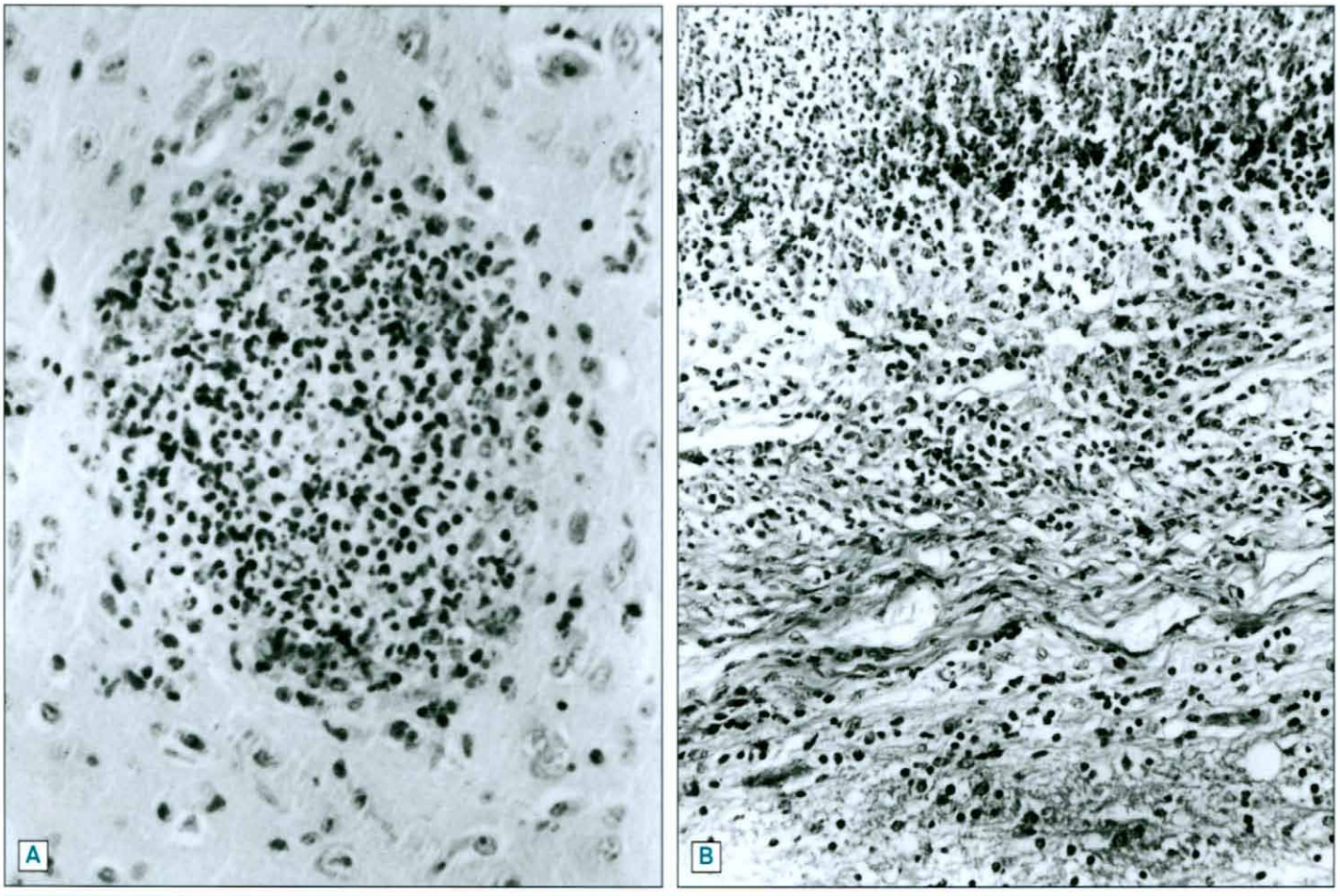

Figure 3.109 **A.** Early **cerebral abscess** from septic embolus in a pig. **B.** Structure of wall of **cerebral abscess**. Abscess (above) is separated from normal brain by a thin capsule.

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Granulomatous and pyogranulomatous meningoencephalomyelitis

Granulomatous to pyogranulomatous meningoencephalomyelitis is observed in many systemic mycotic (e.g., blastomycosis, cryptococcosis) or algal (e.g., protothecosis) diseases, which are described elsewhere in this book. Granulomatous inflammation can also be caused by bacteria (e.g., *Mycobacterium bovis, Nocardia* sp.) (Fig. 3.111), and migrating helminths or arthropod larvae (see below). The diagnosis and differentiation among these etiologies requires culture or demonstration of the causative pathogen using histochemical or immunohistochemical stains.

Listeriosis

Listeriosis is caused by *Listeria monocytogenes*, a Gram-positive, facultative anaerobic bacillus that is ubiquitous in the environment and can multiply in diverse environmental conditions – it can grow in a temperature range from 4 to 45°C and at a pH range of 5 to 9. It is remarkably viable in the external environment, being able to survive in dried media for several months and in suitably moist soil for ~1 year. The organism is commonly isolated from tissues of normal animals, including tonsils and other gut-associated lymphoid tissue, and in large numbers from the feces of ruminants. *L. monocytogenes* has more than 11 serotypes; almost all animal infections are caused by serotypes 1/2a, 1/2b, and 4b.

Listeriosis is of worldwide distribution, possibly excepting the tropics. The organism has been isolated from diseased mammals and birds of many species and produces septicemia, meningitis, and abortion in humans. In domestic animals, the disease is most important in ruminants. *L. monocytogenes* is an intracellular pathogen of macrophages, neutrophils, and epithelial cells. Important virulence factor include the surface protein *internalin,* which internalizes with *E-cadherin*, an adherans junction protein, to overcome the intestinal, placental, and blood–brain barriers. Also, it relies on another virulence factor, *cholesterol-binding hemolysin*, to lyse phagocytic cell phagosomes and escape to the cytoplasm. The organism proliferates in the host cell cytoplasm and many migrate against the cell membrane to form protrusions that can then be taken up by other cells. It is one of the few organisms known to co-opt the host cell contractile actin to facilitate cell-to-cell transfer.

Listeriosis behaves as three separate diseases or syndromes. They seldom overlap so that each syndrome probably has a separate

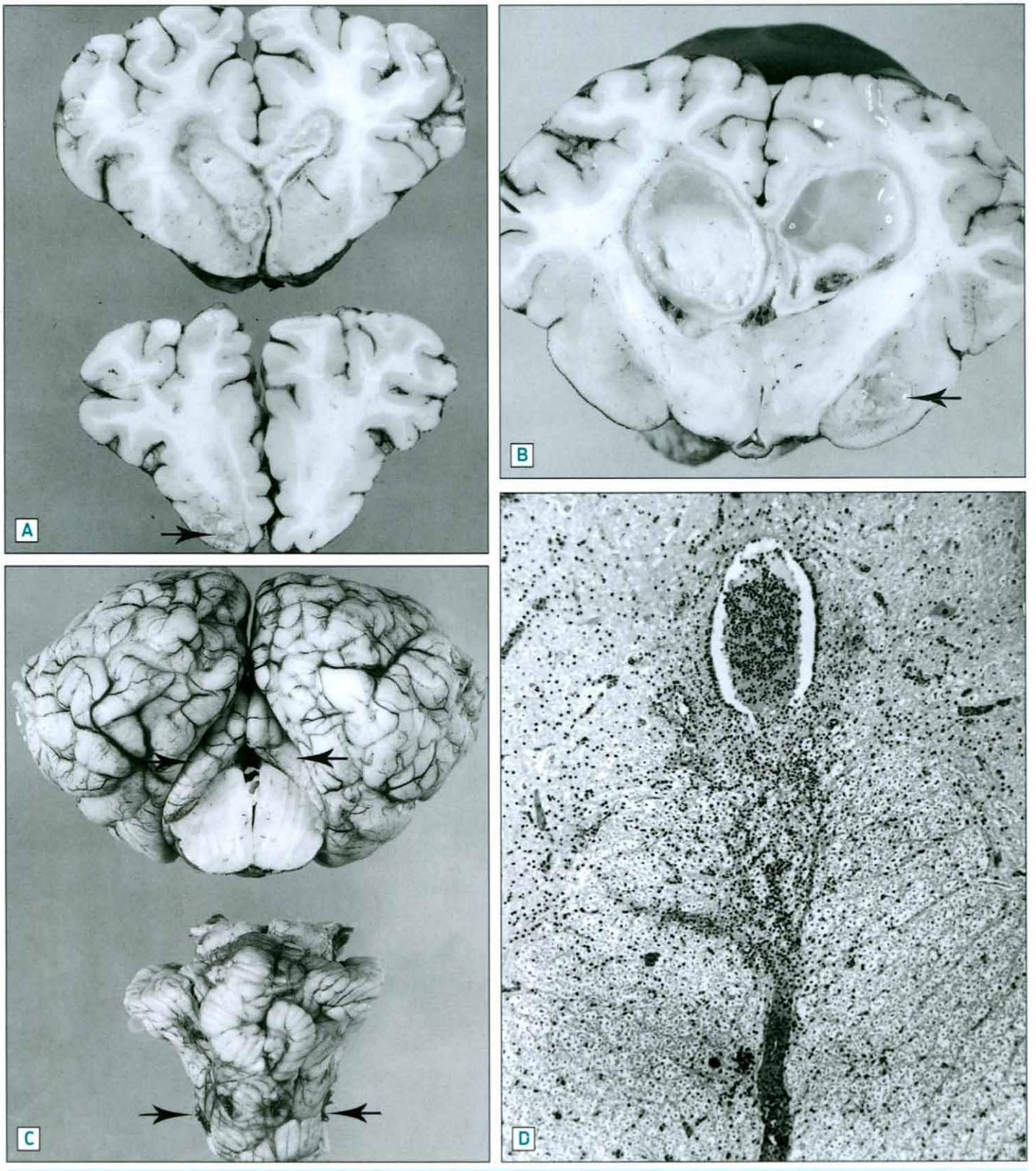

Figure 3.110 Pyencephaly in a calf. **A.** Pus in lateral ventricles (above) and left olfactory ventricle (arrow, below). **B.** Dilation of lateral ventricles by fibrinopurulent exudate (arrow). **C.** Brain swelling with cerebellar coning and hemorrhage (arrows, below) and subtentorial herniation of hemispheres (arrows, above). **D.** Inflammatory exudate in aqueduct.

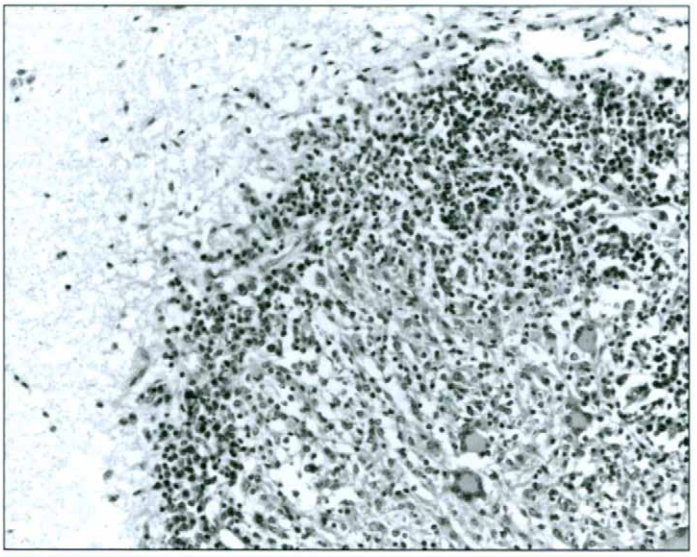

Figure 3.111 Granulomatous meningoencephalitis in bovine tuberculosis. (Courtesy of D Driemeier.)

pathogenesis. *The three recognized syndromes are: infection of the pregnant uterus with abortion, septicemia with miliary visceral abscesses, and encephalitis.* Additional syndromes of clinical significance in ruminants include conjunctivitis, possibly from contaminated silage dust, endocarditis, and mastitis. The uterine infection is discussed with Diseases of the pregnant uterus (see Vol. 3, Female genital system). Aborting ruminants are not usually ill, and abortion is usually late in gestation. The uterine infection is probably hematogenous and the bacteremic phase is asymptomatic, and localization occurs only in the uterus. Infection of the uterine contents can be established quite readily by oral exposure of pregnant animals and by intravenous inoculation.

Septicemic (systemic) listeriosis occurs in aborted fetuses and neonatal lambs, calves, and foals up to 1 week of age and in others that are several months of age, and is characterized by multisystemic bacterial colonization and multifocal multisystemic areas of coagulative necrosis or microabscess formation. The necrotic areas or microabscesses are miliary in distribution, very numerous in the liver, but much less numerous in the heart and other viscera, and characterized by tissue lytic necrosis with infiltration of neutrophils and fewer macrophages. Neonates generally become infected in utero.

Listerial encephalitis occurs almost solely in adult ruminants; its pathogenesis is partially understood. Listerial encephalitis may be sporadic or occur in outbreaks in which the morbidity may be 10% or higher. Outbreaks are usually associated with *heavy feeding of silage*, with disease most likely occurring in winter and early spring when the animals are indoors. This association of outbreaks of cerebral listeriosis with silage feeding is a circumstantial observation, but the association is so common that silage is fed as a calculated risk and removed from the ration when the first case occurs. The association with silage may indicate an acquired susceptibility of the animals or the provision of a growth medium that leads to heavy infection pressure. The organism will multiply in spoiled silage that is incompletely fermented and with a pH of 5.5 or above. Ingested *Listeria* is likely to breach the oral mucosal barrier through pathological or physiological wounds, e.g., erupted teeth wounds. *After invading the oral mucosa, the bacteria invade the trigeminal nerves and travel centripetally via axons to the brain. Listeria* can also breach the blood–brain barrier under experimental conditions; however the specific distribution of listerial encephalitis in the natural disease is inconsistent with a hematogenous infection. In animals, *Listeria has a remarkable affinity for the brain stem*, the lesions being most severe in the medulla and pons and less severe rostrally in the thalamus and caudally in the cervical parts of the spinal cord. Intravenous or oral dosing of pregnant ruminants will regularly produce intrauterine infection but seldom produce intracranial infection and probably never produce encephalitis of the specific distribution. Bacteremias with localization in the CNS regularly cause meningitis, choroiditis, and cerebral abscesses, which is what *L. monocytogenes* does, but only as an experimental hematogenous infection. When a pregnant animal dies of encephalitic listeriosis, the uterine contents are usually sterile.

Conjunctivitis and keratitis follow experimental conjunctival exposure, but this should not imply that the endophthalmitis of the natural disease is produced by local invasion. Rhinitis is clinically apparent in many cases of encephalitic listeriosis, but histological evidence does not support the idea that the olfactory nerves are a route of invasion of the brain. The position with respect to other cranial nerves and the internal ear has not been examined.

The *neurological signs* and lesions of listeriosis in the various ruminants are qualitatively the same, differing only in severity. The signs are combinations of mental confusion and depression, head pressing, and paralysis of one or more medullary centers. Characteristically, there is deviation of the head to one or other side without rotation of the head; when such an animal moves it does so in circles, hence the name "*circling disease*." There is frequently *unilateral paralysis of the seventh nerve* causing drooping of an ear, eyelid, and lips. There may also be paralysis of the masticatory muscles and of the pharynx. *Purulent endophthalmitis*, which is usually unilateral, is often present and has caused listeriosis to be confused with malignant catarrhal fever. The course of the disease in sheep and goats is a few hours to 2 days; survival occurs but usually with neurologic handicaps.

Listeriosis in *swine* is comparable to the disease in ruminants, but is relatively rare. Outbreaks of encephalitis may be observed with lesions of usual distribution in the brainstem. Alternatively, there may be abortion and neonatal death. The usual expression of the disease is visceral with miliary abscesses in the liver and heart.

The patterns of listeriosis in *other domestic species* appear to follow the general scheme but are rarely observed. The encephalitic form in adult horses, the septicemic form in foals, and abortions in mares are reported. Several cases of encephalitis caused by *L. monocytogenes* are reported in dogs.

Gross lesions are usually not observed in the brain in listerial encephalitis. Occasionally, the medullary meninges are thickened by green gelatinous edema, and gray foci of softening may be found in the cross-section of the medulla. The initial lesions are parenchymal; involvement of the meninges, which is almost constant, is secondary to the parenchymal lesions. Mild meningitis commonly affects the cerebellum and cranial cervical cord, and less commonly is found in patches over the cerebrum and down the spinal cord. *The characteristic parenchymal lesion is a microabscess.* It may begin in a tiny collection of neutrophils (Fig. 3.112A), but more usually begins in a minute focus of microglial reaction. The glial nodules may persist as such, the cells taking on the characters of histiocytes, but the tendency is always for the nodules to be infiltrated by neutrophils and for their centers to liquefy (Fig. 3.112B). The focal lesions do not

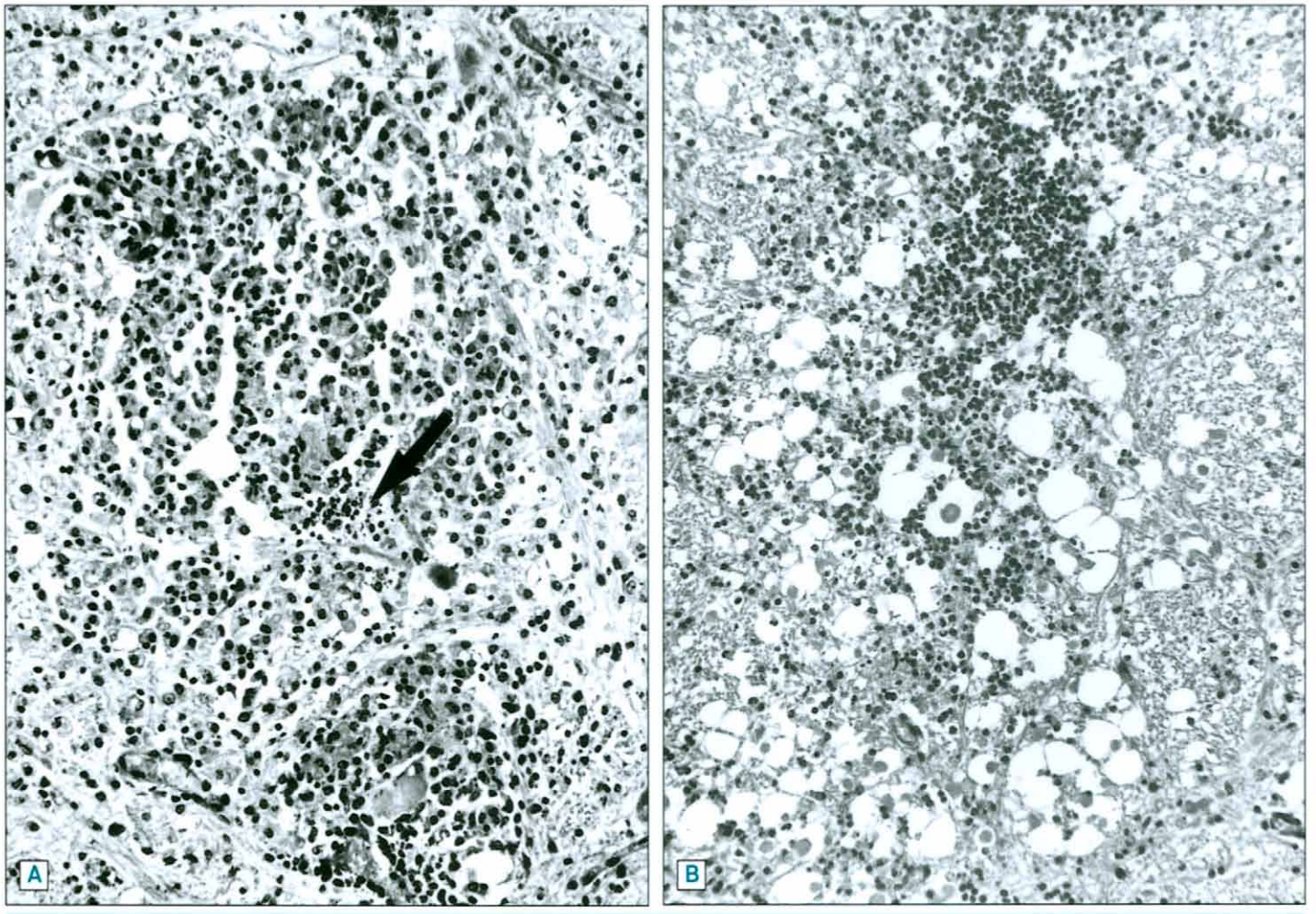

Figure 3.112 Listeriosis. A. Microglial reaction with small focus of **suppuration** (arrow) in a sheep. **B. Suppurative encephalitis** in an ox.

expand much, but suppurative foci may streak through the white matter. Apparently, the organism is not highly toxigenic because the parenchyma surrounding the glial nodules and focal abscesses may be little changed. Commonly however, the white matter is edematous and rarefied. Such areas may be large and lightly, but diffusely, infiltrated by neutrophils and hypertrophied microglia. Focal softening occurs and may coalesce. They are related to vessels that are occluded by inflammatory and thrombotic changes.

Acute vasculitis with exudation of fibrin occurs in the white matter in relation to suppurative foci. The vasculitis is secondary to drainage in the Virchow–Robin spaces from the primary parenchymal foci. It is in this manner that the meningeal infiltrates develop. Perivascular cuffing is heavy. The cuffs are composed mainly of lymphocytes and histiocytes with a few admixed neutrophils and eosinophils; granulocytes predominate in some cases.

Confirmation of the *diagnosis* is by culture, which is usually difficult and needs special procedures. Demonstrating gram-positive intramonocytic or intraneutrophilic bacilli in tissues in association with the aforementioned lesions is pathognomonic for listerial encephalitis.

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Histophilus somni infections (histophilosis, or H. somni disease complex)

Histophilus somni (formerly *Haemophilus somnus*) is the only species of the genus *Histophilus*, family Pasteurellaceae, and encompasses bacteria isolated from cattle and previously described as *Haemophilus somnus*, as well as ovine isolates formerly referred to as *Histophilus ovis* and *Haemophilus agni*. *H. somni* is a fastidious gram-negative coccobacillus, and a facultative anaerobic organism that is considered normal flora of the male and female bovine genital tract and to lesser extent the bovine nasal cavity. Calves are infected by carrier cows in the first months of life, and they in turn disseminate the infection in feedlots. The mechanism, site, and circumstance by which the bacteria invade the bloodstream are not known, but it is possible that organisms in genital discharges or aerosolized urine invade via the respiratory tract. Infection, especially the respiratory form, is usually preceded by stress factors such as transportation.

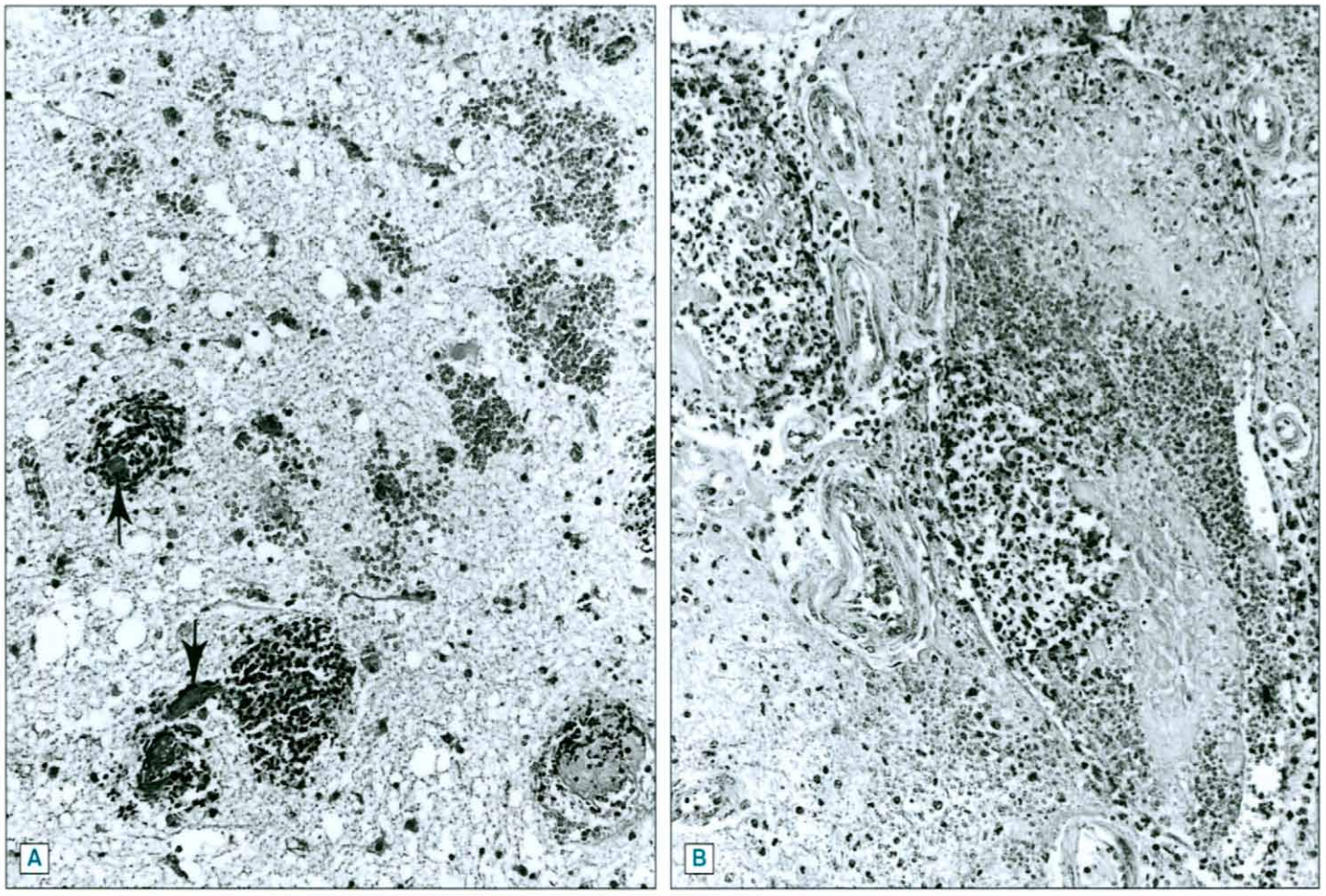

Figure 3.113 ***Histophilus somni*** infection in an ox. **A.** Thrombosis, hemorrhage, and bacterial colonies (arrows) in cerebral white matter. **B.** Thrombosis of meningeal vessels.

These bacteria have virulent and avirulent strains. Important *virulence factors* include lipo-oligosaccharide (LOS), immunoglobulin Fc binding proteins, inhibition of oxygen radicals, and intracellular survival. The mechanism of vasculitis in *H. somni* infection is complex but it can be partially explained by the effect of LSO on endothelial cells. LSO triggers apoptosis of bovine endothelial cells in vitro by caspase-3 activation. This effect is associated with the production of reactive oxygen and nitrogen intermediates. Cerebral blood vessels are particularly vulnerable to damage by the organism, but vasculitis can develop in most organs.

Histophilus somni causes a *septicemia* that may result in acute death or it may localize in one or several organs causing subacute or chronic, fatal or nonfatal disease. The septicemic phase of the disease is brief, and accompanied by fever and stiffness with few other signs. In some cases, the infection is controlled at this stage without localization, but often it leads to cerebral vasculitis with acute thrombosis, hemorrhage, and necrosis (Fig. 3.113A, B).

Histophilus somni can infect several bovine organ systems and cause infectious thrombotic meningoencephalitis (ITME), otitis externa, pneumonia, laryngitis/tracheitis, myocarditis, abortion, metritis/infertility, arthritis, mastitis, orchitis, and conjunctivitis. *Vasculitis with secondary thrombosis is the hallmark of the infection.* Bacterial embolism does not occur but may be simulated microscopically by intravascular proliferation of bacteria at sites of thrombosis. Thus, the former name "thromboembolic meningoencephalitis" is inaccurate. Histophilosis is an important disease of young cattle, but acute and chronic infections involving other organs are also economically significant.

Septicemia caused by *H. somni* develops in cattle of various ages maintained under various management systems, but in North America the disease is more prevalent in feedlots. It is most common in early winter, shortly after susceptible animals are moved there from pastures. Infection occurs in a large proportion of animals, but disease occurs in a minority. *H. somni* induces conditions in sheep identical to the bovine disease, i.e., septicemia, ITME, abortion, etc.

Cerebral localization produces a variety of neurologic signs, and without treatment affected animals become comatose and die within 1–2 days. The cerebral lesions are distinctive, and are visible in a large majority of untreated cases. The cerebrospinal fluid is cloudy and may contain pus and fibrin. *Scattered throughout the brain and spinal cord are multiple foci of hemorrhage and necrosis* (Fig. 3.114A, B). These foci may be 1–30 mm in diameter, and range from the bright red of recent hemorrhage to dark red-brown in older lesions. They have near-random distribution throughout the brain, but there may be some predilection for the thalamus and junction of the gray and white matter of the cerebral cortex. Meningitis is usually visible grossly and is most easily identified over the hemorrhagic foci. In animals that

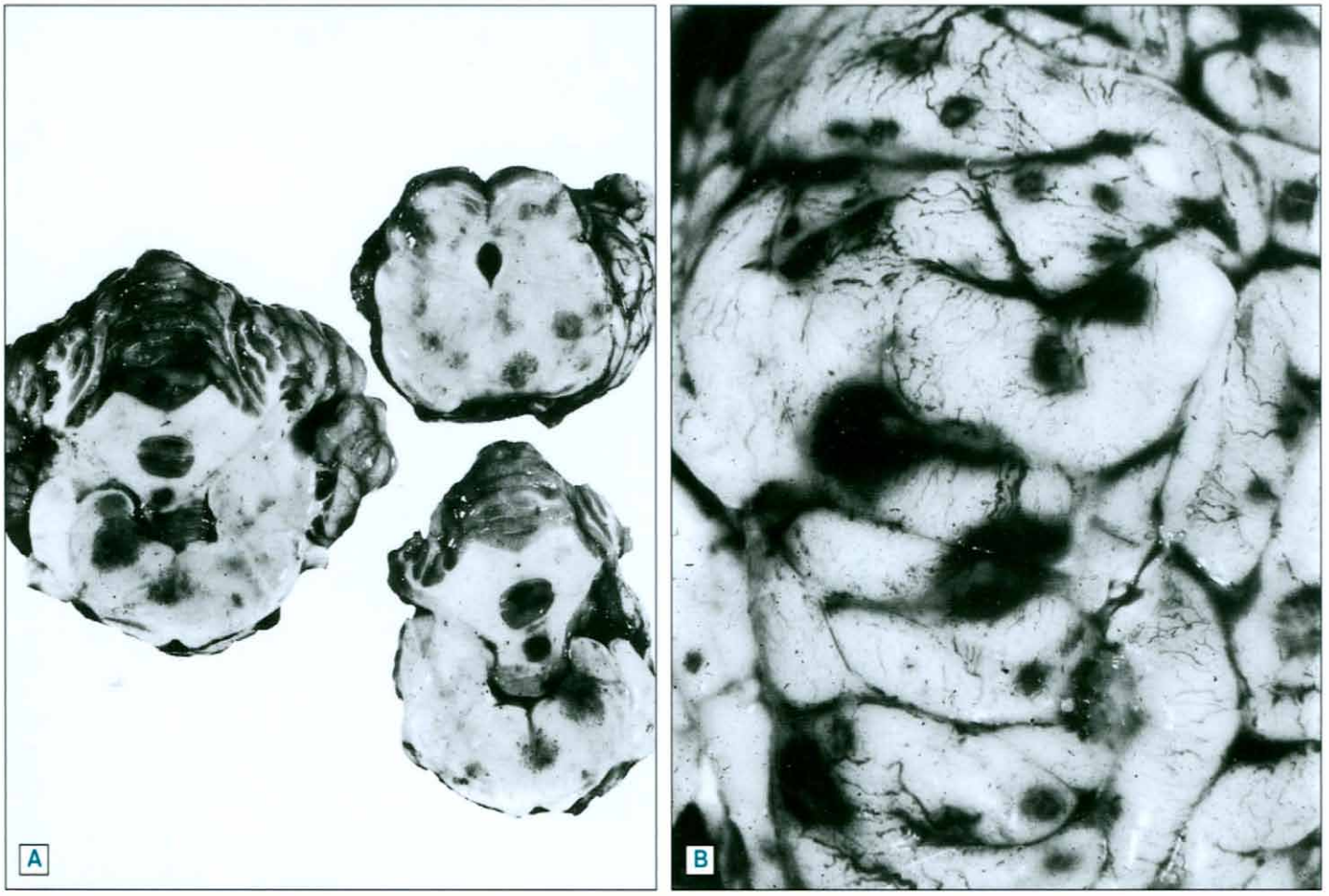

Figure 3.114 ***Histophilus somni*** infection in an ox. Multiple areas of hemorrhage and necrosis in brain stem (**A**) and cerebral cortex (**B**).

survive for a day or more, diffuse purulent leptomeningitis involves the basilar portions of the brain, and in these animals the older parenchymal lesions may have begun to soften.

The *histologic lesions* are similar in all organs but are usually most severe in the brain and consist of *intense vasculitis with thrombosis* and extension of the inflammation into the surrounding parenchyma, with or without infarction (Fig. 3.113A, B). Small venules (thrombophlebitis) are primarily affected, with thrombi often containing colonies of bacteria. The inflammatory response is neutrophilic, and cerebral lesions are quickly converted to abscesses.

Although cerebral vascular localization is a common and most dramatic result of the septicemia, *petechiation and evidence of inflammation are often visible throughout the body*, even in animals that die from fulminating disease. Foci of inflammation are easiest to identify in the renal medulla, skeletal muscle, lung, and laryngeal mucosa, but may also be visible in myocardium, intestine, and urinary bladder. Subacute to chronic disease develops commonly in some organs, especially joints, lungs, and heart, and is an important manifestation of *H. somni* infections.

In the acute disease, there is excess fluid in many *joints*, particularly the atlanto-occipital, where the capsule is distended by fluid that contains fibrin and sometimes blood. The synovial membranes and connective tissues around the affected joints are edematous and petechiated. The organism is sensitive to antimicrobials, and the course of the disease is often modified by therapy. The joints of animals that have survived several days contain thick mats of fibrin and pus, and the periarticular tissues are browned by old hemorrhage. Erosion of articular cartilages is rare.

Histophilus somni has been isolated from cattle with a variety of types of *pneumonia*, and its role in the bovine respiratory complex is discussed in the chapter on respiratory diseases. Pneumonia is an uncommon feature of the acute encephalitic form of the disease, but the lung can be involved as part of widespread vasculitis. *Ulcers of the larynx* occur in other diseases of feedlot animals, but, like atlanto-occipital arthritis, they are a regular enough feature of *H. somni* infection to serve as a valuable clue to the diagnosis and prompt a search for lesions in the brain. Similarly, *retinal hemorrhages* are grossly visible in a percentage of animals, and are of diagnostic assistance clinically and when gross brain lesions are absent.

A major manifestation of *H. somni* infection in some parts of North America, especially in western Canada, is *myocardial localization* following asymptomatic septicemia. Infarction, myocarditis, or abscess formation may result, and can lead to cardiac failure with or without mural and valvular endocarditis. In many animals, myocardial abscesses are found only when the myocardium of animals with chronic pneumonia or pleuritis is incised. Abscesses are most common in the left ventricular free wall, particularly in the papillary muscles.

Histophilus somni causes sporadic disease involving many other organs, including the ear, mammary gland, and those of the male and female genital tracts. It can also colonize the pregnant uterus and produce fetal disease and abortion (see The female genital system). The reported cases have not involved animals with cerebral localization, and may result from asymptomatic septicemia or transcervical invasion.

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Viral infections of the nervous system

Viral infections of the central nervous system are common, usually as part of systemic infections rather than examples of a specialized affinity for nervous tissue. Several viruses are neurotropic, however only a few are neurovirulent. A neurovirulent virus is a virus that multiplies in neural tissue and is able to induce lesions.

The **routes of invasion** of the nervous system available to viruses are *via nerves*, including the olfactory tracts, and *hematogenous*. Centripetal spread in axons does not depend on viral replication in axons, but passage is provided by the mechanisms of fast axoplasmic transport. Invasion by the olfactory route is theoretically simpler since olfactory receptors extend into and beyond the olfactory epithelium, and a cuff of arachnoid extends through the cribriform plate to the olfactory submucosa. This arrangement would allow viruses to spread along nerves without first penetrating to the submucosa or, having penetrated to the submucosa, to reach the CSF directly. This may be the route taken by *Bovine herpesvirus 1*, *Porcine teschovirus*, and Pseudorabies virus in young pigs. The olfactory route could be used following intranasal exposure or following hematogenous seeding of the olfactory epithelium or mucosa.

For most viruses, spread to the CNS is *hematogenous* after multiplication in some other tissue and the development of viremia of sufficient magnitude and duration. Viruses are susceptible to removal from blood by histiocytes, but viremia can be sustained if the viruses are small, associated with cells of blood, or replicated in endothelium or lymphatic tissues. Some viruses, such as *Canine distemper virus*, infect vascular endothelial cells whereas others infect surrounding glia suggesting transport across endothelium in pinocytotic vesicles. Invasion across the choroid plexus is not impeded by the fenestrated endothelial cells there but would require active infection of the epithelium and ependyma. There are areas of selective permeability to indicator dyes in the brain, such as the tuber cinereum and area postrema, but there is no evidence that these are selectively used by viruses.

The means by which viruses *spread in nervous tissue* are not known. Rapid dissemination can occur in the CSF, but some viruses, such as *Rabies virus*, extend rapidly through the parenchyma. The rate of spread of *Rabies virus*, assuming cell-to-cell growth and transmission, is probably more rapid than its generation time would permit, and permeation of the limited extracellular spaces of the brain by large viruses seems unlikely.

Separation of the specialized cells of the CNS into neurons, oligodendrocytes, astrocytes, and ependymocytes understates the diversity of cell populations in the brain and cord. Different cell populations may show different susceptibilities to infection by different viruses. Thus, Pseudorabies virus is nonselective in the destruction of cells in the rostral cortex of piglets, *Feline panleukopenia virus* selects rapidly proliferating cells of ependyma and cerebellar cortex, and *Porcine teschovirus 1* appears to affect particularly the spinal motor neurons.

Degeneration of neurons, reactivity of the glia, and perivascular reactions are the general hallmarks of viral infection of the CNS, and imply a sequence of viral cytopathogenicity and reaction to cellular degeneration. However, viruses that produce manifestations deviating from this rather simple system are many. *Classical swine fever virus* and *Bluetongue virus* at a suitably early fetal stage of development may produce **malformations** characterized by degeneration of tissue without reaction; later when the animal is immunologically competent, these viruses may produce ordinary encephalomyelitis. *Feline panleukopenia virus* causes cerebellar hypoplasia in the neonate but is without effect at a later stage of development.

Some viruses may produce *persistent tolerated infection* without clinical signs or lesions. At the other end of the spectrum is *Rabies virus*, which can cause death with minimal cytopathic effect and reaction, or no morphological change at all. Some virus infections are characterized by long latency and slow attrition, visna/maedi of sheep being the standard example expressed as either degeneration or chronic inflammation. *Transformation of nervous system cells by viruses* can be demonstrated in vitro, and a variety of tumors of the nervous system can be produced by viruses in experimental animals, but they have, as yet, no natural counterpart. The contribution of an immunological response to both the progress and morphology of encephalomyelitis is very difficult to determine.

General pathology of viral inflammation of the nervous system

Viral infections of the CNS typically induce **nonsuppurative inflammation**, a term that includes quite a variety of quantitative and qualitative changes. The changes are not specific for viral infections, being produced in some bacterial infections such as salmonellosis in swine, in the rickettsial infection, "salmon poisoning," of dogs, and probably in other rickettsioses. Nor are the lesions qualitatively the same in all viral infections, a fact that is of considerable usefulness in differential diagnosis. The differences are due in part to inherent characters of the agents, routes of invasion, patterns of localization, success of viral replication and release, duration and degree of cellular injury, and host defense reactions. As well as the differences, there

are also the very considerable similarities that allow them all to be included with the "nonsuppurative encephalomyelitides."

The distribution of lesions in different viral infections is a reflection of the varied affinities of the viruses, and is useful in differential diagnosis but only generally applicable. The distributions of lesions or of inclusion bodies are only very rough guides to the distribution and activity of the virus.

Perivascular cuffing, or accumulation of cells in the adventitia of vessels and in the perivascular Virchow–Robin space, is almost constant in encephalitis, and, when present, is usually the most striking microscopic change. The accumulated cells are usually leukocytes, but in some diseases there may be very few hematogenous elements recognizable, the cuffs being composed instead of histiocytic cells that appear to have proliferated in situ from adventitial elements. These latter frequently fragment to resemble degenerate neutrophils if the postmortem interval is prolonged. Injury to the vessel wall proper is not constant, but when it occurs it may affect the arteries as a hyalinizing or fibrinoid change. This is characteristic of malignant catarrhal fever, for example, and occurs also in equine encephalitis. The endothelium may be selectively injured in classical swine fever and infectious canine hepatitis. The lesions associated with *Equid herpesvirus* infection may be limited to quite subtle endothelial swelling and proliferation in small blood vessels. When, in inflammation, the perivascular cuffs are large enough to disorganize the wall of the vessel and compress it, the endothelium frequently shows signs of swelling and proliferation, and there may also be altered adhesiveness so that leukocytes and red cells tend to stick to it. Thrombosis is incidental and very seldom observed, but compression of the vessels probably accounts for the ischemic parenchymal softenings that occur.

Infiltrating cells are predominantly lymphocytes, and they accumulate in the perivascular spaces (see Fig. 3.19). The earliest cells in the perivascular spaces may be neutrophils; in acute lesions, some of these can be found wandering in parenchyma or grouped in dense clusters. They soon disappear but may be found later for a short time in areas that soften. Lymphocytes remain in the cuffs and are admixed after a week or so with an increasing number of plasma cells and macrophages. A few eosinophils may also be found in pigs. Perivascular cuffing is not specific for viral infections. It is also a reaction to degeneration of neural tissue.

Glial reactions occur if the parenchyma is injured, even though the injury may not be appreciable, but the reaction may be absent in those infections that selectively involve the vessel walls. In inflamed areas, the oligodendroglia degenerate. Astrocytes degenerate or react depending on how strictly and severely they are injured – the stimuli for astrocytic reaction were discussed earlier in this chapter. *The gliosis that is so frequently a feature of nonsuppurative encephalomyelitis is almost solely microglial. The gliosis may be diffuse or focal but is commonly both* (see Fig. 3.17). Diffuse gliosis may be more apparent than real if due more to hypertrophy than to proliferation of these glia. Focal gliosis may occur anywhere in the parenchyma and may be related to small vessels and injury to microvasculature. When there are more than a dozen or so cells in such foci, some of the cells are likely to be lymphocytes, and occasionally there are a few plasma cells. The microglia in the center of a focus are frequently degenerate. There are two specifically named forms of microgliosis: "*neuronophagic nodules*" are foci of microglia about degenerating neurons (see Fig. 3.2D); "*glial shrubbery*" is an accumulation of these cells in the molecular layer of the cerebellum in relation to degenerating Purkinje cells (Fig. 3.115).

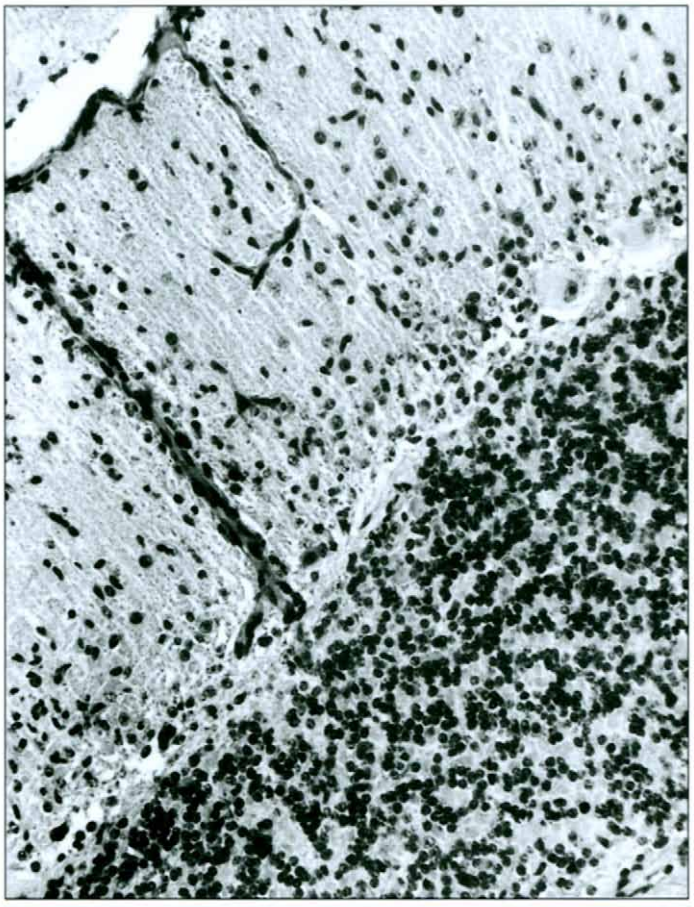

Figure 3.115 Encephalitis in **louping-ill** in a sheep. Destruction of Purkinje cells and gliosis in molecular layer of cerebellum ("glial shrubbery").

Neuronal changes must be the principal determinants of the outcome of the infection. The distribution of neuronal degeneration is to some slight extent specific, but the extensiveness is nonspecific and varies considerably. The morphological features of the degenerate cells are nonspecific. As a rule, the more severe degrees of neuronal degeneration are caused by viruses that are highly neurotropic, such as *Rabies virus*, but the severity of neuronal degeneration is not a dependable "lead" in differential diagnosis. The fact that *Rabies virus* can be lethal without morphological change in the CNS raises the possibility that other viruses may cause severe encephalopathy without inflammatory change. *The usual form of neuronal degeneration is central chromatolysis*, which may extend to completion with the cell then swollen, pale, and devoid of a nucleus. This is typical of the axonal reaction to injury, but the axons are intact. Many neurons appear as if coagulated, being shrunken, rounded, and isolated, and staining darkly with eosin. The nucleus is pyknotic or has disappeared. The coagulated neuron stimulates the formation of the neuronophagic nodule, but not all necrotic neurons elicit the reaction. Usually, intact neurons can be found adjacent to degenerate ones.

Lesions in white matter occur consistently even though many viruses are supposed to be specifically tropic for gray matter. Cuffing reactions are to be expected even if degeneration is limited to adjacent gray matter. *Microgliosis* is focal rather than diffuse and the nodules are small. Some degree of *disintegration of myelin* is inevitable, but conspicuous demyelination is a feature only of canine distemper,

lentivirus leukoencephalitis of goats, and visna. Demyelination associated with viral diseases may be due to direct infection of melanin-forming cells, i.e., oligodendroglia, as in infection with *Canine distemper virus*, or may be a bystander lesion due to injury from inflammatory cytokines associated with viral infection.

Meningitis is seldom severe except in local distributions, and these tend to overlie parenchymal lesions. Some agents, of which typical examples are those of sporadic bovine encephalomyelitis (see Fig. 3.60) and malignant catarrhal fever, have a selective affinity for meningeal structures in the CNS. Others, such as *Canine distemper virus*, share the affinities so that leptomeningitis is part of the primary response. In the more purely neurotropic infections, such as rabies, the meningitis, or more precisely the meningeal infiltration, is due probably to drainage of products of reaction via the Virchow–Robin spaces from the brain or cord. The reacting cells in the meninges are of the same type as those in the brain, and they float freely in the arachnoid spaces.

No virus is known to be tropic for peripheral nerves in the sense of selectively producing direct lesions in them. Degenerative changes occur fairly early in the end plates and terminal parts of axons when the central cell body is destroyed. Foci of microglia and lymphocytes occur in the nerve roots quite commonly. Inflammation of the paravertebral ganglia, and especially the trigeminal (Gasserian) ganglia, is characteristic of rabies and of Teschen disease and related infections in pigs, but the frequency and distribution of this lesion in other viral encephalomyelitides and in other ganglia is unknown.

Inclusion bodies may form in neurons, neuroglia, or microglia and other mesenchymal cells. Inclusion bodies in the nervous system are usually acidophilic. They may be found only in neurons as in rabies, in glia, or in both. They may be cytoplasmic, nuclear, or both. Intranuclear inclusions, which must be distinguished from altered nucleoli, have considerable specificity; somewhat less reliance can be placed on intracytoplasmic inclusions. Cytoplasmic viral inclusions must be distinguished from normal inclusions.

Lyssavirus infections

Rabies is caused by *Rabies virus* (RABV), which belongs to the genus *Lyssavirus* of the family Rhabdoviridae. The RABV glycoprotein (RVG), which is a trimeric and surface-exposed viral coat protein, is responsible for RABV neurotropism by binding to several neural tissue receptors including the neuronal cell adhesion molecule (NCAM), and the p75 neurotrophin receptor (p75NTR). Evolutionary studies based on genes encoding the surface glycoprotein *suggest that RABV evolved first in bats*, possibly in vampire bats much more widely distributed than at present, and only later became adapted to terrestrial carnivores. There is a single major antigenic type with minor variations that allow epidemiological surveillance. *Seven genotypes* are defined by phylogenetic analysis. Type 1 is the classical *Rabies virus* of animals and vampire bats, and of all other bat lyssaviruses in North America. Type 2 (*Lagos bat virus*), type 3 (*Mokola virus*), type 4 (*Duvenhage virus*) are African genotypes. Types 5 (EBLV-1) and 6 (EBLV-2) are *European bat lyssavirus* 1 and 2, and type 7 (Ballina virus) is the *Australian bat lyssavirus*. The seven genotypes may further be allocated into *two major phylogroups* based on pathogenicity for mice and cross-neutralization. Phylogroup 1 includes genotypes 1, 4–7, and phylogroup 2 includes genotypes 2 and 3. Excepting *Mokola virus*, bats may be the preferential vector species for genotypes 2–7.

Rabies virus has two biotypes: "fixed" virus and "street" virus. *Fixed RABV*, which is the basis of vaccine strains, is a laboratory biotype stabilized in its properties by serial intracerebral passage. It is highly neurotropic, is not secreted in saliva, and does not produce Negri bodies. *Street RABV* is the feral biotype that circulates in enzootics and epizootics. In addition to neurotropism, it is tropic for salivary glands, in which it reaches high concentration, and possibly in other mucus-secreting epithelia, and produces Negri bodies.

The establishment of infection ordinarily depends on inoculation of the virus into a wound, such usually being inflicted by the bite of a rabid animal. Contamination of a fresh wound by infected saliva or tissues is much less dangerous. The virus replicates in myocytes around a bite wound for a short period of time, and then buds from the plasma membrane. Viral particles invade the local neuromuscular junction through conjugation of the RVG with the nicotinic acetylcholine receptor, and then invade neurotendinous spindles and ascend to the CNS and paravertebral ganglia via axoplasmic flow. Viral replication in the CNS is followed by centrifugal spread to major exit portals, such as the adrenal gland, nasal mucosa, and salivary glands; the virus is secreted with the saliva for a few days prior to the appearance of clinical signs. The incubation period is variable from weeks to months.

Although there are species differences in susceptibility, rabies is one disease to which *all mammals are susceptible*. The disease can be regarded as one of carnivores because it is almost always transmitted naturally only by bites, and man, herbivores, etc. are dead-end hosts. There are exceptions to the rule that RABV is bite-transmitted: *oral infection* can occur in diverse species and the application of modified RABV in "baits" utilizes this potential; *aerosol infection* can occur, as in dense congregations of colonial bats in bat caves, probably as droplet infection from salivary secretions; and a variety of aberrant circumstances may provide transfer opportunities for infectious virus, as has been reported for *corneal transplants*.

Reservoir hosts vary from time to time and from region to region. The principal reservoir vectors are: foxes and skunks in the USA and Canada, with the raccoon of importance on the Atlantic seaboard; foxes and dogs in northern Canada; foxes moving from east to west in Europe; wolves in eastern Europe and Iran; jackals in India and Northern Africa; the mongoose and genet cat in South Africa; and the mongoose in the Caribbean. *Sylvatic vectors* are responsible for most transmissions to man and domestic animals in countries where dog populations are controlled. Oral vaccination of wild carnivores, by using vaccine-laden baits, and routine vaccination of dogs have led to almost complete elimination of canine-transmitted rabies in developed countries. Rarely, vaccination of severely stressed animals with vaccines containing modified-live virus may induce post-vaccinal rabies. In tropical areas where domestic and feral dogs are not controlled, these animals are the principal hazards for man and livestock.

Bats present a special epidemiologic problem. Fructivorous and insectivorous bats as well as vampires are capable of transmitting RABV. Vampire bats inhabit South and Central America extending into northern Mexico and are, historically, responsible for a high incidence of rabies in mammals, especially cattle but including humans. When clinically affected, vampire bats manifest the disease as the furious form and show unnatural daylight activity.

The **clinical course** of rabies is usually acute, from 1–2 days, but can be as long as 10 days. It is seldom that a clinical diagnosis of rabies can be made with confidence. The terms "*furious rabies*" and "*dumb rabies*" place emphasis on particular features within a spectrum of behavioral changes and are inappropriate for noncarnivorous animals. *Aberrant behavioral patterns* can be recognized in affected animals during epizootics. The period of salivary excretion of virus before the onset of neurological signs is expected to be not more than a few days, vampire bats possibly excepted, and the duration of clinical disease to be a few days only. Once expressed clinically as neurologic disease, *rabies is almost invariably fatal*; recovery with or without neurologic deficit is quite rare but has been observed in several species following experimental exposure. Progressive infection and clinical disease do not inevitably follow exposure; up to 25% of feral populations may have specific antibodies as evidence that the infection provoked an immune response without progression to neurologic disease.

Specific gross lesions are not present at necropsy, but self-inflicted wounds and foreign bodies in the stomach of a carnivore should raise suspicion. The **histologic lesions** of rabies, when present, are *typical of nonsuppurative encephalomyelitis, with ganglioneuritis and parotid adenitis*. Inflammatory changes are usually present, but they may be very mild or absent. To some extent at least, the severity of lesions reflects the duration of the clinical disease. In the CNS, inflammatory and degenerative changes are most severe from the pons to the hypothalamus and in the cervical spinal cord, with relative sparing of the medulla. This relative sparing of the medulla appears to apply to all domestic species. The most severe lesions of the disease are generally found in dogs whereas other species, especially ruminants, which are highly susceptible, may show little more than an occasional vessel with a few cuffing lymphocytes and a few very small glial nodules (*Babès' nodules* in this disease), and this in spite of having numerous Negri bodies. These reactive phenomena probably reflect largely the degree of neuronal degeneration, and this may be remarkably slight in herbivores and remarkably severe in dogs.

The reaction is typically one of *perivascular cuffing and focal gliosis*. The cuffs are 1 to several cells thick and composed solely of lymphocytes (Fig. 3.116A); ring hemorrhages confined largely to the perivascular space are common about cuffed vessels. Hemorrhages are occasionally severe enough to be visible grossly in the spinal cord of horses and cattle (Fig. 3.116B). The Babès' nodules are composed of microglia, and they occur in both white and gray matter. The nodules vary greatly in size, some containing only six or seven cells and

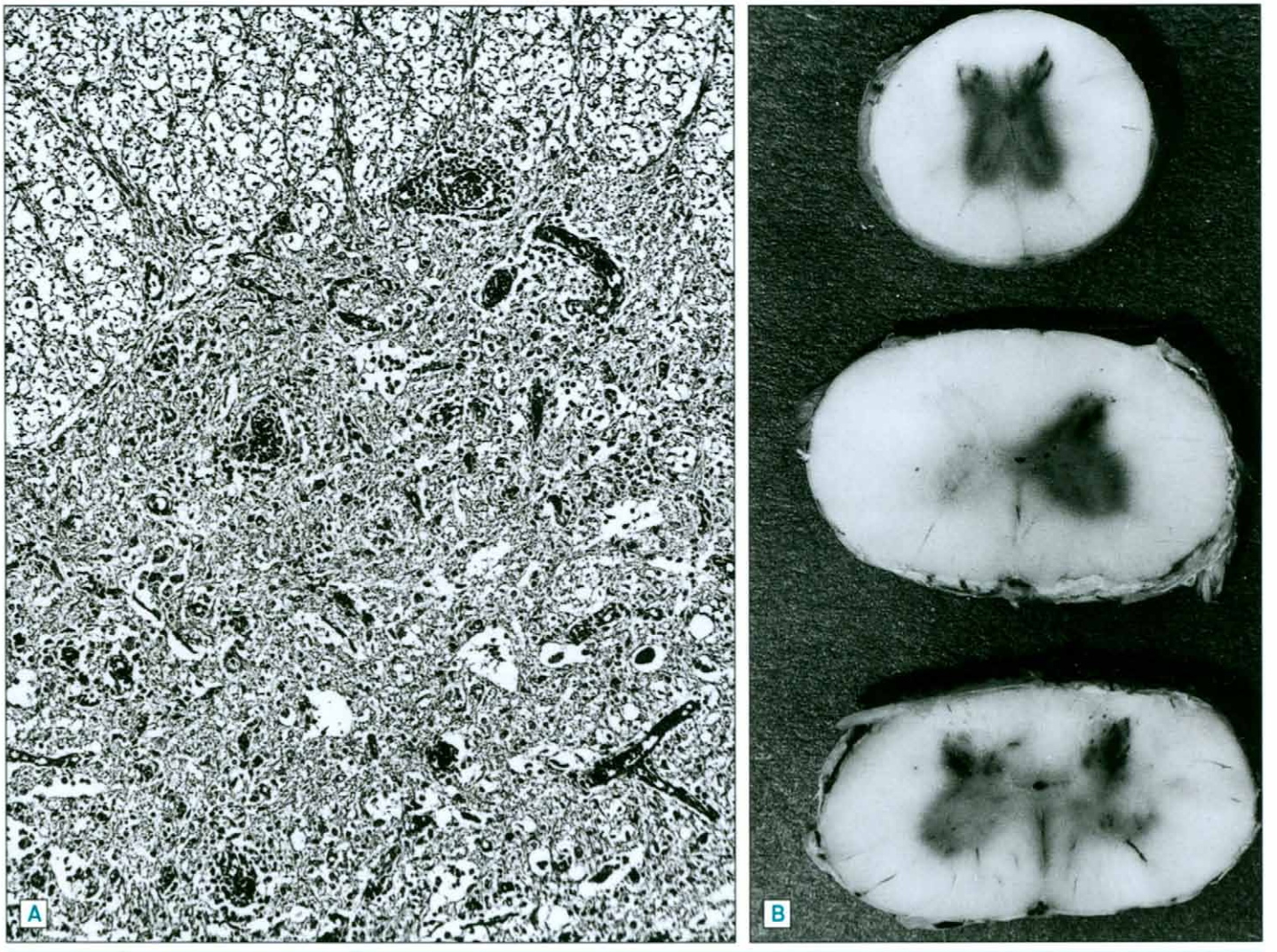

Figure 3.116 Rabies. A. Perivascular cuffs and focal gliosis in a horse. **B.** Hemorrhage in gray matter of spinal cord.

some containing 100 or more. Diffuse as well as focal gliosis occurs in areas of gray matter such as the pons and in the spinal cord, both horns of the latter being involved.

Neuronal degeneration in carnivores may be very extensive and quite out of proportion to the observed reactive changes, but may be very slight in pigs and herbivores. Neuronal and/or gray matter neuropilar vacuolation (*rabies-induced spongiform encephalopathy*) is reported to occur in experimental and natural rabies. The specificity of the neuronal changes and of the whole pathologic picture depends on the *inclusion bodies of Negri*. These are always *intracytoplasmic* and are present most commonly in the hippocampus of carnivores and in the Purkinje cells of herbivores. Fixed RABV does not produce Negri bodies, and street RABV fails to do so in up to 30% of cases. Neurons of any distribution may contain inclusion bodies, but they tend to be scarce where the inflammatory reaction is severe. Indeed Negri bodies may be found only in neurons that are otherwise histologically normal; they are not present in degenerate neurons. They have also been found, but rarely, in ganglion cells of the adrenal medulla, salivary glands, and retina. While the number of Negri bodies has little relation to the length of the incubation period, there is a relation to the duration of the clinical disease. They may not be found if the animal is killed instead of being allowed to die. They are produced consistently in white mice, the usual test animal.

Negri bodies are round or oval structures usually ~2–8 μm in diameter (Fig. 3.117A). They are plastic, their shape being molded to their environment. Those in the dendrites, seldom observed except in Purkinje cells, are oval and those in the cell body are usually rounded. There may be one or more per cell, and affected cells are otherwise only little changed. The inclusions are surrounded by a clear thin halo. Nonspecific homogeneous inclusions may be found in the pyramidal cells of the hippocampus in cats, skunks, and dogs. There may be several such inclusions per cell but each is minute, not measuring more than 1.5 μm. In old sheep and cattle, larger neurons, especially of the medulla and cord, may contain nonspecific inclusions. These have a dust-like distribution, are usually numerous, and are brightly acidophilic, angulated, and ~1.0 μm in size. Nonspecific inclusions that are indistinguishable from Negri bodies by light microscopy occur in the lateral geniculate neurons in cats. *Fluorescent antibody techniques are required for positive identification* and are essential in the rare chronic cases which may not yield virus on mouse inoculation.

If there is no *ganglioneuritis* in the paravertebral ganglia, then the possibility of the animal having rabies is very remote. If there is ganglioneuritis, it may be part of rabies or something else. Pigs, for example, get ganglioneuritis in the Teschen group of infections. Inflammatory changes in the trigeminal (Gasserian) ganglion in rabies may be present without inflammatory or neuronal changes being clearly evident in the brain. The ganglionic changes are of the same character as those in the brain, namely acute degeneration of ganglion cells, proliferation of capsule cells, and microglial nodules (Fig. 3.117B).

The natural transmission of RABV depends on virus being present in the saliva and, therefore, in the salivary glands. Fixed virus

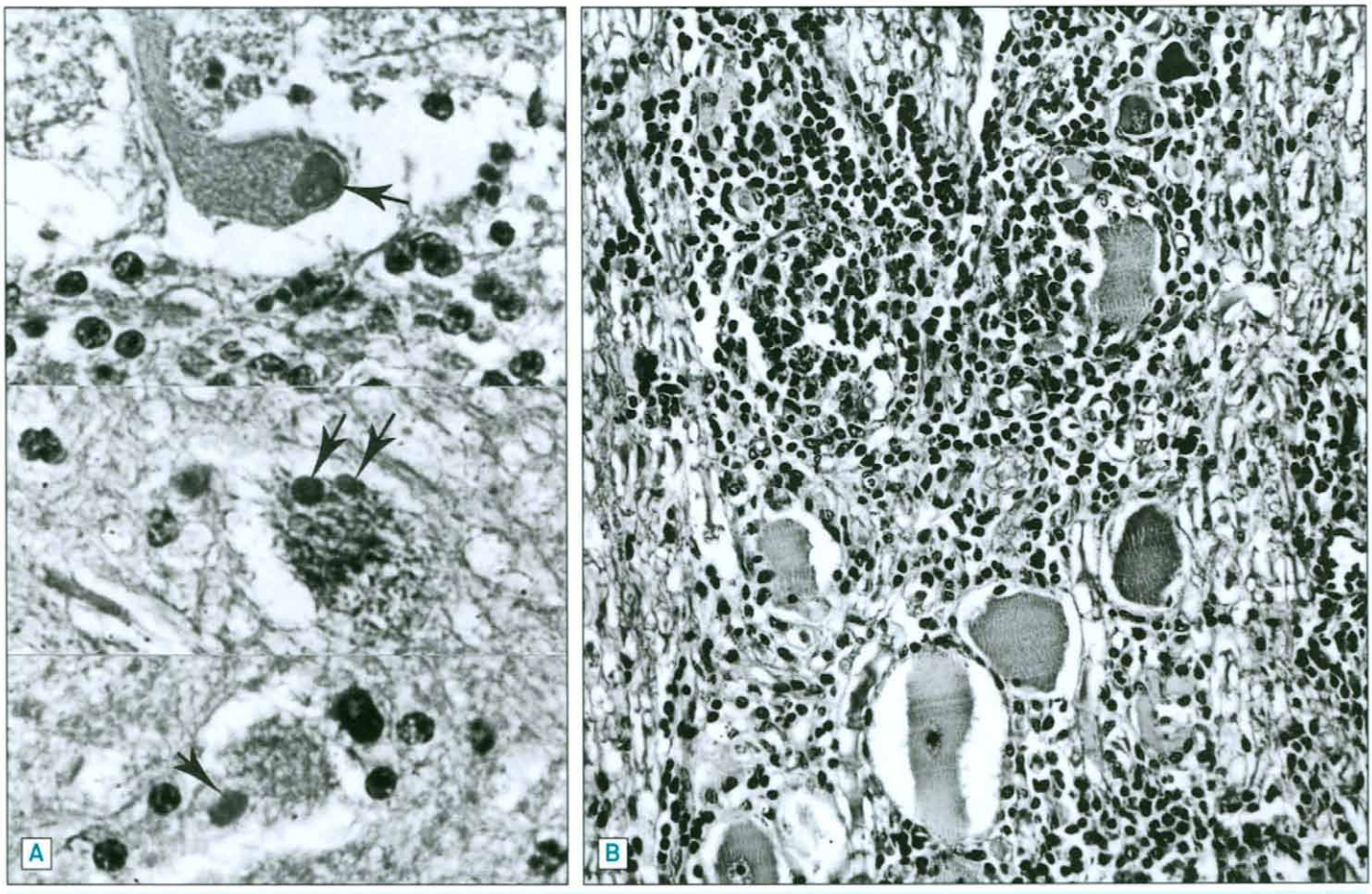

Figure 3.117 Rabies. A. Composite picture showing Negri bodies (arrows) in neuronal cytoplasm. **B.** Severe nonsuppurative inflammation of trigeminal ganglion.

has no affinity for the salivary glands, and none is present in some cases of infection with the street virus. Degenerative changes are reported in the epithelium of the mandibular salivary gland, but not in the parotid, in dogs.

The **diagnosis** of rabies is made by utilizing fluorescent antibody labeling on fresh or fixed tissue, or by virus isolation in cell culture.

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Pseudorabies

Pseudorabies is also known as Aujeszky's disease, mad itch, infectious bulbar paralysis, and porcine herpesvirus infection. The causative agent, ***Suid herpesvirus 1*** (SuHV-1; Pseudorabies virus, PRV), belongs to the genus *Varicellovirus*, subfamily Alphaherpesvirinae, family Herpesviridae, but is unusual for a member of that group in its relative lack of host specificity and by being spread laterally as well as vertically in swine. A number of strains have been identified which exhibit a wide range of virulence. Pseudorabies virus is capable, as are other members of the family Herpesviridae, of establishing latent infection. Trigeminal ganglion, olfactory bulb, and tonsil are the most consistent sites of latency of PRV. In these organs, viral DNA can be detected in the absence of infectious virus. The pig is the only natural host, but the common domestic species are naturally susceptible; there are very few reports in horses and goats. Progressive infections do not occur in humans. The disease is reported worldwide, except for Canada and Australia. Natural infections occur in rats and mice and various species of wildlife and on fur farms. Of the laboratory animals, the rabbit is the most susceptible and is preferred for identification of the virus because of the fairly consistent development of intense local pruritus following subcutaneous inoculation. Guinea pigs are less susceptible and may resist subcutaneous inoculation but succumb to intracerebral and, occasionally, to intraperitoneal inoculation.

The virus is maintained in enzootic areas in wild and domestic swine, for which it is highly contagious but usually asymptomatic, and probably in brown rats. *Transmission* can occur by ingestion, but the usual method of spread between pigs is thought to be by contact of infective secretions with nasal mucosa or abraded skin. Animals are susceptible to intranasal inoculation and, regardless of the route of infection, the *virus can be found in nasal secretions*. The virus may also be present in saliva and urine. It is also present in blood, but this is of no significance for epidemiology or transmission. The infection will occur in pigs by contact very readily and probably by direct nose-to-nose transmission, but it does not appear to be contagious between individuals of other species and they probably acquire their infection by contact with swine or, possibly, rats. Pigs may harbor virus for many months in tonsils and nasopharyngeal secretions after exposure, but in other domestic species the virus is fairly strictly neurotropic, and therefore is not excreted unless given experimentally in large doses. Ingestion of *infected pig meat* is the usual source of infection for dogs and cats. Cattle and sheep may become infected by direct contact with carrier swine or by aerosol exposure, but there is strong circumstantial evidence implicating contaminated feed.

The *pathogenesis* of the infection following local inoculation is well established for the rabbit and is probably comparable in other species. The virus causes a local reaction at the site of inoculation if percutaneous and then spreads centripetally along the related nerve to the spinal cord; it then spreads outwards again along other peripheral nerves as other segments of cord are progressively invaded by spread within the CNS. Because of the progressive advance of infection along the cord, death may occur before demonstrable amounts of virus reach the brain and before lesions have time to develop there. Intracerebral inoculation produces encephalitis, and virus spreads to the cord and centrifugally along peripheral nerves to an extent that depends on survival time. Because the virus also circulates in the blood, there is some possibility but no evidence that it invades the brain directly, the evidence instead suggesting that it localizes in viscera and invades the nervous system along autonomic nerves. Following nasal or intraocular exposure, the virus spreads along the related nerves. The route of invasion following ingestion is by retrograde transneuronal infection. Transplacental infections occur in pigs causing abortion in about 50% of sows pregnant in the first month, and the delivery of macerated, mummified, and normal fetuses when infection occurs at later stages of gestation. The virus is reported to be present in the semen of carrier boars.

The *signs and course* of pseudorabies in pigs are very variable. Most cases are of mild febrile illness without pruritus or nervous signs, and with recovery expected in a week or so. Sows may subsequently produce mummified litters. Age is a very important factor governing the severity of the disease in swine; the mortality rate in nursing pigs and young weaners may be very high. Very young sucklings do not show specific nervous signs but rapidly become prostrate and die in 12–24 hours. In slightly older piglets, incoordination progresses rapidly to paralysis with muscular twitchings, tremors, and convulsions. Some pigs showing severe signs of encephalitis recover. Experimental peripheral inoculation will produce asymptomatic meningitis and encephalitis in swine, the inflammatory lesions being severe. The disease in older pigs is often characterized by fever, rhinitis, and coughing. There may be generalized pruritus in natural cases but it is not severe, being expressed usually by rubbing of the nose or head. Fetal resorption, mummification, stillbirths, and abortions are frequently reported.

The characteristic clinical sign of pseudorabies in animals other than pigs is *intense cutaneous irritation* developing at the point of inoculation or at the terminal distribution of a nerve trunk which passes the point of inoculation. This does not occur until the virus reaches the related segment of cord. Dogs may become frenzied, and besides the intense pruritus (mad itch) there may be jaw paralysis and drooling reminiscent of rabies. The clinical course in these species, which always ends in death, is frequently acute (a few hours) and never longer than 1 week. Pseudorabies may occur in sporadic, although significant, outbreaks in sheep and cattle. The mortality rate is very high. Death may occur without signs of illness or within 1–2 days of the onset of clinical signs. There is fever, and the itching may be on any part of the body but is most frequently about the head or hindlimbs. Other neurological signs are variable but constantly present.

There are *no specific gross lesions* of pseudorabies. At the site of cutaneous infection, there is acute serofibrinous inflammation, ballooning degeneration, and epithelial necrosis with rare intranuclear inclusions. Self-trauma due to intense itching may exacerbate these lesions. The intense pruritus at the site of inoculation is likely due to stimulation of regional sensory nerves by viral spread and multiplication. Gross changes are seen mostly in young pigs. There may be necrosis of tonsils and sometimes of the trachea and esophagus. Rhinitis with patchy epithelial necrosis is common. The lungs may be edematous. Tiny foci (1–2 mm) of hemorrhagic necrosis typical of alpha-herpesviral infection may be seen in liver, spleen, lung, intestines, adrenals, and placenta.

The **histologic lesions** reflect the neurotropic and epitheliotropic nature of the virus. Lesions are similar in all susceptible species, however, epitheliotropic lesions are more commonly seen in young, aborted, or stillbirth piglets and rarely seen in ruminants or carnivores, where the brain lesions are more common. In brain, the gray matter especially is affected, but death may occur before there are clear indications of neuronal degeneration or inflammatory reaction in the brain. With naturally acquired infections, the inflammatory changes are *nonsuppurative*. In addition, focal gliosis and lesions typical of neuronal degeneration (neuronophagia and satellitosis) are usually present (Fig. 3.118A, B). There is severe ganglioneuritis in paravertebral ganglia. The specificity of the reaction in the brain depends on the development of *acidophilic intranuclear inclusion bodies in neurons and astroglia* (Fig. 3.118C). These inclusion bodies occur in all species, including pigs; fixation in a mercurial fixative is helpful for their demonstration. Inclusions in swine are *solid and amphophilic*, but in other species the inclusions are granular and often small and multiple in an affected nucleus. By any route of infection, piglets tend to develop panencephalitis with most severe lesions in the cerebral cortex, brain stem, spinal ganglia, and basal ganglia of the brain (Fig. 3.118B); in other domestic species, the distribution of lesions in the CNS is local to, and determined by, the route of exposure. Lymphoplasmacytic inflammation with neuronal degeneration of the gastric myenteric plexi is also described.

Epitheliotropic lesions include the presence of tiny areas of coagulative or lytic necrosis in the liver, tonsils, lung, spleen, placenta, and adrenals with the presence of the characteristic intranuclear inclusions. Pulmonary lesions may be mild or severe. Edema and mild cellular infiltration may be diffuse and there may be focal or confluent necrotizing, hemorrhagic pneumonia (Fig. 3.118D). Hemorrhage and necrosis is present in lymph nodes, and foci of necrosis may be found in tonsils, liver, spleen, and adrenal. Necrotizing vasculitis is described in natural infections in sheep and experimentally in piglets. In aborted or stillborn piglets, which are suitable for examination, there is usually no evidence of encephalitis, but foci of necrosis may be found in liver and other parenchymatous tissues together with focal bronchiolar necrosis and interstitial pneumonia.

Rapid **diagnosis** can be achieved by fluorescent antibody tests on frozen sections of tissue, e.g., tonsils, liver, or brain. Isolation in eggs or tissue culture is also available.

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Porcine hemagglutinating encephalomyelitis virus

Porcine hemagglutinating encephalomyelitis virus (HEV), a member of genus *Coronavirus*, family Coronaviridae, can be isolated from the respiratory tract of normal pigs, and is present worldwide. Other porcine coronaviruses include *Transmissible gastroenteritis virus*, *Porcine epidemic diarrhea virus*, and *Porcine respiratory coronavirus*. HEV is a group 2 species coronavirus antigenically related to *Bovine coronavirus, Human coronavirus OC43*, and *Murine hepatitis virus*. The pig is the only natural host for HEV. Although there is serological evidence of wide distribution in many swine-raising areas, clinical disease is rare because most piglets receive protective levels of colostral antibodies to HEV. Disease occurs in piglets 1–3 weeks of age and follows a clinical course of about 3 days to 3 weeks. The mortality rate is very high and survivors are usually unthrifty.

Following exposure, replication of virus occurs in the epithelium of nose, tonsil, lung, and small intestine, with spread to the CNS along peripheral nerves rather than hematogenously; viremia is not important in the pathogenesis. Viral antigen is detectable in alimentary ganglia during the incubation period of the disease. It is first demonstrable in the brain in trigeminal and vagal sensory nuclei, with later rostral spread in brain stem. Viral replication occurs in the myenteric plexus of the stomach, and involvement of the autonomic system probably can explain the predominant clinical signs of vomition and constipation.

Two *clinical syndromes* are recognized. Neurologic signs occur in 4–7-day-old piglets in some outbreaks and consist of stilted gait, hyperesthesia, progressive paresis, and convulsions in some cases. Clinical signs in 4–14-day-old piglets are dominated by anorexia and vomiting, and this syndrome is called "*vomiting and wasting disease*."

Lesions in the CNS may be found in some affected piglets that do not show clinical signs of nervous disease. The frequency with which inflammatory change is found is quite variable. Lesions when present are those of *nonsuppurative encephalomyelitis* affecting particularly the gray matter of medulla and brain stem. In such cases

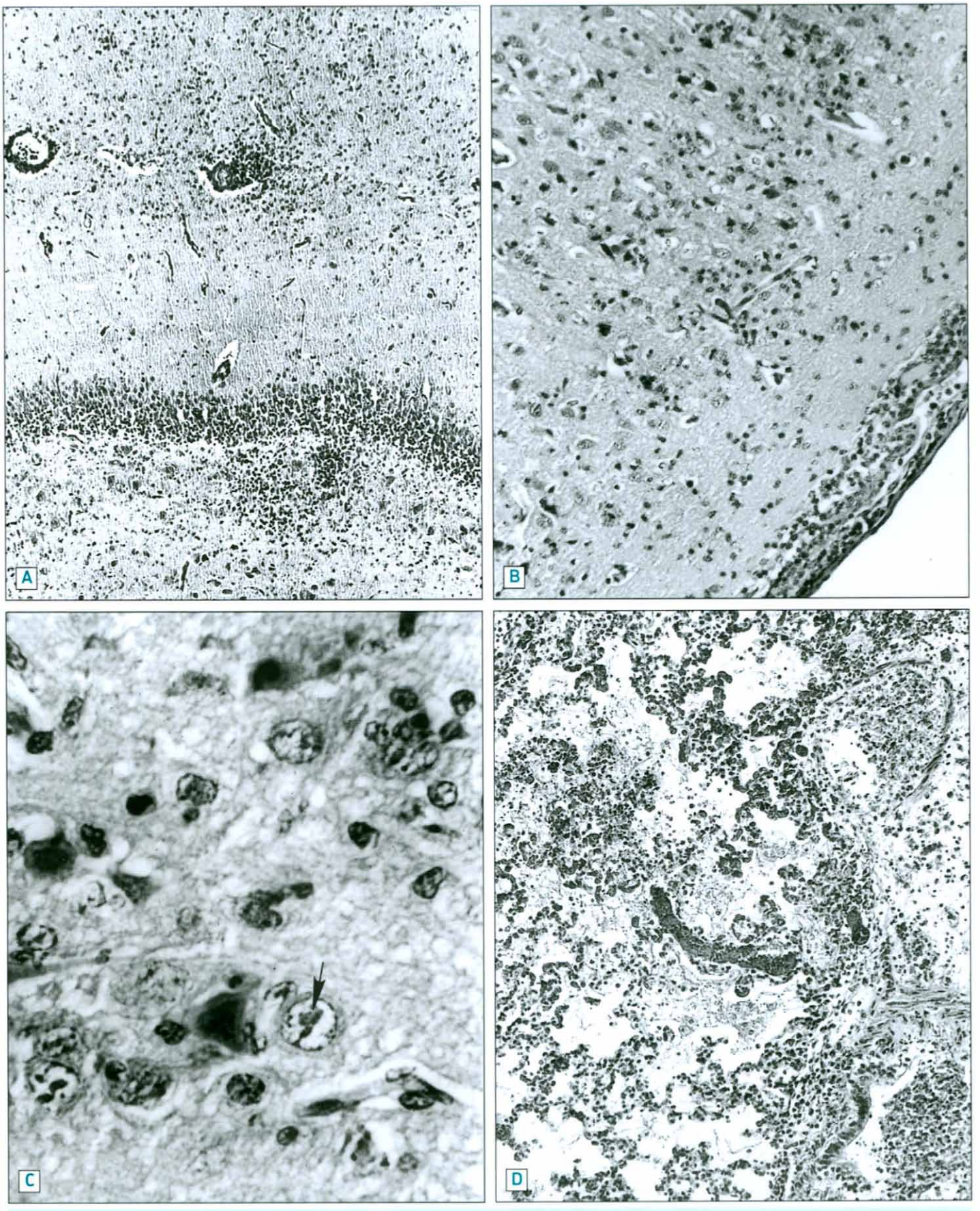

Figure 3.118 Pseudorabies in a pig. **A.** Perivascular cuffing, focal and diffuse gliosis in dentate gyrus. **B.** Meningitis and necrosis of cells in cerebrum. **C.** Neuronal necrosis and irregular inclusion bodies in nuclei (arrow). **D.** Necrotizing bronchopneumonia.

there is inflammation of the trigeminal, paravertebral, and autonomic ganglia. The gastric myenteric plexi are occasionally infiltrated with a few lymphocytes and plasma cells.

Diagnosis of HEV is problematic. Serology on acute and convalescent sera may help in detecting acute infection. Isolation of HEV can be attempted from brain stem of acutely ill piglets. Differential diagnoses of nervous conditions with high mortality in piglets include pseudorabies, classical swine fever, polioencephalomyelitis (Teschen disease), bacterial meningitis, streptococcal septicemia, and hypoglycemia.

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Enterovirus/teschovirus polioencephalomyelitis of pigs

Encephalomyelitis of pigs caused by porcine enteroviruses occurs in many countries and is distinguishable only by a study of the agents. Porcine enteroviruses are ubiquitous but are limited in their pathogenicity to swine. ***Porcine enterovirus*** *A* (PEV-A, formerly PEV serotype 8) and *Porcine enterovirus B* (formerly serotypes 9, 10) are in the genus *Enterovirus*, family Picornaviridae. Porcine enteroviruses serotypes 1–7 and 11–13 have been reclassified as ***Porcine teschovirus*** *1–7, 11–13*, genus *Teschovirus*, family Picornaviridae. Further reclassifications of picornaviruses can be expected. Infection by one enterovirus/teschovirus serotype does not confer protection against infection by another.

Infection is most commonly acquired by pigs after weaning due to waning maternal immunity and mixing of pigs from different sources. Infection follows the fecal–oral route and indirectly through contaminated fomites. Initial replication occurs in the tonsils and the intestinal epithelium, especially of ileum and colon; the enteric phase is not clinically significant or accompanied by tissue change. The enteric phase is followed by viremia and then invasion of the CNS. Viremia by some serotypes may lead to localization in the pregnant uterus and death of fetuses.

Infection with virulent virus may produce nervous signs as soon as 6 days after exposure. The virus is present in large amounts in tonsils and cervical lymph nodes by 24 hours, and in the mesenteric nodes and feces by 48 hours. The disease has two clinical forms: the highly fatal and severe form (**Teschen disease**) and a less virulent milder form (**Talfan disease**, poliomyelitis suum, benign enzootic paresis, Ontario encephalomyelitis, and polioencephalomyelitis.). Teschen disease, first recognized in 1929 in Teschen, Czech Republic, is caused by highly virulent ***Porcine teschovirus 1*** and is limited mostly to Europe, but sporadic epizootics occur in Africa. Talfan disease, caused by infection with less virulent strains of the virus, is more common than Teschen disease and occurs worldwide. Teschen disease is of high morbidity and high mortality affecting all age groups and expressed clinically as convulsions, opisthotonos, nystagmus and coma. Death commonly occurs in 3–4 days. Survivors may have residual paralysis. Talfan disease is characterized by lower morbidity and mortality, and the clinical signs are expressed as paresis and ataxia that seldom progresses to complete paralysis. The infection is asymptomatic in the absence of neurological signs, and up to 95% of exposed pigs develop latent or inapparent infections.

The *pathological changes* in these syndromes are the same although minor differences in severity and distribution of the lesions are reported. There are no gross changes. The histological changes are those of *nonsuppurative polioencephalomyelitis* extending throughout the cerebrospinal axis from the olfactory bulbs to the lumbar cord. Any series of cases of each of the syndromes provides a continuous spectrum of severity and distribution of the lesions. Lymphocytic meningitis is mild in the cerebral meninges and usually overlies areas of parenchymal injury in the cerebrum. In weaners and older animals in which the course is more prolonged than in very young pigs, intense lymphocytic meningitis develops over the cerebellum, usually in conjunction with inflammatory lesions in the underlying molecular layer (Fig. 3.119). Cerebellar meningitis is very slight if the course of the disease is 4–5 days or less, so that, although emphasized in reports of Teschen disease, it is not a feature in very young animals in which the course is short. The most severe lesions occur in the brain stem from the hypothalamus through the medulla and

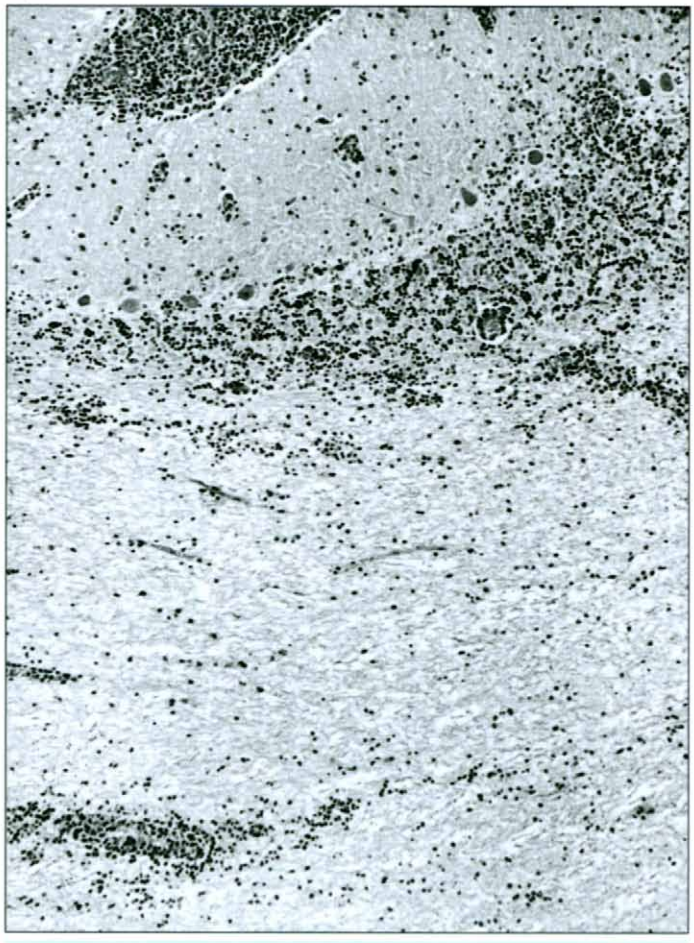

Figure 3.119 Nonsuppurative meningitis and encephalitis (cerebellum) in **enteroviral encephalomyelitis** in a pig.

decrease in intensity and diffuseness down the spinal cord. There is relative sparing of the cerebral and cerebellar cortices, but the deep substance of the cerebellum is consistently and often severely involved. Lesions in the spinal cord in each syndrome are largely confined to the gray matter, particularly the ventral horns, but may selectively involve the dorsal horns in very young pigs. Cord lesions are those of nonsuppurative myelitis and the motor neurons, particularly in gray matter of the ventral horns, experience different stages of neuronal degenerative and necrotic changes (neuronal swelling, chromatolysis, satellitosis, and finally neuronophagia). Lesions are consistently present in the dorsal root ganglia, and especially the trigeminal ganglia (Fig. 3.120).

Diagnosis can be achieved by virus isolation or immunohistochemistry.

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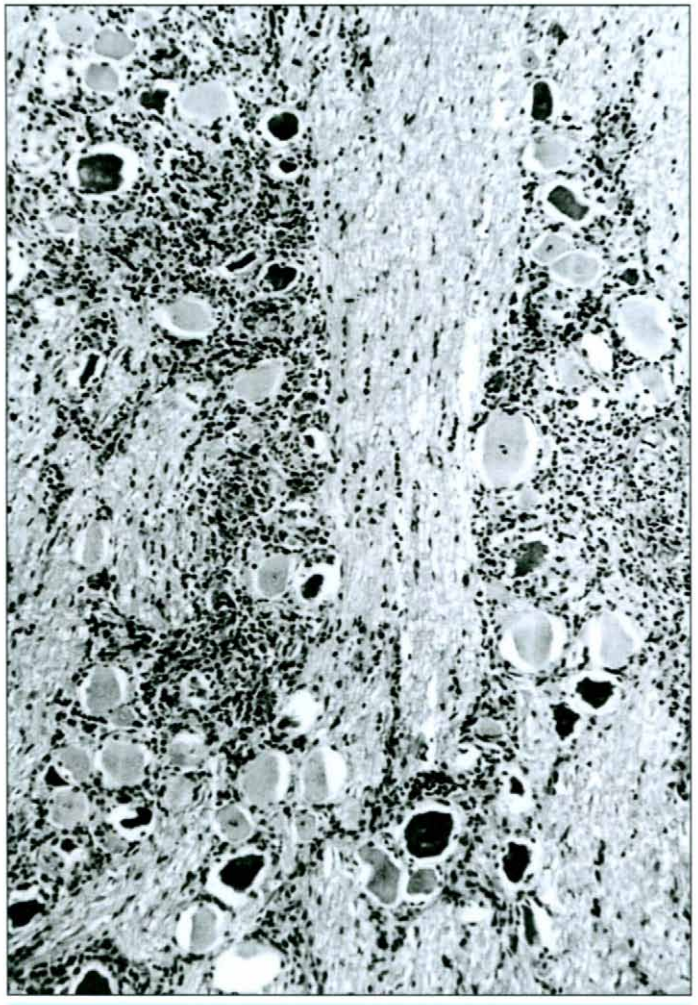

Figure 3.120 Ganglioneuritis in enteroviral encephalomyelitis in a pig.

Flaviviral encephalitides

The genus *Flavivirus* of the family Flaviviridae contains several important viruses that cause encephalitis in domestic and wild animals. Some of these viruses are emerging as very important not only for animal health but also for public health as they are highly zoonotic. The viruses of veterinary importance in this genus belong either to the *tick-borne virus group* or the *mosquito-borne virus group*. Viruses of both groups are maintained in a cycle involving ticks or mosquitoes respectively as invertebrate vectors, and wild vertebrate hosts as reservoirs. In most cases, infections of humans and/or domestic animals are incidental, and are not important for viral transmission or maintenance in the environment.

Diseases caused by tick-borne flaviviruses

Important veterinary viruses in this group include *Louping ill virus* and *Tick-borne encephalitis virus*; these two viruses are very closely related, and may have originated from a common ancestor. The group also includes several other viruses – *Langat virus, Kyasanur Forest disease virus*, *Omsk hemorrhagic fever virus*, and *Powassan virus* (POWV) – that are primarily of importance in humans. POWV causes severe encephalitis in humans in the USA, Canada, and Siberia, but induces encephalitis in animals only under experimental conditions.

Louping ill (ovine encephalomyelitis)

Louping ill is a tick-borne viral encephalomyelitis of sheep caused by *Louping ill virus* (LIV), which has been enzootic in England, Scotland, and Northern Ireland for more than a century and has been reported in Norway. The disease is named after the leaping (or louping) demonstrated by the diseased sheep. A similar disease has been reported in Spain, Greece, and Turkey affecting sheep or goats but because the etiologic viruses are different by nucleotide sequencing from LIV, each was considered a subtype of LIV but assigned different names: *Spanish sheep encephalomyelitis virus*, *Greek goat encephalomyelitis virus*, and *Turkish sheep encephalomyelitis virus*. Cattle, horses, goats, and deer pastured with affected sheep sometimes contract the disease, and nonfatal human infections are known. The virus causes fatal encephalomyelitis in red grouse (*Lagopus scoticus*). Outbreaks in piglets have followed the feeding of raw meat from lambs, and a case has been described in a dog.

The tick responsible for transmission in Great Britain is *Ixodes ricinus*, the castor-bean tick. Other species of *Ixodes*, and perhaps other arthropods, are potential vectors. *Ixodes ricinus* is parasitic on a variety of mammals in addition to sheep and on birds, however, the most

significant wildlife host is the red grouse. Larval and nymphal ticks acquire the virus when feeding on infected sheep, and transmit the infection to new hosts in the succeeding nymphal and adult phases. Because of its natural mode of transmission, louping ill is most prevalent in early summer and early autumn when the ticks are active. After infection, the virus propagates in regional lymph nodes, proceeds to viremia, and then enters the CNS via the hematogenous route. Alternatively, the virus may localize indirectly from the blood in nasal structures and enter the brain via the olfactory nerves. Under experimental conditions, a number of factors may facilitate entry of virus into the brain, and facilitation is apparently given in natural cases by concurrent tick-borne fever, a rickettsiosis also transmitted by *I. ricinus*, and known to impair humoral and cellular defense mechanisms.

Although tick transmission is the usual mode of infection, the disease can be contracted in humans, monkeys, and mice by inhalation of infective droplets, but this route is not thought to be important naturally. Rabbits and guinea pigs are not susceptible even by intracerebral inoculation.

Louping ill is a systemic infection and, while it remains so, the disease is mildly febrile but otherwise of no consequence. When it invades the CNS and produces signs of encephalitis, the mortality rate is very high. The morbidity in endemic areas is quite low, and the disease is largely confined to either naïve lambs or to older lambs and yearlings whose colostral immunity is not reinforced by natural exposure. The viremic phase of louping ill is clinically silent or a febrile phase with dullness. Recovery may occur in a couple of days and leave solid immunity. If neurologic signs are to develop, they do so at about day 5 and are characterized by incoordination, tremors, cerebellar ataxia, and terminal paralysis.

There are no gross lesions. The disease is an *acute polioencephalomyelitis*. There is mild leptomeningitis corresponding to areas of inflammation of the parenchyma. Inflammation of the cerebellar leptomeninges may be quite severe when the cerebellar cortex is acutely affected (Fig. 3.115). The inflammatory lesions are more obvious than in most viral encephalitides, but are of the usual type, although unusually large numbers of neutrophils may be present in very severe cases, and largely restricted to gray matter, although cuffing and focal gliosis occur in the white matter. Neuronal degeneration may be severe and neuronophagia prominent. Some degree of selective vulnerability of the Purkinje and Golgi cells of the cerebellum is generally accepted and, although it can be demonstrated in many cases, its detection probably depends to a large extent on the duration of active infection. The spinal lesion is poliomyelitis affecting particularly the ventral horns (see Fig. 3.17). Inclusion bodies have not been observed in sheep but acidophilic, intracytoplasmic inclusions in neurons of the brain stem and cord are reported in experimentally affected monkeys and mice. Immunohistochemistry is available, and viral antigen can be identified easily, especially in the Purkinje cells of the cerebellum and their dendritic processes.

Encephalitis caused by *Tick-borne encephalitis virus*

Tick-borne encephalitis virus (TBEV) is a serious human threat that causes thousands of cases of encephalitis every year in endemic areas in Europe and Asia. Several wild and domestic animals are susceptible to infection but the infection is frequently subclinical, however TBEV is pathogenic for dogs and is able to cause fatal meningoencephalitis. The virus is transmitted to humans and animals mainly by *Ixodes ricinus* or *Ixodes persulcatus*. Humans can also become infected through consumption of milk from infected ruminants. Most infected dogs seroconvert without developing TBE, but the peracute disease in dogs has a high fatality rate. Affected dogs are usually euthanized due to associated severe convulsions, tremors, and ataxia. The histologic lesions are those of severe necrotizing lymphoplasmacytic and histiocytic meningoencephalomyelitis with severe glial nodule formation affecting mostly the basal ganglia, thalamus, mesencephalon, neuroparenchyma surrounding the fourth ventricle, and the medulla oblongata.

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Diseases caused by mosquito-borne viruses

The important veterinary viruses in this group include *West Nile virus* and *Japanese encephalitis virus*. Also included in the mosquito-borne, Japanese encephalitis virus group, are *Murray Valley encephalitis virus* and *St. Louis encephalitis virus*.

West Nile virus encephalomyelitis

West Nile virus (WNV) was first discovered in 1937 in the West Nile district of Uganda. In 1999 it was introduced into New York City where it caused a massive outbreak in animals and humans. During the period of 1999 to 2004, the virus spread rapidly to most of the USA and southern parts of Canada. It has been suggested that the virus was imported from the Middle East, due to genetic similarity between strains isolated in the Middle East and New York. The virus is now distributed throughout Africa, central and southern Asia, Australia (where it is called *Kunjin virus*), the USA, Canada, Mexico, and the Caribbean. The virus is divided genetically into two lineages – lineage 1 WNV is present in North America and some other parts of the world, lineage 2 is restricted to enzootic areas in Africa. Lineage 2 WNV strains are either nonpathogenic or occasionally cause mild human and equine disease. Some clades in lineage 1 (e.g., clade 1a) are highly virulent and are believed to be responsible for the recent outbreaks in North America. The virus has a wide host range, but is maintained in the environment mainly by a bird–mosquito–bird cycle. Wild birds, especially corvids, i.e., crows, are the main amplifying hosts. Wild birds usually develop prolonged viremia and the virus is distributed in almost every organ. In contrast, the viral antigen in infected horses, which is by far the most susceptible species of domestic animal, is sparse and limited to the CNS. Infection between birds or between birds and mammals or reptiles is mainly via mosquitoes. Mosquitoes of the *Culex* spp. are the main maintenance vectors. The virus is also found in other vectors such as ticks, but the biological importance of these vectors is

yet to be determined. Rare methods of virus transmission include direct contact with infected materials and ingestion. Transplacental WNV transmission is only reported in human.

The *pathogenesis* of the encephalitis induced by WNV is not completely understood, however after the virus is injected by an infected mosquito, it probably propagates in regional endothelial cells and fibroblasts, viremia develops, and the virus reaches the brain hematogenously.

Equids, especially horses, are very susceptible to the infection. In naive areas, the first signs of WNV are the marked increase in cases of equine encephalitis and increased numbers of wild bird, especially corvid, mortalities. WN fever is a seasonal disease, related to the time of the year of mosquito activity, i.e., summer and fall. When naive horses are infected by the virus, mortality can reach up to 50% of affected horses, and clinical signs range from weakness and anorexia to severe acute ataxia or recumbency. However, the mortality rate decreases dramatically in the following seasons. Gross lesions are usually absent, but a few cases may have acute areas of hemorrhage or malacia affecting the thoracic and/or lumbar spinal cord. *Histologic lesions* are present mainly in the brain stem and thoracolumbar spinal cord, and to a lesser extent in cerebral cortex and cervical cord. The cerebellum is usually spared. *Lesions are those of nonsuppurative encephalomyelitis, gliosis, and glial nodule formation with occasional neuronal degeneration and necrosis* (Fig. 3.121A, B). Lesions are more pronounced in the gray matter. The glial nodules usually contain a few neutrophils amid the glial cells. Areas of hemorrhage and malacia are present in severe cases, especially in brain stem and the ventral horn of the thoracic and lumbar spinal cord. Axonal swelling and spheroid formation is frequent. The severity of lesions is greatly variable between outbreaks, and frequently the severity of clinical signs is not correlated with the severity of lesions. In most cases, the lesions are mild and confined to thin cuffs of a few blood vessels in the brain stem. Extraneural lesions, e.g., hepatitis, myocarditis, etc., which occur in avian WNV infection, do not occur in equine WNV infection.

The information about clinical signs and lesions in non-equine domestic species other than birds is very limited. Ruminants, canids, felids, and swine are far less susceptible to the disease than are horses or birds. These species are susceptible to the infection and develop very short viremia with subclinical disease; histologic lesions are very similar to those described in horses.

Diagnosis of WNV infection can be achieved by detection of WNV antigen in the brain using PCR or immunohistochemistry. WNV antigen in many cases can be very sparse, which makes the interpretation of IHC difficult. Positive IHC staining in most cases is limited to sparse axonal immunostaining.

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Japanese encephalitis

Japanese encephalitis virus (JEV) is found through much of eastern, southern, and southeastern Asia, Papua New Guinea, and the Torres Strait of Northern Australia, where the disease is endemic with dramatic annual epidemics. In humans, there is a high ratio of subclinical to overt infections, with a case fatality rate of 10–15% and a high incidence of residual neurologic deficits in survivors. Transplacental infection followed by abortion occurs in humans and this is also the most serious expression of the disease in *pigs, the domestic species most importantly infected*.

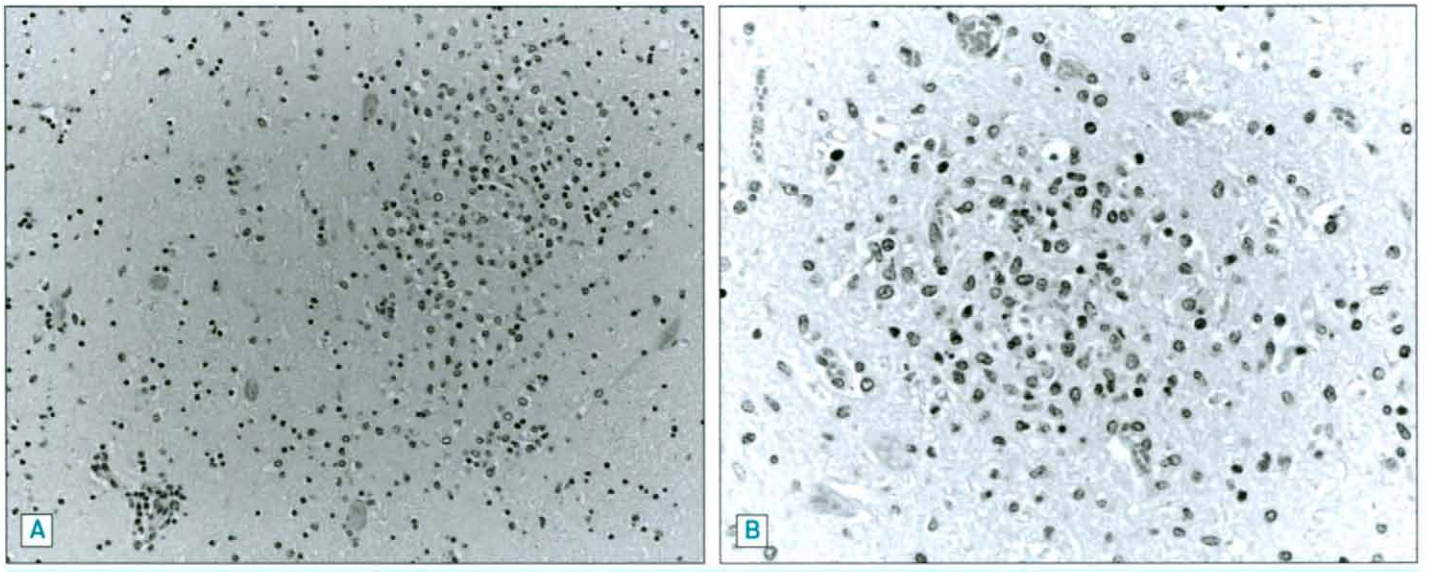

Figure 3.121 Brain stem of a horse with **West Nile viral encephalomyelitis. A.** Perivascular cuffs composed of lymphocytes and plasma cells are usually thin. **B.** Multifocal glial nodules are common and usually contain only a few neutrophils. (Courtesy of MJ Hazlett.)

The virus is maintained through mosquito–bird or mosquito–pig cycles. The virus is transmitted mainly by the mosquito, *Culex tritaeniorhynchus*, but other species of this genus and of the genera *Aedes* and *Armigeres* may be important as the virus is known to be vertically transmitted through some of them. *Ardeid water birds (e.g., herons and egrets) are the main maintenance reservoirs.* Many species of animals and birds are susceptible to mosquito-borne infection and develop antibody responses in timing with suitable climatic and habitat cycles. The pig is a very important domestic animal in many of the endemic areas and it is the most important amplifier host for the virus, developing sustained viremia of sufficient titer to infect feeding mosquitoes and indeed is probably the preferred host for *C. tritaeniohynchus*. Infection of humans and horses is incidental and both species are considered to be dead-end hosts.

Most horses, pigs, and cattle in endemic areas possess neutralizing antibodies against the virus. Intranasal and intracerebral inoculation can produce fatal encephalitis in calves, but natural cases of encephalitis in this species are quite rare. Among animals infected naturally with the virus, *only horses and donkeys develop clinical encephalitis.* There are no clinical signs of encephalitis in pigs, but pregnant susceptible sows may produce *stillborn piglets*. Infected stillborn and neonatal pigs may show hydrocephalus, cerebellar hypoplasia, and hypomyelinogenesis and anasarca; histological changes are restricted to the nervous system and may include *nonsuppurative encephalitis*. The lesions in these neonatal and stillborn piglets probably reflect the timing of infection in relation to the development of immune competence. Diffuse nonsuppurative encephalitis occurs in the brain and cord of piglets up to 6 months of age, but in the cerebellum it affects rather selectively the molecular and Purkinje layers. The histological pattern of Japanese encephalitis in pigs appears similar to that of Teschen and related diseases. In boars, the virus induces orchitis.

Severe epidemics of encephalitis have occurred in horses in Japan. The incubation period in horses ranges from 4–14 days, and case fatality is 5–15%. Lesions are confined to the CNS, are more prevalent in the cerebral hemispheres, and include extensive perivascular lymphoplasmacytic cuffing, gliosis, and areas of malacia with hemorrhage. The lesions in quality and distribution are the same as those produced by the *Eastern and Western equine encephalitis viruses*. Inclusion bodies are not reported in the Japanese disease. *Diagnosis* is best achieved by detection of viral RNA using PCR.

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Alphaviruses – equine encephalitides

Several members of the genus *Alphavirus*, family Togaviridae, cause either overt or subclinical encephalitis in horses or other animals. They all require an arthropod vector (frequently mosquitoes) for transmission.

Eastern, Western, and Venezuelan encephalitis in horses

Western equine encephalitis virus (WEEV), Eastern equine encephalitis virus (EEEV), and Venezuelan equine encephalitis virus (VEEV) are all members of the genus Alphavirus, family Togaviridae. Horses were originally regarded as the primary hosts of the EEVs, but horses are actually accidental and unfortunate hosts; birds for the American viruses (eastern and western type) or rodents for the Venezuelan virus are the most common vertebrate reservoir hosts, and mosquitoes are the principal vectors. Horses and humans, in both of which species the disease is of very considerable importance, are now known to be, in terms of transmission and often literally as well, dead-end hosts in which the titer of virus in blood is ordinarily too low to be a source of infection for mosquitoes.

Not all birds are capable of acting as reservoir hosts. Red-winged blackbirds, cardinals, sparrows, cedar waxwings, and the captive Chinese pheasant are highly susceptible to infection and nearly always die. Many other species, including adult domestic fowl and turkeys, are not sickened by the infection although fatalities can be produced in the young of these species.

EEEV is endemic along the North American Atlantic course, in the Caribbean, Central America, and along the northeastern coast of South America. The virus cycles between water birds and the mosquito, *Culiseta melanura*, which feeds on birds and does not feed on large mammals. Horses are likely to get infected by other mosquitoes, *Aedes sollicitans* and *A. vexans*, which feed on both horses and birds.

WEEV is present mostly in the valleys of western North American states, where the cycle is between wild birds, especially passerines, and the mosquito, *Culex tarsalis*. This mosquito feeds readily on animals, and human and animal cases occur regularly.

VEEV has two major different strain groups, the enzootic strains that are avirulent and cycle between *Culex* spp. mosquito and small rodents in the Caribbean areas, and the epizootic strains that are virulent to human and horse, found mainly in Venezuela, Colombia, and Peru, and circulate between several mosquito species and horses, which produce high titered viremia sufficient to infect the vector mosquitoes. Outbreaks of EEE and WEE occur in seasonal patterns related to the time of the year when mosquitoes are active. VEE outbreaks usually occur in a cyclical pattern approximately every 10 years.

Once infected, mosquitoes are known to remain so for life, and there is evidence that the virus is capable of multiplying in the insects. Arthropods other than mosquitoes may also be of some, but lesser, importance. The virus has been found in chicken mites (*Dermanyssus gallinae*), chicken lice (*Menopon pallidum, Eomenocanthus stramineus*), and assassin bugs (*Triatoma sanguisuga*). The spotted-fever tick, *Dermacentor andersoni*, is capable of transmitting the infection stage to stage and hereditarily. Transmission by aerosolization is reported only in humans; laboratory workers are at high risk of infection by aerosols.

Although humans and horses are the principal mammalian victims, other species are susceptible. Pigs readily develop asymptomatic infections but a few outbreaks have been reported in this species with histology typical of EEE. Pigs are not of significance for natural propagation of the virus because they do not develop significant viremia. Calves are susceptible to intracerebral inoculation but recover in 2 weeks. Guinea pigs and white mice are highly susceptible, rabbits are less so, and sheep, dogs, and cats are refractory.

The three viruses are similar in their pathogenesis. After the mosquito bite, the virus replicates in the regional blood vessels and lymph nodes, viremia develops, followed by secondary replication in lymph nodes and muscles. A second viremia then develops and is followed by brain invasion via the blood. In the CNS, the virus replicates in neurons, glial cells, and blood vessels. The virus causes neuronal necrosis, likely via stimulation of apoptosis.

Young horses are more susceptible than the old. Initially, there is viremia with fever and depression, usually unnoticed. The animal may then recover or the virus may invade the CNS, by which time the fever has subsided. The neurologic signs are characterized by derangements of consciousness and terminal paralysis. There may be early restlessness with compulsive walking, often in circles. There is central blindness. The animal becomes somnolent and assumes unnatural postures. At this stage, the course may remain static and the animal lives as a "dummy," or paralysis may develop, often first affecting cranial nerves but later general and flaccid. *The signs are largely cortical and the cortex is the principal site of the lesions.* The course, if fatal, is usually 2–4 days.

There are no gross changes. The microscopic changes are limited almost exclusively to *gray matter* (see Fig. 3.2D). When the course is short, 1 day or less, the reaction is largely on the part of neutrophils. These infiltrate the gray matter diffusely and may be found in foci suggestive of malacia (Fig. 3.122). There is early microglial reaction to produce rod cells. Endothelial cells, especially of veins are swollen, and hyaline or granular thrombi are common in these vessels. There are narrow cuffs of lymphocytes and neutrophils with perivenous hemorrhage and edema. After a couple of days, the neutrophils disappear, the cuffs are composed of lymphocytes, and there are both focal and diffuse microglial proliferations as in the standard nonsuppurative reactions. Neuronal degeneration and neuronophagia are common findings. Intranuclear inclusions similar to those in Borna disease may be present, but may be very difficult to identify.

The most severe lesions are in the cerebral cortex, especially the frontal, rhinencephalic, and occipital areas, with lesions of lesser intensity in the pyriform lobes. Severe lesions are also present in thalamus and hypothalamus. From the thalamus caudally, the intensity of inflammation diminishes but reveals no selectivity for particular nuclear masses. The cerebellum is less severely injured than other portions, although inflammatory changes may be found in the deep nuclei and spottily in the cortex. Mild changes occur in both dorsal and ventral horns of the cord, but their distribution is irregular. The trigeminal ganglia are not affected. The encephalomyelitis in the Venezuelan type may be purely nonsuppurative. Extraneural lesions are common in humans and birds but are rare in susceptible domestic mammals. Small intestinal lesions in a horse with EEE include multifocal myonecrosis and lymphomonocytic infiltration in the muscular layer and focal mild perivascular lymphocytic infiltration in the submucosa. Myocarditis is not uncommon in pigs suffering from EEE. Horses infected with VEEV can occasionally have some nonspecific extraneural lesions such as myeloid depletion in bone marrow and lympholysis in spleen and lymph nodes.

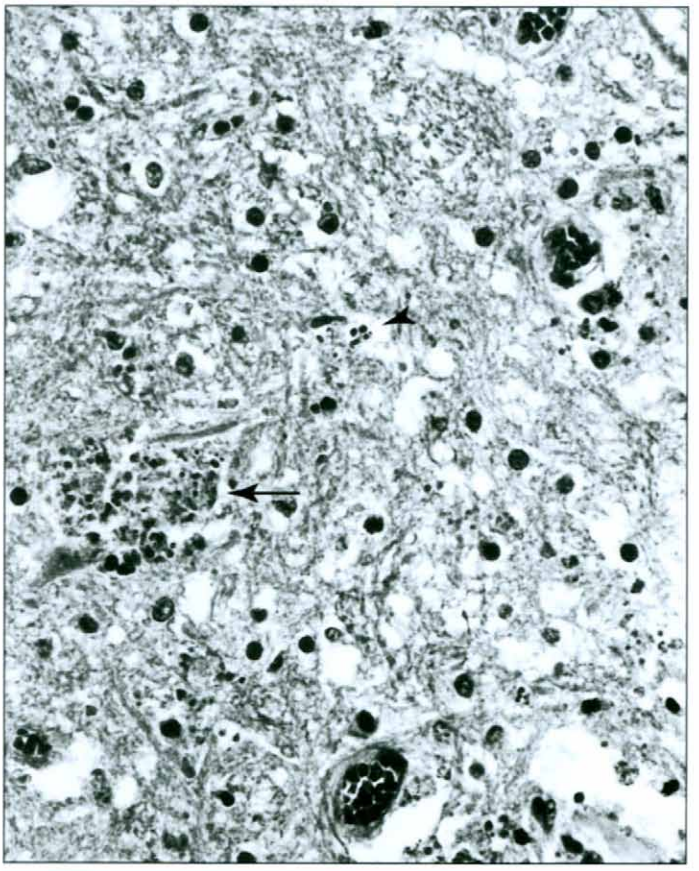

Figure 3.122 Neuronal necrosis (arrow), glial necrosis (arrowhead) in cerebrum in **equine encephalitis** in a horse.

Other *Alphavirus* encephalitides

Highlands J virus of America's east coast, ***Getah virus*** of southeast Asia, and ***Semliki forest virus*** of the Americas are all equine pathogens that are able to induce at least a febrile disease. All of these viruses are maintained in the environment by a mosquito–bird–mosquito cycle. Several mammals and birds seroconvert to these viruses, however overt disease is rare. *Highlands J virus* was reported as the cause of encephalitis in two horses. *Getah virus* does not induce encephalitis but clinical signs and lesions with some similarities to equine viral arteritis.

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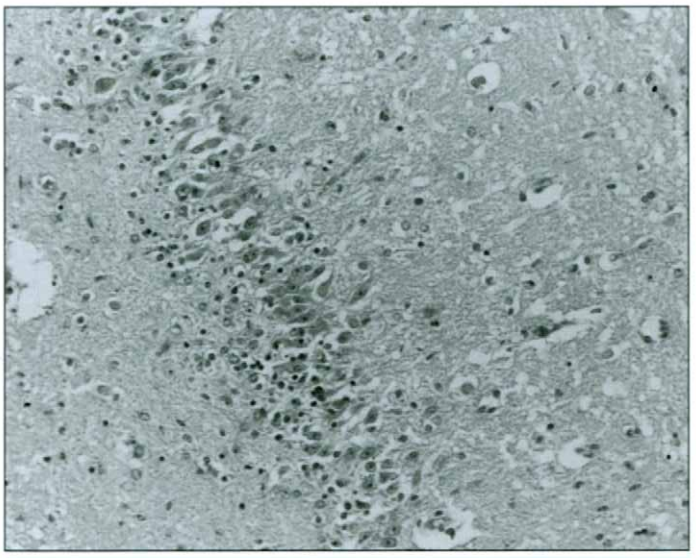

Figure 3.123 Nonsuppurative encephalitis and gliosis in the hippocampus of a horse with **Borna disease.**

Borna disease

Borna disease, named after the village of Borna in Germany, is caused by *Borna disease virus* (BDV), which is the only member of the genus *Bornavirus*, family Bornaviridae. The virus exists worldwide in many vertebrates but most commonly infects horses, sheep, cattle, cats, dogs, and ostriches. The traditional endemic area is central Europe, but antibodies to the virus are found in horses outside Europe, including the USA and Japan. The mortality rate may be high (>80% in horses, 5–40% in sheep); surviving horses may be asymptomatic carriers, or may suffer relapses of disease. The virus has a controversial link to several human neuropsychiatric illnesses. In experimental hosts (tree shrews, rats), infection with BDV not only produces pathoanatomic changes, i.e., nonsuppurative encephalitis, but also behavioral changes and learning deficits.

The virus replicates in the nucleolus of the host cell without cytopathic effect, persistently infects cells, and induces brain lesions by *immune-mediated mechanisms*. In Lewis rats, acute (4–8 weeks postinfection) BDV infection is followed by massive infiltrates in the brain of CD4+ Th1, CD8+ T, and NK cells with a predominance of Th1 cytokines that favors cell-mediated immunity. In the chronic stage (beyond 15 weeks of infection), the aforementioned cellular infiltrates significantly decrease and the predominant cytokines are of Th2 type, favoring the shift to a humoral immune response; the resultant antibodies are not protective and have no significant effect on the disease. Due to this unique feature, infection of neonatal or immunocompromised animals does not lead to disease or to encephalitis.

The epidemiology of Borna disease, including reservoir, methods of transmission, and infection, remains obscure. Inflammation of the olfactory bulbs at the early stages of natural infection in humans suggests an intranasal route of infection followed by transaxonal migration to the olfactory bulb. Vertical transmission in horses and rats with life-long persistent infection is also suggested.

Clinically, the disease occurs sporadically or in clusters, however severe outbreaks are described in different species. *Equids and sheep are the most susceptible animals*, but natural disease is reported in many domestic species including but not limited to cattle, alpacas, cats, dogs, and ostriches. Most infections in horses remain subclinical and BDV-specific antibodies are frequently found in clinically healthy horses. The incubation period is not less than 4 weeks and introduces a clinical syndrome that is purely neurologic but of varied course, death occurring in 1–3 weeks. The mortality rate in diseased horses is 90–100%. Recurrent episodes at time of stress occur in surviving animals. Clinical signs include pharyngeal paralysis, hyperesthesia, standing in awkward positions, circling, muscular tremors, and spasms; blindness is common. Drowsiness and flaccid paresis develop terminally.

There are no gross lesions. The distribution of lesions in Borna disease differs from that in other equine encephalomyelitides and parallels closely the distribution of viral antigen, as displayed by immunohistochemistry, and the distribution of infectivity, as determined by titration in cell cultures. Virus and lesions are present mostly in the gray matter of olfactory bulbs (early stage), hippocampus (Fig 3.123), limbic system, basal ganglia, and brain stem. The dorsal cerebrum and the cerebellum are relatively spared. Lesions may be present in optic nerves and retina. Histologic lesions are those of *nonsuppurative encephalomyelitis* with predilection for the aforementioned areas. Perivascular cuffs can be dramatically thick (>7 cell layer) and usually there are neuropilar clusters of lymphocytes and plasma cells. Other lesions include neuronophagia and focal gliosis. The presence of inclusion bodies (Joest–Degen bodies) is fairly pathognomonic; these are mainly in nuclei, especially in the hippocampus, and are very occasionally cytoplasmic. They stain well and red with Giemsa, and have a clear halo. Commercial PCR and immunohistochemistry kits are available for diagnosis.

Borna disease virus has been proposed as the cause of a chronic, slowly progressive neurologic disease affecting *cats* of all ages, sexes, and breeds. The disease is known clinically as *staggering disease,* and clinical signs include ataxia, paraparesis, and tetraparesis. Behavioral change is not a constant finding. Lesions are more prevalent in the gray matter of brain stem and in dorsal and ventral horns of the thoracic and/or cervical spinal cord segments. Lesions include mild to moderate lymphoplasmacytic cuffing with neuronophagia and neuronal degeneration and astrogliosis. Severe Wallerian degeneration is usually present in ventral and lateral columns of the cervical and thoracic spinal cord.

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Lentiviral encephalomyelitis of sheep and goats

Caprine arthritis encephalitis virus (CAEV) of goats and *Visna/maedi virus* (VISNA) of sheep, in the genus *Lentivirus* of the family Retroviridae, are small-ruminant lentiviruses (SRLV). CAEV is the causative agent of caprine arthritis-encephalitis of goats and VISNA is the causative agent of the visna/maedi disease complex of sheep; at least some strains of the SRLV are transmissible between sheep and goats. In both natural hosts, *four clinical and pathological syndromes are recognized*, namely **mastitis, arthritis, interstitial pneumonia** (maedi and ovine progressive pneumonia) and **encephalomyelitis** (visna of sheep). Within endemic situations, any one or combination of the four syndromes may be present and when in combination one syndrome usually predominates.

Once infected, the virus is never eliminated and, while present, it is active even though there may be no clinical sign of neurologic deficit. Typically for this type of virus infection, the virus is highly cell-associated and replicates only slowly, infection persists for the life of the animal, the incubation period before seroconversion may be several months and before clinical disease may be months or years, the clinical disease is progressive, and the lesions are dominated by active mononuclear inflammatory cells. The pathogenesis and epidemiology of the various conditions are described in detail in Vol. 2, Respiratory system. Described below are the gross and histologic lesions and clinical signs found in the encephalomyelitis form of these diseases.

The encephalomyelitis form in sheep is called **visna** (Icelandic for wasting). As a natural disease, visna occurs in sheep of both sexes but clinical signs are seldom, if ever, observed in animals less than 2 years of age. Disease onset is insidious. The earliest sign may be barely perceptible caudal ataxia and fine trembling of the lips. The first sign to be noticed may be extensor paralysis of the hindlimbs. Once paralytic signs are evident, a fatal outcome appears certain. There is no fever and no sign of cerebral dysfunction, and death is due to starvation or secondary infection. The incidence of visna is relatively low. The course of the infection can be followed fairly well by routine examination of the CSF for lymphocytosis.

Normal sheep are expected to have $\leq 0.005 \times 10^9$ cells/L ($\leq 5/mm^3$) of CSF; in visna, cell numbers, chiefly lymphocytes, can be markedly elevated. After intracerebral inoculation, there is a latent period of up to 8 weeks, after which the CSF cell count begins to increase. The cell count may remain high for several months without other signs of disease. Thereafter, the animal may recover, as indicated by a drop in the CSF cell count, or the cell count may remain high, paralysis develops, and death follows.

The disease in the brain is chronic and demyelinating. There are no gross neural changes in this disease, and the histologic change is one of *patchy demyelinating encephalomyelitis*. The distribution of lesions, involving principally the white matter, is unlike the distribution produced by other neurotropic viruses. There is a mild to severe mononuclear type of cerebrospinal meningitis. The parenchymal lesion may be well-established by 1–2 months, and these early lesions are intensely inflammatory with perivascular cuffing and gliosis. They reveal clearly that the process begins in, and immediately beneath, the ependyma diffusely throughout the cerebrospinal axis. In this early stage, the myelinated fibers in the inflammatory foci remain remarkably intact; the gray matter of the cord is irregularly but often intensely affected by a nonsuppurative reaction even 2–3 months after inoculation. In the paralytic and terminal stages of the disease, the periventricular destruction of white matter in the cerebrum and cerebellum is extensive, and in some sections of the brain, especially in the cerebellum, almost every bit of white matter is destroyed leaving the gray matter free.

Destruction of myelinated fibers in the spinal cord is patchy and not due to progressive spread of the pericentral inflammation. The demyelinated plaques are characteristically peripheral and triangular in shape with a base on the pia mater. Although dorsal and lateral tracts are most frequently involved, there is no selectivity for particular fiber tracts and no symmetry. The degenerating foci are almost malacic in their severity, and the plaques contain numerous reactive microglia and astroglia. Spinal nerve roots share in the degenerative process. Germinal centers may form in the choroid plexus. In areas of intense inflammation, liquefactive foci of necrosis occur in the white matter and the loss of myelin is expected to be of Wallerian type. In the spinal cord, evidence of remyelination can be found indicating that oligodendrocytes are not target cells and that demyelination may be primary.

Caprine arthritis-encephalitis (CAE) appears to be widely distributed, but the expression of the infection is highly variable, and many infected goats show little or no clinical disease. Clinical disease of the nervous system affects kids 2–4 months of age and is frequently fatal. Animals that develop the early nervous disease or have early inapparent infections tend to develop synovitis and periarthritis in adulthood (see Bones and joints).

The clinical signs of CAE are referable to motor spinal dysfunction without signs of cerebral disease. Onset is indicated by hindlimb lameness and ataxia with paresis that progresses over several weeks to paralysis. The inflammatory lesions in the CNS may remain active for several years in goats that survive (see Fig. 3.124A, B). In the early clinical phase of the disease, changes are widely distributed in the white matter of the brain and cord, particularly in the subependyma and beneath the pia in the cord. The distribution and character of the lesions in the nervous tissue in the goat are, in general, similar to those in visna of sheep. There is, however, less tendency for the periventricular lesions to progress to gross cavitation of cerebral white matter. Instead, there is a tendency for the inflammatory and myelinoclastic areas to increase in number and severity caudally from the mesencephalon. As in visna, the spinal cord changes are discontinuous and, where present, involve the myelin in subpial plaques or in one or

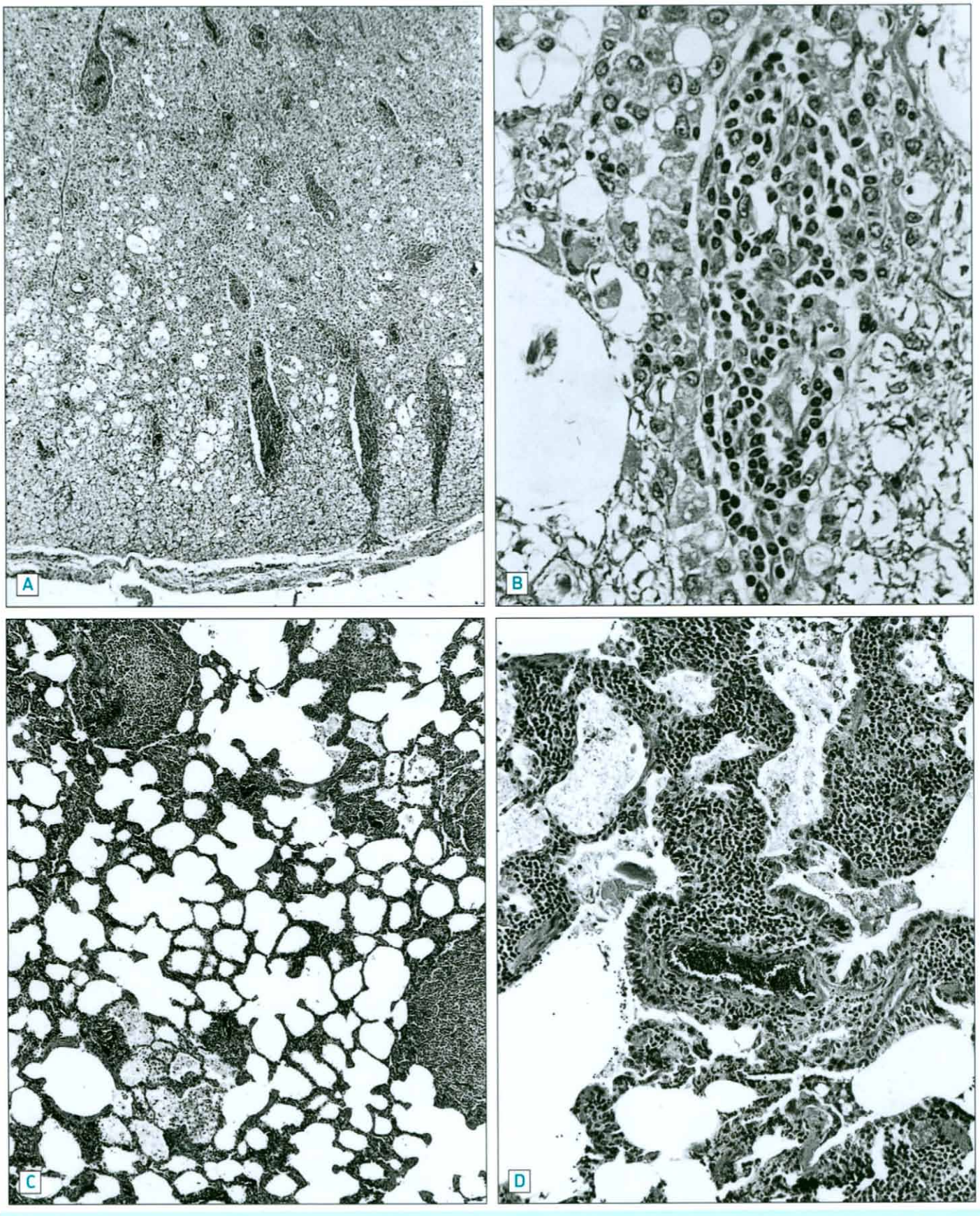

Figure 3.124 Caprine arthritis-encephalitis. A. Leukomyelitis. **B.** Detail of perivascular reaction. Note macrophages bordering vessel. **C.** Prominent perivascular and peribronchiolar lymphoid cuffs and focal interstitial pneumonia. **D.** Detail of (**C**) showing lymphocytes around vessels and bronchioles, and in alveolar walls.

more quadrants of the cord. The extent of perivascular infiltration by mononuclear cells (see Fig. 3.124B) is also greater in kids than in sheep. In addition to the encephalomyelitis, mastitis, and arthritis seen in CAE, interstitial pneumonia occurs in some natural and experimental cases (Fig. 3.124C, D).

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Paramyxoviral encephalomyelitis of pigs

Porcine rubulavirus encephalomyelitis (blue eye disease)

Blue eye disease is caused by *Porcine rubulavirus* (La-Piedad-Michoacan-Mexico virus) of the genus *Rubulavirus*, family Paramyxoviridae. The disease is characterized by encephalomyelitis, reproductive failure, and corneal opacity. Outbreaks have been recorded in Mexico since 1980, but appear to be self-limiting in commercial pigs. In pregnant sows, the infection may be subclinical or responsible for *fetal death, mummification, and stillbirths,* and for the occasional appearance of corneal opacity in the sow. Piglets up to 2 weeks of age are most susceptible with up to 50% morbidity and very high mortality. The clinical signs are of encephalomyelitis leading to death within 2–4 days, although subclinical infections are also frequent and may be manifested only by corneal opacity.

The lesion is a typical *nonsuppurative encephalomyelitis* affecting mainly gray matter of the thalamus, midbrain, and cortex. Inclusion bodies have not been demonstrated. Anterior uveitis is mild, the inflammatory cells congregating in the iridocorneal angle and the corneoscleral junction. The corneal opacity is due to edema, which will resolve if the animal survives.

In mature male pigs, experimental exposure will result in epididymitis in almost all exposed and in a lesser number with orchitis and testicular atrophy. Interstitial pneumonia is part of the description.

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Nipah virus encephalitis

Nipah encephalitis, an emerging disease characterized by severe and rapidly progressive encephalitis, is caused by *Nipah virus* (NiV) of the genus *Henipavirus*, a novel genus in the family Paramyxoviridae. This genus also contains *Hendra virus*. Both are newly emerging viruses that can cause fatal encephalitis and pneumonia in humans and several animal species. The first severe outbreak of NiV encephalitis in humans occurred in 1998 near Ipoh, Malaysia, primarily among pig farmers and their families; the outbreak was preceded by an outbreak of encephalitis and pneumonia affecting pigs on many local farms. *Fruit bats* of the *Pteropid* species were later confirmed to be the natural reservoir host of NiV. Bats shed virus in their urine and saliva, which contaminates fruit that falls into pig pens and is eaten by pigs; bats in these trees also urinate directly on pigs. Initial human infection occurred in pig farmers by direct contact or aerosolization from infected pens. Pig-to-pig or pig-to-domestic-animal infections occur by direct contact with infected pig or mechanically by contact with contaminated utensils or feed. Direct transmission from bats-to-human or from human-to-human is controversial.

Pigs are the animals most susceptible to infection, but natural infection is reported in horses, cats, goats, and dogs; these species were infected by direct contact with infected pigs. Morbidity rates in pigs are ~10%, with case mortality rates of <15%. The incubation period is estimated to be 1–2 weeks. The virus targets two systems, the CNS and the respiratory system. Clinical signs are those of acute dyspnea (labored and harsh respiration, open-mouth breathing, severe cough) and acute nervous signs (trembling, seizures, or tetanus-like spasms). Abortion may occur to pregnant sows.

The lung is diffusely edematous with patchy acute hemorrhage. Meningeal blood vessels are severely congested. The histologic hallmark is *necrotizing vasculitis affecting arterioles, venules, and capillaries* with the presence of binucleated or multinucleated syncytial cells attached to the endothelium of affected blood vessels. Blood vessels undergo fibrinoid degeneration and leukocytoclastic vasculitis. Affected blood vessels are present most commonly in lung, brain, renal glomeruli, and lymphoid organs. Other pulmonary lesions include moderate lymphoplasmacytic bronchointerstitial pneumonia with mild necrotizing bronchiolitis and mild-to-moderate filling of alveoli with neutrophils, even in the absence of significant secondary bacterial infection. Severe lymphocytic and neutrophilic meningitis with mild lymphoplasmacytic encephalitis and occasional gliosis are consistent findings. Due to vasculitis, large areas of hemorrhage and infarction are common in affected organs. Occasionally, *eosinophilic intracytoplasmic and intranuclear inclusions* are present in neurons and syncytial endothelial cells. Syncytial cells can also be found attached within lymphatic vessels and to pulmonary alveolar septa.

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Other porcine paramyxoviral encephalitides

An outbreak of respiratory disease (necrotizing bronchointerstitial pneumonia) and encephalitis was recorded in a large pig farm affecting all ages. The etiologic agent was a previously unknown, as yet unclassified, paramyxovirus different than the other known porcine paramyxoviruses. CNS signs were characterized by recurring episodes of distress, head pressing, tremors, and hindlimb ataxia. No gross lesions were observed in brain. CNS lesions were lymphocytic perivasculitis and diffuse gliosis.

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Akabane viral encephalitis

Akabane disease is caused by *Akabane virus* (AKAV) of the *Simbu virus group*, in the genus *Bunyavirus,* family Bunyaviridae. Iriki virus, a strain of AKAV, causes similar disease. The group also contains *Aino virus,* which causes congenital disease identical to that caused by AKAV. As mentioned earlier in this chapter, AKAV is a common cause of congenital CNS defects in infected bovine fetuses, however the virus has also been associated with nonsuppurative meningoencephalomyelitis in adult cows and young calves. Histologic lesions are more prominent in brain stem, pons, medulla oblongata, and the spinal cord ventral horn. Lesions are those of lymphohistiocytic cuffing with multifocal gliosis, neuronal necrosis, and occasional neuronophagia with microglial cells.

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Bovine herpesviral encephalitis

Bovine necrotizing meningoencephalitis caused by *Bovine herpesvirus 5*

Bovine herpesvirus 5 (BoHV-5), the cause of bovine necrotizing meningoencephalitis, is antigenically related to *Bovine herpesvirus 1* (BoHV-1), the cause of infectious bovine rhinotracheitis. Both viruses are neurotropic, undergo latency in the trigeminal ganglia, and can be reactivated by natural or experimental stress; however, BoHV-1 rarely causes encephalitis. Both of these herpesviruses are in family Herpesviridae, subfamily Alphaherpesvirinae, genus *Varicellovirus*. Outbreaks of severe BoHV-5 necrotizing meningoencephalitis have occurred most frequently in South America, but the disease has been observed in other countries including the USA. Infection is by direct contact or aerosolization. Following intranasal inoculation, BoHV-5 reaches and invades the brain through the olfactory pathway. BoHV-5 envelope glycoproteins E (gE), gI, and Us9 convey viral neurovirulence and neuroinvasiveness by affecting anterograde viral spread via the olfactory pathway.

BoHV-5 encephalitis occurs as a sporadic disease or sometimes as outbreaks in calves and yearlings. The morbidity in herds may be as high as 50%, but is usually much lower; few recognizably sick animals survive. The incubation period is 1–2 weeks, followed by anorexia, apathy, circling, jaw chomping, and finally paddling and recumbency. These clinical signs may be associated with mild to severe rhinitis.

Gross lesions are usually absent, however in the severe form of the disease, bilaterally symmetrical areas of malacia, hemorrhage, and necrosis are described in the gray matter of the rostral cerebrum (Fig. 3.125). The hallmark histologic lesion is *severe cytonecrotizing nonsuppurative meningoencephalitis with marked gliosis* (Fig. 3.126A, B). Lesions are more commonly present in the gray matter of the rostral cerebrum, including olfactory bulb, and to a lesser extent in the cerebellum and diencephalon. Perivascular cuffs can be markedly thick (more than six layers of lymphocytes, plasma cells, and fewer histiocytes). Necrotic neurons are usually swollen, have lost their angularity, are basophilic, and have pyknotic nuclei. Typical *intranuclear alpha-herpesviral inclusions* are occasionally present in degenerate neurons and astrocytes (Fig. 3.126B). Trigeminal ganglioneuritis, neuronophagia, and satellitosis are commonly present. Necrotic or malacic areas can take the laminar cortical necrosis pattern of bovine polioencephalomalacia, however, the latter syndrome is not associated with the severe perivascular cuffing present in BoHV-5 encephalitis. Vasculitis affecting the cerebral microvasculature is only described in rabbits experimentally infected with the virus. The histologic lesions are fairly pathognomonic, however, confirmation of the diagnosis by PCR is recommended.

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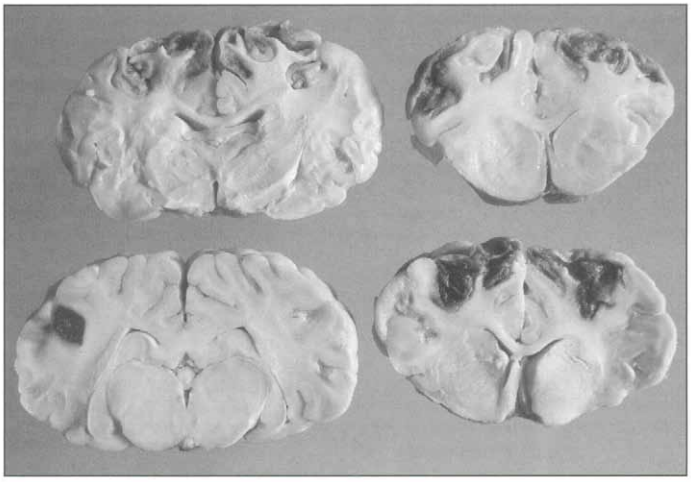

Figure 3.125 Areas of malacia, hemorrhage, and necrosis affecting the gray matter of the rostral cerebrum mostly in a bilaterally symmetrical pattern in **bovine necrotizing meningoencephalitis** caused by BoHV-5. (Courtesy of D. Driemeier.)

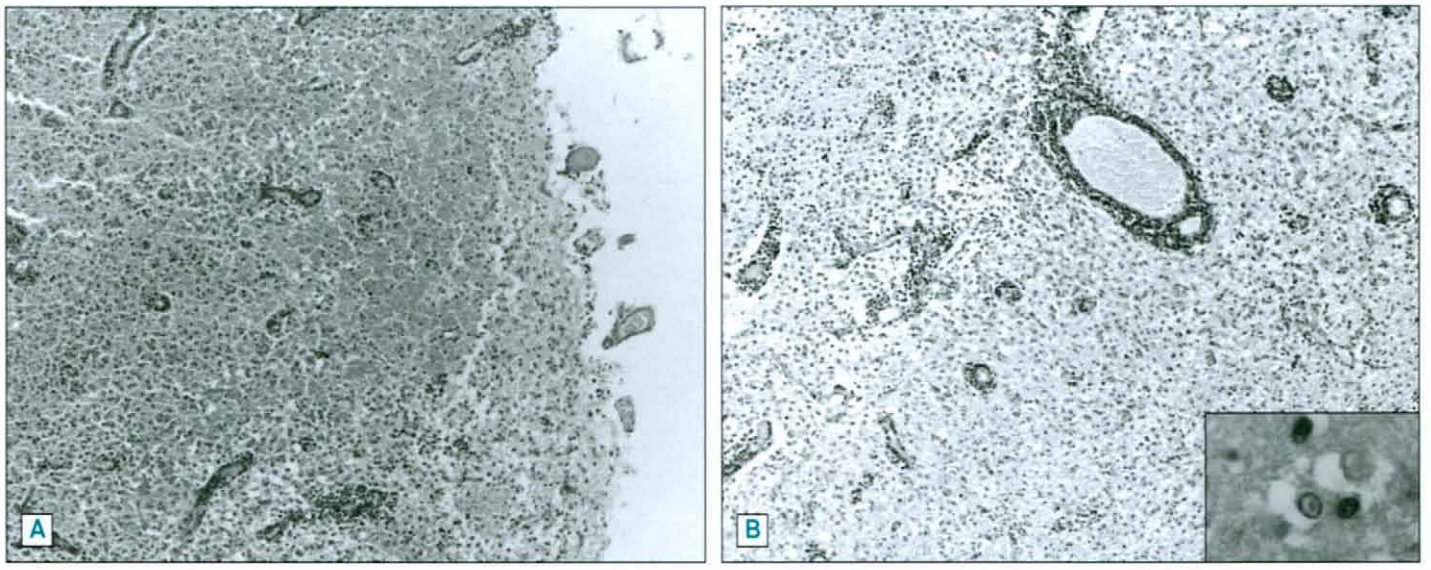

Figure 3.126 Severe hemorrhagic necrosis and malacia (**A**) with perivascular lymphocytic and plasmacytic cuffing (**B**) affecting the external cortical layers of the rostral cerebrum in **bovine necrotizing meningoencephalitis** caused by BoHV-5. Intra-astrocytic intranuclear herpesviral inclusion (inset in **B**). (Courtesy of D Driemeier.)

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Bovine meningoencephalomyelitis caused by *Bovine herpesvirus 1*

Nonsuppurative encephalomyelitis due to *Bovine herpesvirus 1* (BoHV-1) is reported worldwide. BoHV-1 causes multiple and diverse conditions in cattle such as abortion, infectious bovine rhinotracheitis, infectious bovine vulvovaginitis, and balanoposthitis. Some BoHV-1 serotypes are neurovirulent and are able to induce encephalitis. Marked upper respiratory disease typically precedes or occurs concurrently with the encephalitis. The pathogenesis and clinical signs are similar to those described for BoHV-5. Histological lesions are those of *nonsuppurative encephalomyelitis with occasional intranuclear herpetic inclusions*. The massive neuronal necrosis and gliosis described in BoHV-5 are not usually seen in association with BoHV-1. BoHV-1 encephalitis is more prevalent in calves; however sporadic cases can affect adult cattle particularly in the Near and Middle East.

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Malignant catarrhal fever

Malignant catarrhal fever (MCF) is a fatal multisystemic lymphoproliferative and inflammatory disease affecting many ruminant species. The details of MCF, including the lesions associated with its encephalomyelitic form, are described in Vol. 2, Alimentary system.

Nonsuppurative meningoencephalitis is reported in "malignant catarrhal fever" in *swine* in Europe resulting from infection with *Ovine herpesvirus 2*. *Caprine herpesvirus 2*, a gamma-herpesvirus, does not cause overt disease in goats, but causes fatal goat-associated MCF in certain species of deer.

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Bovine paramyxoviral meningoencephalomyelitis

Sporadic cases of nonsuppurative meningoencephalomyelitis due to paramyxovirus are rarely reported. The causative virus is restricted to the European continent and is still not classified within the Paramyxoviridae but is distinct from the other bovine paramyxoviruses such as *Bovine parainfluenza virus 3*. The disease should be differentiated from the sporadic bovine encephalitis caused by *Chlamydophila* spp.

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Porcine circovirus type 2 encephalopathies

Porcine circovirus type 2 (PCV2), the cause of porcine postweaning multisystemic wasting syndrome, produces nonsuppurative or granulomatous encephalitis with gliosis under experimental conditions,

either alone or in association with porcine parvovirus. The PCV2 antigen has been identified in brain in these cases demonstrating neurotropism of the virus under experimental conditions. The role of PCV2 in encephalitis associated with natural infection is controversial. PCV2 antigen has been detected in brains of pigs with naturally occurring encephalitis but always in association with other pathogens that can cause encephalitis alone and under natural conditions (e.g., PRRSV or *Streptococcus suis*). Also, the PCV2 antigen was demonstrated in neonatal pigs in association with naturally occurring congenital tremor type A2 (see Porcine hypomyelinogenesis); however, the exact role of PCV2 in this condition is yet to be determined.

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Porcine encephalitis associated with PRRSV infection

Porcine reproductive and respiratory syndrome virus (PRRSV) is neurovirulent especially in young pigs and can cause encephalitis under natural conditions, often in association with other PRRSV syndromes (e.g., interstitial pneumonia) (see Vol. 2, Respiratory system).

California encephalitis virus meningoencephalomyelitis

Several serotypes of species *California encephalitis virus* of genus *Orthobunyavirus*, family Bunyaviridae, usually cause only asymptomatic infections, but are capable of causing encephalitis. These include La Crosse virus (LACV), Snowshoe hare virus, and Jamestown Canyon virus.

La Crosse virus is maintained in the environment and transmitted between susceptible hosts by *Aedes triseriatus* mosquitoes. Chipmunks (*Tamias striatus*) and squirrels (*Sciurus carolinensis*) are the principal amplifying vertebrate hosts. Other wild mammals such as foxes (*Vulpes fulva* and *Urocyon cinereoargenteus*) and woodchucks (*Marmota monax*) may also contribute to virus maintenance. The virus causes encephalitis and secondary neurologic deficits in humans, particularly school-aged children. A few cases have been reported in dogs in Florida and Georgia, USA. The most predominant clinical signs in these dogs were seizures and head tilt. Gross lesions were usually unremarkable, but areas of malacia may be present in cortex. Histologic lesions are predominantly in the cerebral cortex and characterized by *histiocytic and lymphoplasmacytic meningoencephalitis* with fairly thick cuffs and multifocal necrotizing panencephalitis. The necrotic areas in the acute stage are histiocyte and neutrophil rich. The lesions of this disease are similar to those seen in idiopathic granulomatous meningoencephalomyelitis (GME) described below.

Antibodies to **Snowshoe hare virus** have been found in a wide range of wild and domestic mammals, but overt disease is very rare. Encephalitis in association with SSHV was reported in two horses from Canada, but the diagnosis was made based on detection of seroconversion; one horse recovered and the pathologic changes found in the second case were not described.

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Canine herpesviral encephalitis

Canid herpesvirus 1 can cause an acute, highly fatal disease of neonates. Puppies after the age of 3 weeks are resistant to infection. The incidence is low, and the disease is only diagnosed at autopsy. Hypothermia predisposes to disease in neonates, in which the infection would otherwise be asymptomatic. Infection at birth is followed by cell-associated viremia and viral replication in vascular endothelium. This tropism is reflected in large hemorrhages at postmortem most apparent in renal surface, adrenal and serosa of gastrointestinal tract. Focal necroses occur in parenchymatous organs and inclusion bodies may be demonstrated in these foci. *Nonsuppurative meningoencephalitis* is most severe in cerebellum and brain stem. It may be accompanied by necrosis especially in the cerebellar cortex. Vascular endothelial hypertrophy and hyperplasia is accompanied by mononuclear infiltrates. There may be inflammatory changes in the retina, peripheral nerves, and ganglia.

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Equine herpesviral myeloencephalopathy

Equid herpesvirus 1 (EHV-1) and *Equid herpesvirus 4* (EHV-4) are two antigenically related but distinct viruses in the genus *Varicellovirus*, subfamily Alphaherpesvirinae, family Herpesviridae. Both viruses are widespread in horses, have significant economic impact on the equine industry, and are responsible for several clinical conditions including respiratory disease, pulmonary vasculotropic disease, enteric disease, and abortion. *Equine myeloencephalopathy is an important neurological disease* characterized clinically by ataxia, paresis, and paralysis, and caused mainly by EHV-1 and incidentally by EHV-4. Almost all recent outbreaks have been associated with EHV-1 infection. Other members of equine alpha-herpesviruses that are pathogenic but do not cause neurologic disease include *Equid herpesvirus 3* (Equine coital exanthema virus) and *Equid herpesvirus 8*

(Asinine herpesvirus 8), which induces interstitial pneumonia in donkeys. *Equid herpesvirus 9* (Gazelle herpesvirus) causes severe encephalitis experimentally in several species of domestic animals; the natural outbreak of fulminant encephalitis has been reported in a herd of Thomson's gazelles that were in close association with zebra. The natural reservoir for EHV-9 is unknown, but zebras or other equidae have been suspected.

Most horses show serologic evidence of exposure to EHV-1 and EHV-4 but are asymptomatic, and vaccination does not necessarily confer protection from neurologic manifestations. Both viruses contain at least 13 glycoproteins, which are important virulence factors for attachment, entry to the host cell, and cell-to-cell dissemination. The natural spread of EHV-1 is through direct horse-to-horse contact, by inhalation of nasal aerosols from infected horses, or through direct contact with an infected aborted fetus or placenta. EHV-1 replicates first in upper respiratory tract epithelium and local lymph nodes, and then induces T-cell and monocyte-associated viremia that ends with invasion of endothelial cells of the CNS and pregnant uterus. This leukocyte-associated viremia protects the virus from humoral immunity. *The virus is endotheliotropic, epitheliotropic, and neurotropic, but not neurovirulent.* The replication of virus in endothelial cells of the CNS leads to initiation of the inflammatory cascade that ends in *thrombo-occlusive necrotizing vasculitis*. The resultant myeloencephalopathy is due to destruction of CNS tissue secondary to vasculitis. The vasculitis is either due to direct viral cytotoxic effect or due to an immune-mediated (Arthus-type reaction) mechanism. A similar mechanism is responsible for EHV-1-induced abortion and pulmonary vasculotropic disease. There are no genetic or antigenic differences between the EHV strains isolated from neurogenic cases versus abortigenic or respiratory cases.

EHV-1 and EHV-4 have life-long latency in T cells and in neural tissue such as trigeminal ganglia. Latent virus can be reactivated experimentally after very high doses of corticosteroids and naturally after stress (such as castration). In contrast to the extensive studies on EHV-1, the pathogenesis of EHV-4 infection is poorly documented.

The disease occurs sporadically, but in several recent outbreaks, most affected horses either died or were euthanized. The disease is common in late winter and spring, which is also the time of greatest prevalence of EHV-1 abortion outbreaks. The incubation period is 6–10 days and usually occurs in association with abortion and/or respiratory disease but can occur without preceding signs. All ages are susceptible, but *pregnant mares and mares nursing foals are over-represented.*

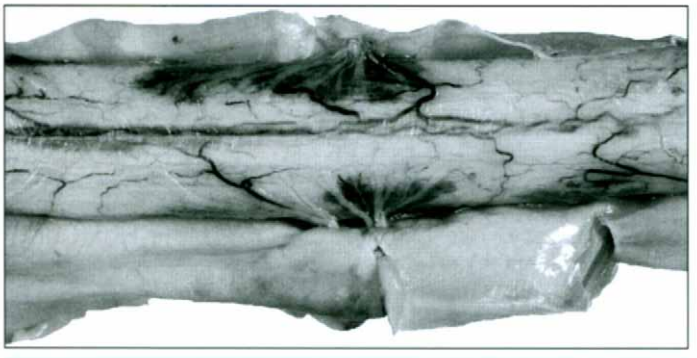

Figure 3.127 Acute spinal cord hemorrhage in a horse with **equine herpesviral myeloencephalopathy**. (Courtesy of RF Slocombe.)

Clinical signs start with fever and mild rhinitis. Neurologic signs are variable and depend on the part of the CNS affected by vasculitis, however common clinical signs include variable degrees of symmetrical ataxia and paresis that are more severe in pelvic limbs. Fecal and urinary incontinence are common, and clinical signs may end in hemi- or paraplegia. Gross and histologic lesions are sequelae to vasculitis. Gross lesions are not always present, but small (0.2–0.5 cm) random multifocal areas of hemorrhage may be present throughout the meninges, brain, and spinal cord (Fig. 3.127). In severe cases, multifocal necrohemorrhagic or malacic areas (up to 1.5 cm in diameter) can be present, especially in the white matter of spinal cord or the white or gray matter of the brain. *The characteristic histologic lesions are nonsuppurative necrotizing vasculitis and thrombosis*, with greater prevalence in the meningeal and parenchymal blood vessels of the brain stem and spinal cord. Perivascular edema, hemorrhage, focal areas of malacia, and infarction are present adjacent to the affected blood vessels. Occasionally, axonal swelling and mild nonsuppurative trigeminal ganglionitis are present. Extraneural lesions include uveal vasculitis and optic neuritis, especially in foals, and testicular and epididymal vasculitis in stallions.

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Canine distemper and related conditions

Canine distemper is discussed in detail in Vol. 2, Respiratory system. Three neurologic conditions are discussed here: multifocal distemper encephalomyelitis in mature dogs, postvaccinal distemper, and old-dog encephalitis.

Multifocal distemper encephalomyelitis in mature dogs

This rare chronic progressive disease occurs when *Canine distemper virus* infects dogs at 4–8 years of age. This disease is not preceded by the classic form of canine distemper, and signs of systemic illness are often absent or transient. Clinical signs have a slow progressive course and include weakness of the pelvic limbs, generalized incoordination, but no seizures or personality changes, and occasionally head tremors. Lesions are restricted to the CNS and are most prevalent in the cerebellum and white matter of the spinal cord. The cerebral cortex is frequently spared. This distribution differentiates this condition from an extremely rare condition, old dog encephalitis, wherein the cerebral cortex is constantly affected. The lesions are those of *multifocal necrotizing nonsuppurative encephalitis* with rare canine distemper intranuclear intra-astrocytic inclusion bodies, and demyelination in the internal capsule and corona radiata.

Post-vaccinal canine distemper encephalitis

This condition occurs in young dogs 1–3 weeks after vaccination with attenuated *Canine distemper virus* vaccines and is characterized by an acute to subacute clinical course (1–5 days). The acute course is characterized by clinical signs reminiscent of the furious form of rabies including aggressive behavior and attempts to attack. It is not completely clear why some dogs develop this condition post-vaccination. Immune stimulation by other canine viruses (e.g., *Canine parvovirus*) at the time of vaccination was suggested. The lesions are not well documented, however, lesions are always restricted to the CNS and are reminiscent of the natural disease, but distinguished by the relative sparing of the white matter.

"Old dog" encephalitis

"Old dog" encephalitis (ODE) is rather rare. Most cases occur in dogs past middle age but it has been observed in dogs as young as 1 year of age. The disease is of insidious onset and is characterized by circling, swaying, and weaving. Compulsive walking with pushing against fixed objects is typical, but there is neither paralysis nor convulsions. The disease progresses over 3–4 months to coma or termination.

ODE is caused by *Canine distemper virus* (CDV), apparently as a consequence of long-term subclinical, persistent infection: CDV appears to persist in a replication-defective state. ODE does not appear to be simply a progression of the encephalomyelitis of canine distemper. Virus can be isolated from affected animals only by explantation of affected brain and then only with difficulty, and the disease is not transmissible by direct inoculation. Inclusion bodies are readily found in some cases, and their structure is identical with paramyxovirus nucleocapsids of CDV in nervous tissue. Antigen that responds to fluorescent antibody prepared against CDV is abundant in cells of the gray matter, and serum antibody titers can be very high.

Lesions are confined to the brain, which appears slightly reduced in size. The ventricles are moderately dilated. Lesions are diffusely distributed throughout the cerebral cortex, thalamus, and midbrain. The reaction is nonsuppurative, qualitatively always the same but varying in degree. The most obvious change is cuffing, and the cuffs are remarkable for their large size and the purity of the lymphocytic populations in them. Plasma cells are present in small numbers. The infiltrating cells are confined to the Virchow–Robin space and seldom spread into the parenchyma. The large cuffs occur in both gray and white matter but are most common at the junction of these two zones. Focal gliosis does not occur in this disease, but there is some proliferation of astrocytes about vessels and neurons. There is uniform and rather diffuse atrophic sclerosis of the cerebral white matter, which gives an impression of gliosis, but astrogliosis is not prominent. There is some demyelination, producing typical punched-out areas in the white matter, and distorted myelin sheaths in the heavily myelinated tracts are quite extensive when specially stained. Lymphocytes may be found in the choroid plexuses where they are inserted into the brain, and about vessels where they enter the parenchyma.

Nerve cells, especially in Ammon's horn and the pons, reveal chromatolysis with only a few remnants of Nissl substance in the periphery of the cytoplasm. The chromatolytic cytoplasm is slightly acidophilic. The neuronal nuclei in the forebrain are remarkably swollen in most of the altered nerve cells. In occasional nuclei, there is pink inclusion-like material. Neuronophagia does not occur. The astrocytic nuclei are remarkably swollen, have an irregular outline, and may contain traces of pink deposit in the nucleoplasm. In a proportion of cases, possibly those of longest duration, prominent *intranuclear and cytoplasmic eosinophilic inclusion bodies* may be found easily.

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Parasitic infections

Protozoal infections

The cerebral complications of infections by protozoa such as *Babesia, Theileria, Trypanosoma*, and *Toxoplasma* are discussed elsewhere in these volumes. *Acanthamoeba*, a free-living ameba, can produce granulomatous meningoencephalitis in dogs as part of an opportunistic generalized infection (Fig. 3.128).

From time to time and in individual cases, pathologists observe *sporozoan parasites* in neural tissues of fetuses, neonates, and adults and lesions presumed to be the consequence of their presence. There are, however, difficulties in specific identification of the parasites and in attribution of pathogenicity. The syndromes considered here are reasonably defined but are subject to revision as the parasites are identified and their lifecycles clarified.

Encephalitozoonosis

Encephalitozoon (Nosema) cuniculi is a microsporidian parasite capable of establishing infection in a wide variety of mammalian species and birds. It is rarely a zoonotic infection. Endemic infection is

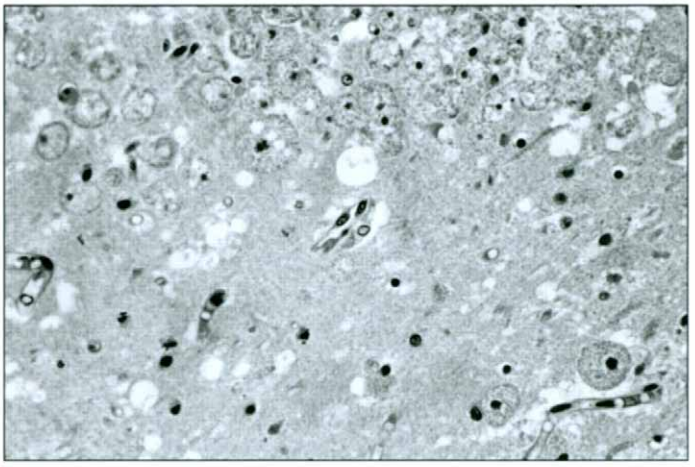

Figure 3.128 Amebic encephalitis in a dog; large numbers of amebae are present in this field, with only minimal reaction. (Courtesy of RF Slocombe.)

common in colonies of laboratory rodents in which the clinical consequences are mild but the pathologic changes may confuse other studies. Amongst domestic species, the disease is of interest in carnivores, especially farmed foxes in which serious mortalities occur, and occasionally in dogs and mink. The incidence of subclinical infection is not known, but a serological survey of an unselected population of asymptomatic stray dogs identified 10–15% to be seropositive.

The organism is an *obligate intracellular parasite* with a direct life cycle. It develops in parasitophorous vacuoles in cells of many tissues, especially endothelial cells, but is most easily found in brain and kidney in acute active infections. In chronic infections, the organisms can be sparse or impossible to find in microscopic sections, although it seems that animals once infected remain permanently so and excrete the organism mainly in urine.

Clinical disease occurs in dog and fox pups; the organism is shed in urine and feces of affected animals. In both hosts, transplacental infections appear to be important, but oral transmission, as by ingestion of infected rabbit carcasses, may occur. Experimental infection of mature dogs does not lead to clinical disease.

Tissue changes in encephalitozoonosis are most prominent in brain and kidney, but the organism selectively parasitizes vascular endothelium, and the *segmental vasculitis* that results is responsible for lesions in many tissues. Gross lesions may be limited to the kidneys as severe, nonsuppurative interstitial nephritis (Fig. 3.129A). Organisms are abundant in sections of kidney early in the disease but they are difficult to find at later stages. They are especially numerous in the epithelium and lumen of tubules, in glomerular capillaries and in the interstitium, and are present in small vessels and in the media and adventitia of intrarenal arteries. Fibrinoid necrosis affects some glomeruli and the arterial lesions resemble those of periarteritis nodosa. Focal hepatic necrosis and nonsuppurative portal infiltrations are associated with organisms in hepatocytes and Kupffer cells and with nodular vasculitis in the triads. Focal myocardial necrosis and inflammation are frequently associated with vasculitis.

The lesions in the nervous system are those of *widespread nonsuppurative meningoencephalomyelitis*. The severity of lesions varies unpredictably in different parts of the nervous system reflecting the random localization of the organism and the irregular distribution of inflammatory vascular change. Focal gliosis and microscopic granulomas surround small vessels (Fig. 3.129B). About larger vessels showing segmental fibrinoid change, mononuclear cells form cuffs involving the adventitia and perivascular space and eventually assume an epithelioid cell appearance. There is astrocytosis in the surrounding parenchyma. The vascular lesions in the meninges in the acute disease resemble those of polyarteritis nodosa and become dominated by sclerotic changes in the chronic disease in which perivascular cuffing and granulomatous reactions persist.

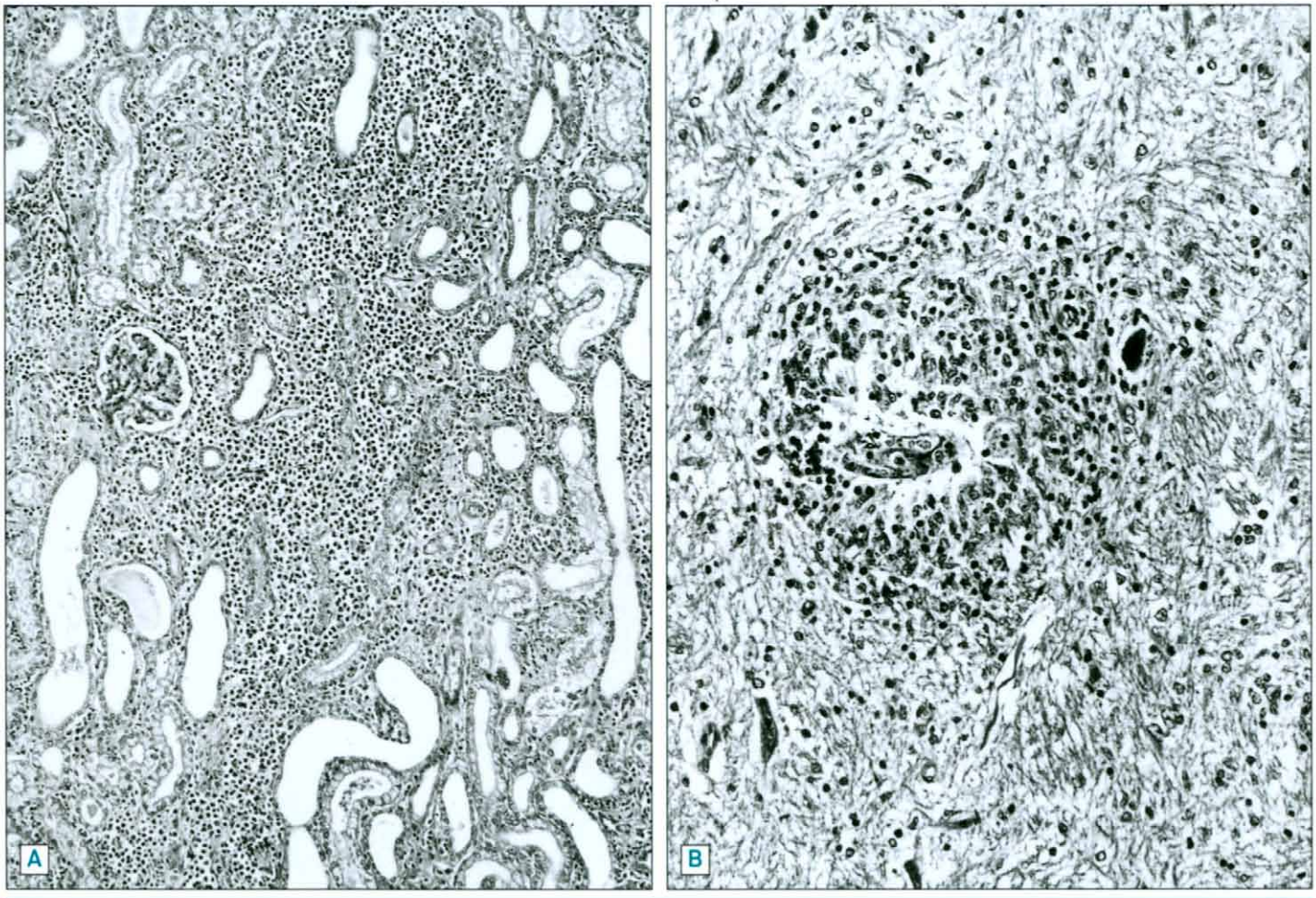

Figure 3.129 Encephalitozoonosis in a dog. **A.** Severe diffuse nonsuppurative interstitial **nephritis.** **B.** Focal granulomatous **encephalitis.**

Puppies which survive the early clinical disease may remain stunted and develop progressive renal disease. It is possible that encephalitozoonosis, as for any sporadic disease, is underdiagnosed especially in chronic infections in which the organism is difficult to demonstrate. Immunohistochemical methods help to identify sparse organisms and to distinguish them from similar parasites, particularly *Toxoplasma* and *Neospora*.

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Equine protozoal myeloencephalitis

Equine protozoal myeloencephalitis (EPM) is caused mainly by ***Sarcocystis neurona***, an apicomplexan protozoan parasite, however identical disease is reported in association with ***N. caninum*** and ***N. hughesi***. Opossums (*Didelphis* spp.) are the definitive host for *S. neurona,* and they are infected by eating intermediate host tissues that contain infective tissue cysts. *S. neurona*-induced EPM is restricted to the Americas in the geographical range of the opossum. Natural intermediate hosts (e.g., armadillos, sea otters, raccoons, skunks, cats) are infected by ingestion of food or water contaminated by sporocysts shed in opossum feces. Horses are assumed to be dead-end hosts, but may also act as intermediate hosts.

Exposure to *S. neurona* is widespread among horses, but the prevalence of the classic progressive disease is much lower. A seropositive horse is positive for exposure but not necessarily for the presence of the disease. However, the presence of seropositivity and the clinical signs of weakness and acute ataxia usually indicate active disease. Infection with *S. neurona* has no age predilection. Most EPM cases due to *S. neurona* infection appear in the summer and fall. Affected horses are presented with ataxia, limb weakness, lameness, and rarely seizures.

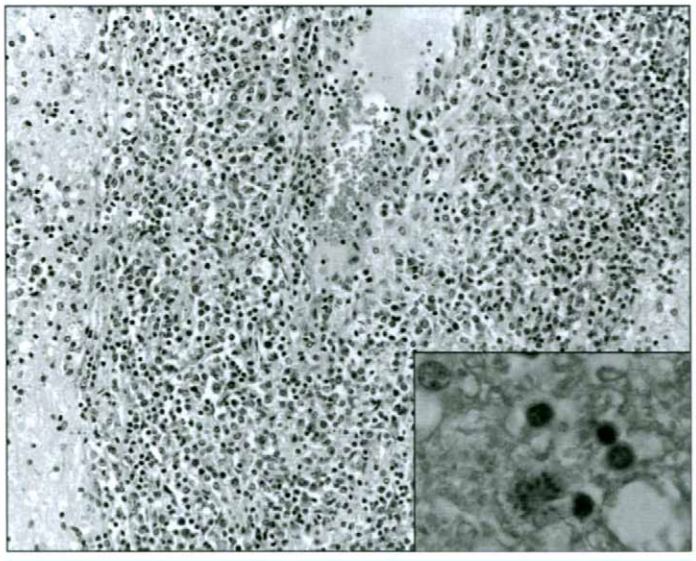

Figure 3.130 Massive mixed inflammatory encephalitis with variable numbers of eosinophils with rare intralesional ***Sarcocystis neurona*** schizonts (inset) in a horse with equine protozoal myeloencephalitis.

Gross lesions are present only in severe cases, and range from multifocal acute hemorrhage to the presence of discrete multifocal gray to dark yellow areas primarily in cross-sections of fixed brain stem, obex, pons, and cervical and thoracic cord. The histologic lesions are usually moderate to severe and characterized by multifocal areas of necrosis, malacia with aggregation of gitter cells, gliosis, and infiltration of large numbers of lymphocytes, histiocytes, plasma cells, and fewer eosinophils and neutrophils with severe involvement of the meninges (Fig. 3.130). The blood vessels in these areas have swollen activated endothelium with thick perivascular cuffs of mononuclear cells and occasional eosinophils. Also and particularly in cord sections, there is axonal swelling or loss besides the appearance of spheroids and some digestion chambers. In chronic cases, the inflammation can be predominantly histiocytic with occasional eosinophils and multinucleated giant cells.

Finding *S. neurona* merozoites or schizonts can be a challenge and serial sections must be examined in most cases. *S. neurona* schizonts are almost always present near areas of inflammation and necrosis, schizonts are oval or irregularly round, have very thin walls (<0.5 μm), are up to 20 μm in diameter, and contain a few basophilic ovoid merozoites 5 μm × 1.5 μm. The stage infective to the definitive host, i.e., sporocysts, can be found in tongue and other skeletal muscles. The *S. neurona* sporocyst is round (50–100 μm) or elongate (500 μm long and 40 μm wide), and contains a number of bradyzoites.

EPM-like disease can occur in other *S. neurona* intermediate hosts, including the cat, and this disease should be considered in the differential diagnosis of inflammatory encephalomyelitis in this species. Both *N. hughesi* and *N. caninum* can cause identical EPM lesions in horses. The complete life cycle and methods of transmission for *N. hughesi* have not been determined. *Neospora hughesi* tachyzoites are crescent-shaped, approximately 5 × 2 μm. Definitive diagnosis of EPM in a live horse is challenging. Detection of *S. neurona* or *N. hughesi* antibodies in serum and cerebrospinal fluid by an immunoblot test is available. Positive results indicate exposure, but do not necessarily indicate that the horse has EPM. The postmortem diagnosis depends on finding characteristic lesions, especially in the presence of the characteristic protozoal stages. Immunohistochemistry kits for *S. neurona* and *N. caninum* are available commercially.

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Neosporosis

Neospora caninum is an apicomplexan coccidian parasite that is a major pathogen of cattle, in which it causes abortion, and for dogs. Other species, such as goats, sheep, deer, and horses, can be infected occasionally. Dogs are the primary definitive host, and they are also considered as an intermediate host. Other canids, e.g., coyotes (*Canis latrans*), may also be important definitive hosts. *N. caninum* has three infectious stages: tachyzoites, tissue cysts, and oocysts. Tachyzoites and tissue cysts are found both in intermediate hosts and the definitive host. However, oocysts are only present in the definitive host. Tachyzoites have been found in neurons, reticuloendothelial cells, hepatocytes, muscle cells including myocardium, and bovine placenta. Tissue cysts have been found in the CNS, muscles, and retina. The exact modes of transmission are not well understood. Dogs become infected by ingesting tissues contaminated with tissue cysts, and then shed oocysts in their feces. Cattle and other intermediate hosts become infected by ingesting sporulated oocyst-contaminated food, water, or soil. However, the principal route for infection in cattle is transplacental (vertical) transmission.

N. caninum does not cause significant clinical disease in adult **cattle**, however it causes abortion in both dairy and beef cows particularly at mid-term, although cows can abort at any time from 3 months to term. Infected fetuses may die in utero, be mummified, stillborn, or born alive with or without clinical signs. Extraneural lesions in bovine fetuses include *lymphocytic, plasmacytic and, to a lesser extent, histiocytic, hepatitis, pancarditis or myocarditis, myositis, and placentitis*. Cotyledonary necrosis may be associated with the placentitis. Intralesional *Neospora caninum* tachyzoites are occasionally present in the aforementioned organs. Tachyzoites appear in groups, either intracellular in neurons, endothelium or epithelial cells, or extracellular. Tachyzoites are spindle-shaped, 4–7 × 2 μm. Tissue cysts are primarily present in the CNS and rarely in skeletal muscles. Cyst diameter is up to 107 μm, with wall thickness of 1–4 μm, and containing numerous bradyzoites 8 × 2 μm.

The most frequent and almost pathognomonic CNS lesion in *bovine fetuses* is the presence of *multifocal discrete foci of necrosis* (~100–300 μm diameter), particularly in the brain and to a lesser extent in the cord (Fig. 3.131A, B). The necrotic areas are fairly well circumscribed, have necrotic centers and are surrounded by a rim of glial cells and macrophages. In advanced lesions, the necrotic area may be completely replaced by macrophages and a few glial cells, which make the lesions appear as discrete granulomas. The recognition of *N. caninum* tachyzoites and tissue cysts in aborted fetal brain or other fetal tissue is usually difficult on H&E stain, and immunohistochemistry must be performed to confirm the diagnosis of neosporosis. Other CNS lesions include mild nonsuppurative meningoencephalomyelitis. Fetal anomalies are not common in association with *Neospora* abortion.

Infection in **dogs** is transmitted either horizontally or vertically (transplacental). Dogs of any age can be affected and the infection can be generalized affecting any organs, including the skin, or can be localized. Infection in adult dogs is usually subclinical. Infection in young congenitally infected dogs is severe and characterized pathologically by encephalomyelitis and myositis/polyradiculoneuritis and clinically by hindlimb paresis that is followed by paralysis. CNS lesions are those of *necrotizing granulomatous, lymphoplasmacytic, and occasionally eosinophilic meningoencephalomyelitis* with diffuse gliosis, occasional axonal swelling, digestion chamber formation, and intralesional *N. caninum* tachyzoites and cysts (Fig. 3.132). These lesions are widely distributed in the brain and cord, however in the cortex the gray matter is affected predominantly. Lesions associated with the neuritis/polyradiculoneuritis is frequently severe, mostly affecting pelvic limbs, and characterized by severe lymphohistiocytic and occasional eosinophilic inflammation with associated secondary degenerative and necrotizing changes either in muscles or nerves with intralesional tachyzoites and rare cysts.

Experimental infection of pregnant **ewes** and **does** produces a disease that is identical pathologically to that observed in cattle, however natural disease is rare.

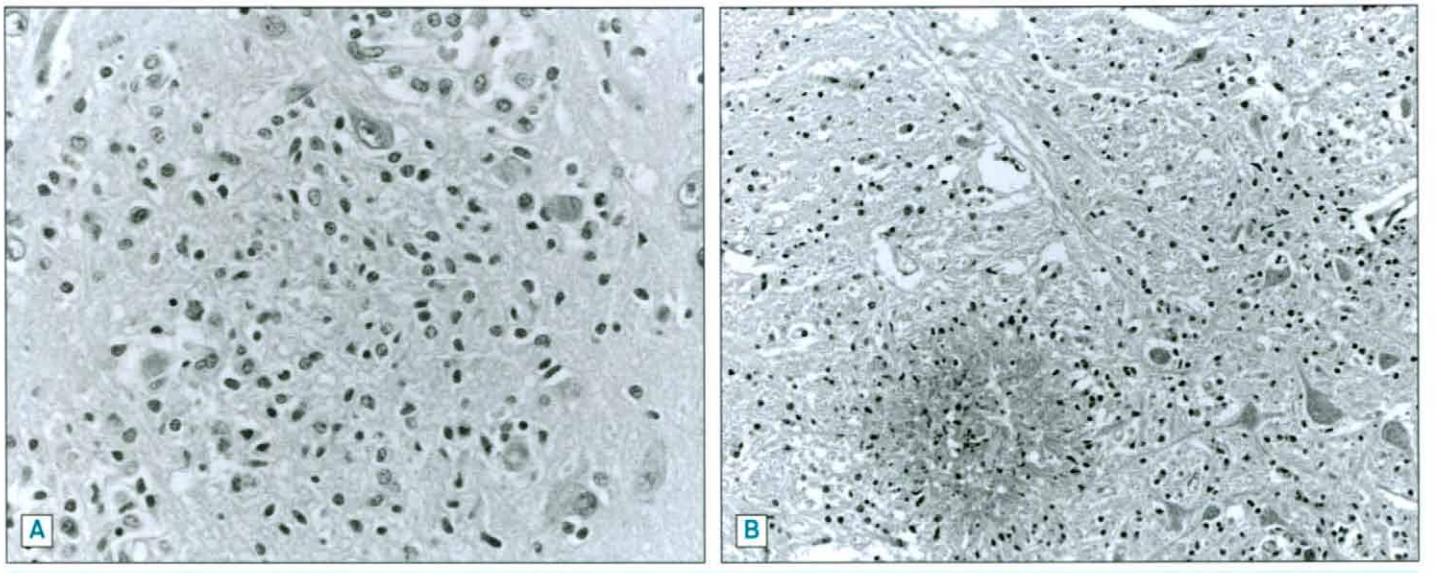

Figure 3.131 Lesions of neosporosis in fetal bovine brains may consist only of focal gliosis (**A**) or may occur as multifocal areas of neuropilar necrosis (**B**) encircled by glial cells and rarely giant cells. *Neospora caninum* cysts are rarely seen.

The epidemiology and methods of transmission of *N. caninum* and other *Neospora* in **horses**, e.g., *N. hughesi*, are not completely understood. Transplacental infection is suggested but not completely confirmed. *N. caninum* has been isolated from a few aborted fetuses. *N. caninum* and *N. hughesi* are rare causes of equine protozoal myeloencephalitis (see above).

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Toxoplasmosis

Toxoplasmosis is one of the most common protozoal diseases affecting humans and animals and is caused by ***Toxoplasma gondii***. Diseases caused by *T. gondii* are very similar in clinical presentation and pathology to those caused by *N. caninum*. Felids are the only definitive host and they also can act as an intermediate host. Other intermediate hosts include humans and other mammals. *T. gondii* has three infectious stages: tachyzoites, tissue cysts, and oocysts. Tachyzoites and tissue cysts are found in both intermediate and definitive hosts, however, oocysts are only present in the definitive host. Tachyzoites and tissue cysts are present more commonly in neural tissue and muscles, but can be present in virtually any tissue. Felids become infected by ingestion of tissues contaminated with tissue cysts, and shed oocysts in their feces. Human and other intermediate hosts including felids can become infected by ingesting sporulated oocyst-contaminated food, water, or soil. Transplacental transmission is important in cats, goats, and sheep. The extraneural pathology of toxoplasmosis is discussed elsewhere in these volumes. The nervous system lesions, including polyradiculoneuritis, are identical to those described above for neosporosis, however *the tissue cyst has a thinner wall (<0.5 μm), is 5–70 μm in size, and contains several bradyzoites 0.7–1.5 μm. Tachyzoites are 2–6 μm in size.* The encephalitic form of toxoplasmosis is most likely to occur in immunosuppressed dog and cats or kittens. Toxoplasmosis in pigs is generalized and can cause devastating disease with lesions including nonsuppurative encephalomyelitis with intralesional *T. gondii* stages.

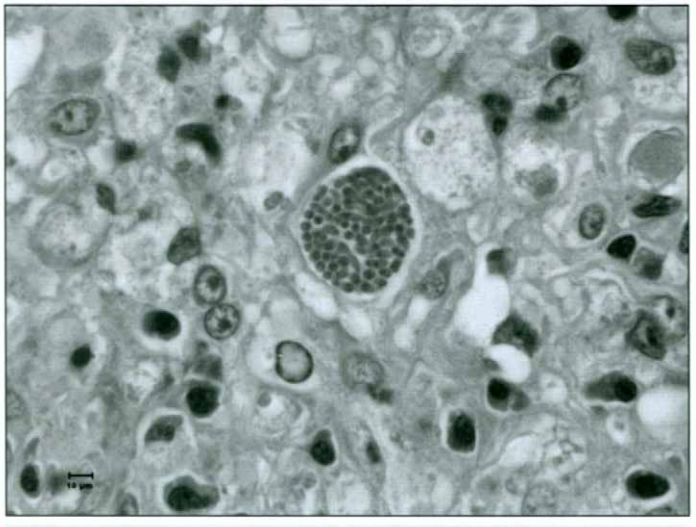

Figure 3.132 *Neospora caninum* cyst in the brain of a dog. (Courtesy of MJ Hazlett.)

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Sarcocystis canis encephalitis

A rare and generalized disease affecting dogs mostly in North America is caused by *S. canis* and characterized histologically by multisystemic vasculitis, hepatitis, and necrotizing lymphohistiocytic encephalitis in association with the presence of intralesional *S. canis* schizonts and merozoites (schizonts are 5–25 × 4–20 μm and contain 6–40 merozoites of 5–7 μm × 1 μm).

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Helminth and arthropod infestations

Nothing is known of what motivates and directs the migration of larval parasites. Those that migrate somatically are apt to go astray, and this appears especially likely when they wander in an alien host. Aberrant pathways include the nervous system with such frequency as to suggest that nematodes have a special propensity for wandering in the CNS. Whether this is indeed the case remains to be proven, but parasitic migrations in nervous tissue are more likely to be symptomatic than aberrant migrations in other tissues, and there is an impressive list of parasites that have been found in brain or cord. Many of these infestations and the parasites in question are discussed elsewhere in these volumes.

Cestodes

Adult cestodes live almost exclusively in the small intestines of the final host, however certain larval stages can infest the brain of the intermediate host. ***Coenurus cerebralis***, the larval stage of ***Taenia***

multiceps, which infests the small intestines of dogs and wild carnivores, is fairly common in the brains of sheep in Europe, less common in other herbivores, and rather rare in horses and humans. About 40% of pigs harboring ***Cysticercus cellulosae*** (the larval stage of the human tapeworm ***Taenia solium***) have cysts in the meninges and brain as well as in the muscle, and the same species has been identified in the brains of dogs. Possibly ***Cysticercus bovis*** (the larval stage of human tapeworm ***Taenia saginata***) and other cysticerci will invade nervous tissue with comparable frequency. Apparently, hydatids are seldom found in brain.

Nematodes

The term **cerebrospinal nematodiasis** is applied to nervous diseases resulting from aberrant nematode larval migrations. The few nematodes that produce the syndrome with any frequency are discussed below.

Parastrongylus *(Angiostrongylus)* ***cantonensis*** is a metastrongylid lungworm whose only known definitive host is the rat. It is widely distributed in the warm Pacific regions, but its distribution is much more limited than that of the gastropod intermediate hosts and the rat. The parasite resides in the pulmonary arteries of rats, eggs lodge as emboli in alveolar capillaries and the larvae, which hatch in about 6 days, and follow the tracheal–intestinal route to the exterior. First-stage larvae actively penetrate terrestrial and aquatic slugs and snails, which act as intermediate hosts. Transport hosts for third-stage larvae include frogs, crabs, and prawns. In addition to the rat, dogs, humans, and occasionally other species are infected by eating intermediate or transport hosts and, possibly, directly by ingestion of infective larvae that have emerged from intermediate hosts. Ingested larvae enter and are dispersed by the circulation to many tissues, but predominantly to brain, kidney, and muscle. Molting larvae in the brain produce a mild to severe inflammatory reaction before re-entering the venous circulation for return to the pulmonary arteries. Aberrant infections are important in humans and dogs, and are reported in horses and macropods. The human disease, eosinophilic meningoencephalitis, is usually mild and without sequelae, but infection in dogs can be accompanied by ascending paralysis. Larvae that enter the brain in dogs are probably inhibited in their development and destroyed there (Fig. 3.133). The lesions are granulomatous, randomly distributed in the cord and brain and are most frequent and severe in the cord (Fig. 3.134). Rarely, degenerate parasites are present in the granulomas, but apparently viable worms in the tissue are not accompanied by an inflammatory reaction. Eosinophils infiltrate the granulomas but are more numerous in affected meninges.

Parelaphostrongylus *(Pneumostrongylus)* ***tenuis*** is a metastrongylid parasite of white-tailed deer, *Odocoileus virginianus*, in North America. The intermediate hosts are terrestrial slugs and snails. Ingested larvae reach the spinal cord of the deer in ~10 days. They develop for up to 1 month in the dorsal horns of the cord at all levels and then migrate into the meningeal spaces. Some penetrate the dural veins and sinuses and mature. Eggs or larvae are carried in venous blood to the lungs. The larvae do very little to the cord in white-tailed deer, but the reaction is more severe in other species, including red deer, elk, moose, and sheep (Fig. 3.135). ***Elaphostrongylus panticola*** and ***E. rangifera*** of deer in northern Europe and Russia have a life cycle similar to that of *P. tenuis,* but infections are usually subclinical.

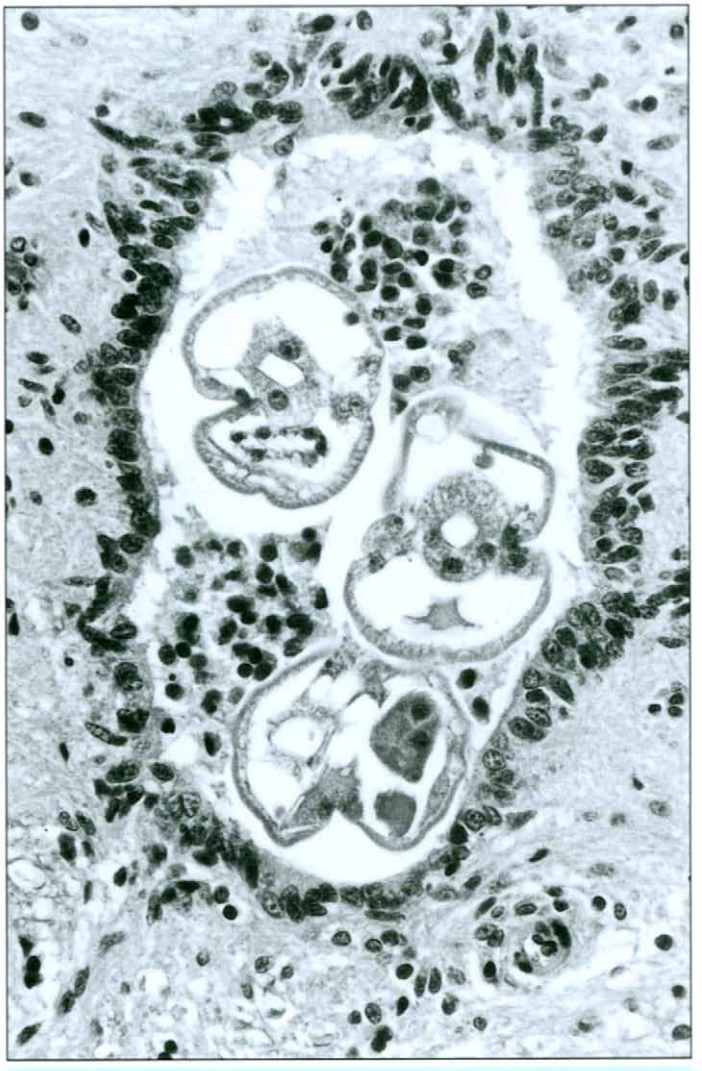

Figure 3.133 Larvae of ***Parastrongylus*** sp. in central canal of spinal cord in a dog.

When larvae of ***Elaeophora schneideri*** – a filarial parasite discussed in the Cardiovascular system – develop in the leptomeningeal arteries of various cervids, sheep and goats, they can cause ischemic necrosis of brain tissue.

Setaria digitata is normally found as an adult in the peritoneal cavity of cattle and buffalo in Asia (see also Peritoneum). Microfilariae can be carried to aberrant hosts such as horses, camels, sheep, and goats by mosquitoes, and larvae wandering in the brain and spinal cord are responsible for the neurological disease known as *kumri* (lumbar paralysis) in Asia. The migrating larvae apparently cause little or no damage in the natural host. The location of the lesions is variable, as are the clinical signs produced. Characteristically, the neurological signs are ataxia, weakness, or paralysis. The severity of the signs varies from slight weakness to quadriplegia, depending on the number and location of the wandering parasites; however, affected animals may remain bright and alert. The CNS lesions produced are fundamentally traumatic, and lead to microcavitation, as described below.

Halicephalobus gingivalis *(Micronema deletrix)* is a free-living nematode that is accidentally, but rarely, a parasite; this nematode is characterized by a rhabditiform esophagus. Massive intracranial invasion is reported in horses. The syndrome is acute and of short

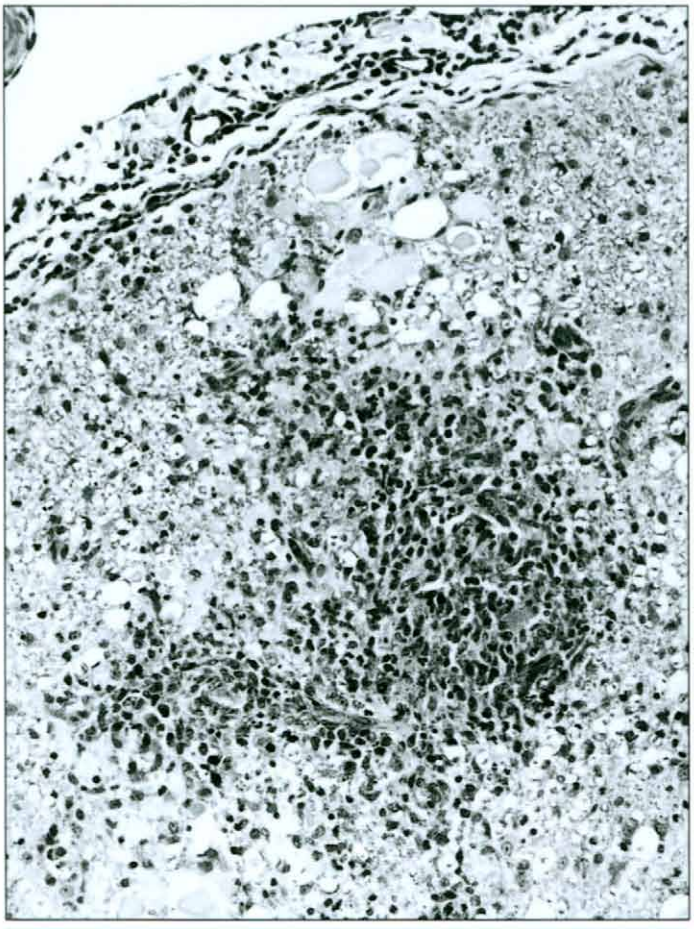

Figure 3.134 Granuloma formation, Wallerian degeneration, and spinal meningitis due to ***Parastrongylus*** infestation in a dog.

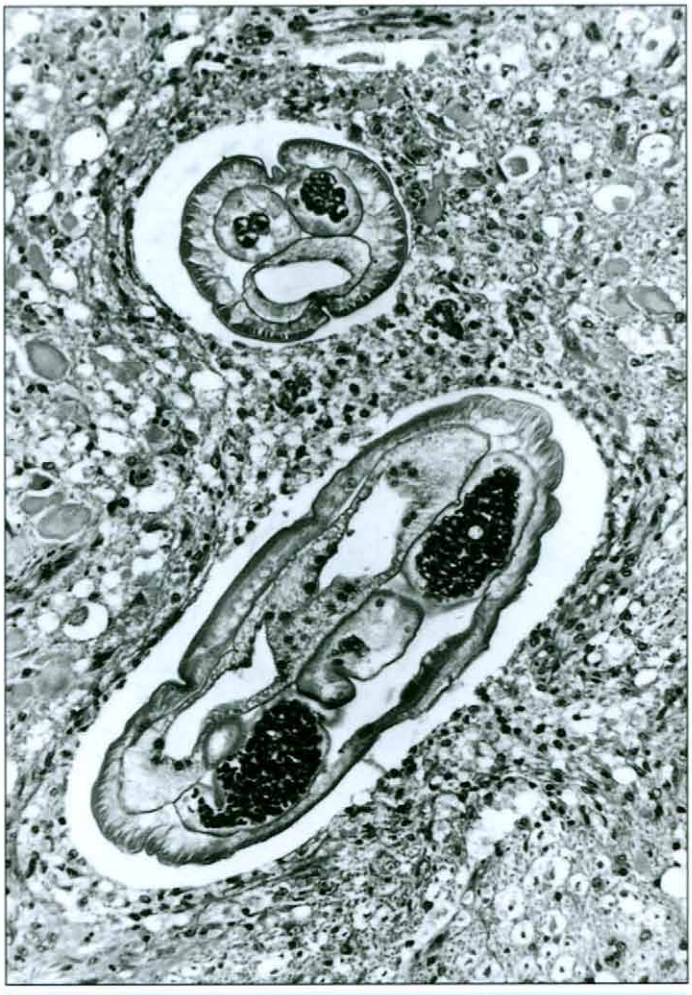

Figure 3.135 ***Parelaphostrongylus*** in spinal cord of a sheep.

duration. There are focal arachnoid hemorrhages and patchy meningeal thickenings. Only parthenogenetic female worms and larvae are found among the specimens in the brain, most easily in perivascular spaces (Fig. 3.136). Depending on the area of the CNS affected, lesions are granulomatous and eosinophilic meningoencephalitis, myelitis, polyradiculitis, or even cauda equine neuritis-like lesions. Parasitic granulomas in the kidney and gingiva may accompany the cerebral invasion. Little is known about the life cycle and method of transmission of this nematode. Oral ingestion or wound contamination then hematogenous distribution is suggested. Also, transmission from infected dam to her foal through milk is described in one case.

Gurltia paralysans, found in the spinal veins of cats, is reported to be responsible for a high incidence of paralysis in this host, and ***Angiostrongylus vasorum*** has caused hemorrhagic malacia in the brains of dogs. Aberrant hosts can develop severe cerebrospinal nematodiasis when they incidentally ingest the eggs of ***Baylisascaris procyonis*** (raccoon ascarid) or *Baylisascaris columnaris* (skunk ascarid).

Larval worms may also migrate aberrantly in the CNS of their natural hosts. ***Stephanurus dentatus*** quite frequently invades the spinal canal and may even encyst in the meninges in pigs. ***Strongylus* spp.** occasionally invade the brains of horses; Figure 3.137 shows the type of lesions that occur, and, although not identified in this case, the larvae were probably of *S. vulgaris* because these were identified in thrombi in the aortic bulb and carotid artery. **Ascarids** have a propensity for wandering in the brain of alien hosts and occasionally do so in their natural hosts.

Trematodes

Trematodes apparently have little tendency to invade nervous tissue. ***Troglotrema acutum*** may invade the brain from its normal habitat in the paranasal sinuses. The eggs of the lung flukes, ***Paragonimus* spp.**, have been observed in the brains of dogs, possibly arriving there as emboli.

Arthropods

The only larval arthropods of interest are ***Hypoderma bovis***, which normally migrates through the spinal canal, and ***Oestrus ovis***, which may invade the brain from the nasal sinuses.

Cuterebra spp. (larva of a rodent or rabbit bot) in an abnormal host, i.e., cat and to a lesser extent dog, can undergo aberrant migration and has been reported in many organs including the eyes and CNS. Adult *Cuterebra* are nonparasitic and are seldom observed. Lesions in the brain are characteristic and indicative of vascular compromise and direct toxicity by toxin released from the larvae. These lesions include superficial laminar cerebrocortical necrosis, cerebral

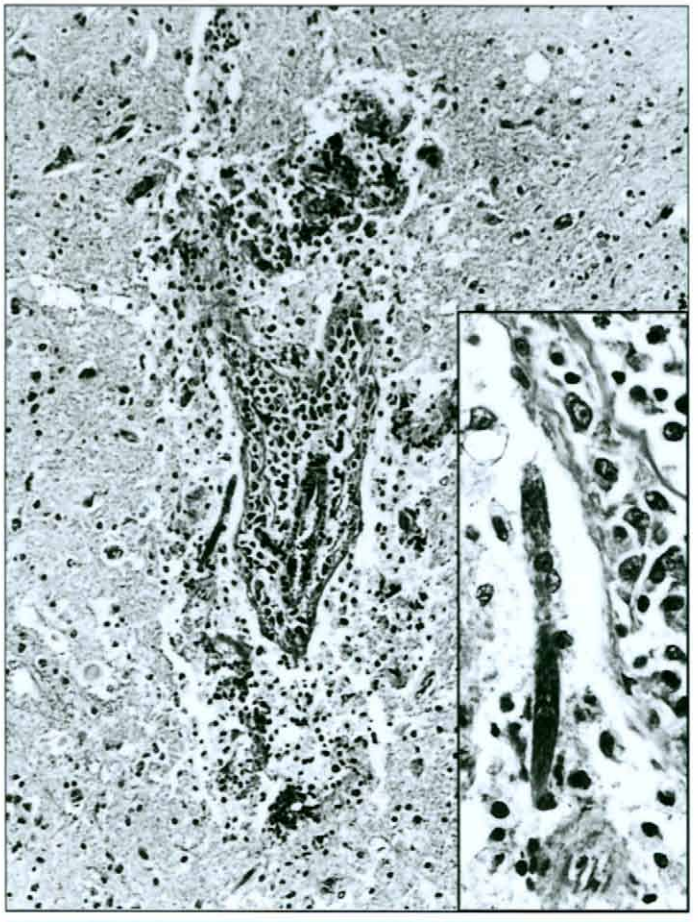

Figure 3.136 Perivascular inflammation in the brain of a horse caused by ***Halicephalobus gingivalis*** (*Micronema deletrix*). Inset: parasite with cellular reaction.

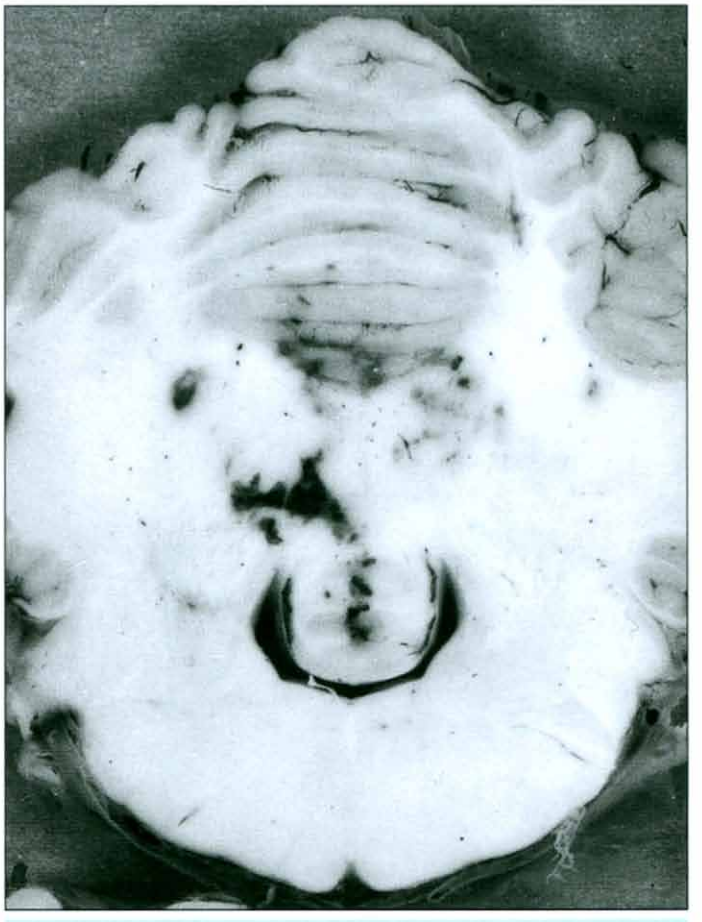

Figure 3.137 Hemorrhagic tracks in cerebellar white matter probably produced by ***Strongylus vulgaris*** in a horse.

(particularly at the olfactory bulbs and peduncles) and subependymal malacia and infarction, and finally larval migratory track lesions that are characterized by focal necrosis, hemorrhage, and infiltration of eosinophils, lymphocytes, plasma cells, and fewer neutrophils. Most of the track lesions are present in caudate nucleus or thalamus. Cuterebral larval migrans in the feline brain is thought to be the cause of *feline ischemic encephalopathy*.

The few parasites specifically mentioned are the most important in terms of neuropathology. Occasionally helminth larvae are discovered accidentally but rarely identified in sections of brain or cord, and it is somewhat more common to find lesions typical of those produced by migratory parasites without being able to locate the parasite. Some parasites, such as *Elaphostrongylus*, usually remain in the CNS whereas others, such as ascarids and strongyles, can be expected to keep moving. Finding the parasite is, therefore, largely a matter of luck, even when it is sought very early after the onset of clinical signs.

The lesions produced in nervous tissue by migratory larvae are mainly *malacic* and, although random, are fairly distinctive in their pattern. *Coenurus cerebralis* produces, in the invasion phase, purulent meningoencephalitis and later acts as a space-occupying lesion, but other invading parasites produce mainly traumatic lesions with very little inflammatory reaction except for a few eosinophils. The lesions produced by nematodes are sometimes grossly visible as *hemorrhagic foci or narrow, slightly tortuous tracks*. Brown, hemorrhagic discoloration depends on the parasite hitting a vein or arteriole, and it appears that some worms have a tendency to migrate along veins. There may be only one or several such tracks in the CNS, and they occur quite at random. Microscopically, the lesion is an irregular focus or pathway of traumatic malacia into which some hemorrhage may have occurred. There may be slight cellular infiltration in the adjacent meninges or nerve roots. The track is liquefied, and its margins not sharp, and apart from lymphocytes, gitter cells, and a few eosinophils, there is no significant reaction in the damaged tissue or in the adjacent vessels. The disruption, which is not selective in the tissues destroyed, leads to *microcavitation*. The disrupted axons, swollen, tortuous and as globose fragments, persist for some time in the microcavitations (Fig. 3.134). Gemistocytic astrocytes may be present in older lesions.

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Chlamydial disease

Sporadic bovine encephalomyelitis (SBE) occurs in calves less than 6 months of age, and is caused by ***Chlamydophila pecorum***. Identical disease is also reported due to infection with *Chlamydophila psittaci*. *Chlamydophila pecorum* also causes a wide range of other conditions in calves, including polyarthritis, metritis, conjunctivitis, and pneumonia. The disease occurs in the USA, Japan, Europe, and Australia; the agent probably has a worldwide distribution and most infections are asymptomatic. Encephalomyelitis is reported to occur naturally only in cattle and buffalo. As a rule, SBE is indeed sporadic, affecting only a few animals in a herd, however outbreaks of the disease with morbidity of 25% are described. Transmission appears to be by direct contact. The clinical syndrome is not particularly characteristic. It is composed of moderate fever and signs of catarrhal inflammation of the respiratory tract. There is some stiffness, weakness of the hindlimbs with staggering and knuckling of the fetlocks, and muscle tremors. There is some dullness; signs of excitement are not present. Death occurs in a few days to a few weeks.

The organism has a tropism for blood vessels, mesenchymal tissue and serous membranes, which make *vasculitis and polyserositis the hallmark of lesions*. Encephalitis is secondary to vascular damage. The gross morbid change that suggests a diagnosis of SBE is serofibrinous inflammation of serous membranes and synoviae. This is most consistently *peritonitis*, and in ~50% of fatal cases there is also *pleuritis and pericarditis*. The meninges appear congested and edematous and occasionally are covered with a few fibrin tags. Microscopically, there is a rather *severe and diffuse meningoencephalomyelitis* (see Fig. 3.60). The leptomeningitis is most severe about the base of the brain. The reactive cells are almost solely histiocytes and plasma cells, with only a few neutrophils. These cells infiltrate the meninges and perivascular spaces and mix with reactive adventitial cells of the vessel walls. The vascular endothelium proliferates secondary to lesions in the vascular walls, and ischemic changes may occur in the parenchyma. Reactive microglial nodules are widespread in the brain.

Cell culture of *Chlamydophila*, the gold standard diagnostic tool, is being displaced by detection by PCR. Elementary bodies produced by this organism occur in the cytoplasm of mononuclear cells in the exudates in the meninges and from serosal membranes and in microglia of nodules, but they are not numerous and their demonstration by special stains or immunohistochemistry is not usually rewarding.

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Idiopathic inflammatory diseases

Necrotizing meningoencephalitis of Pug and other small breed dogs

Canine necrotizing meningoencephalitis (NME), formerly "Pug dog encephalitis," is an idiopathic disease affecting mainly Pug dogs, but also reported rarely in Maltese, Pekingese, Shih Tzu, and Chihuahua. A similar condition, but with lesions more prevalent in the white matter, is reported in Yorkshire Terriers (distinct from *Yorkshire Terrier necrotizing encephalopathy*, which affects brain stem), named necrotizing leukoencephalitis. The cause of NME is unknown; several etiologic agents have been suggested as causes, including alpha-herpesvirus, but none has been confirmed. An autoimmune reaction against canine brain tissue has been suggested as a possible mechanism. A wide age range is affected. Generalized convulsions and their aftermath dominate the clinical picture, which may include lethargy, ataxia, and progression to coma. The clinical signs refer essentially to cortical disease that progresses rapidly over a few weeks, but which may extend to several months.

The lesions are particularly in the cerebral cortex, and are bilateral but asymmetric, often confluent over large areas, and extend to the adjacent white matter with relative sparing of the deeper periventricular tissue. The geography of the lesions therefore helps to distinguish this disease from other encephalitides of the dog. Grossly, localized swellings in the cerebrum contribute to asymmetry, and malacic foci may be seen as typical yellow areas of softening (Fig. 3.138) or, in cases of longer duration, as tiny cystic cavities.

The histological changes are necrotizing and with an affinity for the hemispheres. Numerous foci of meningitis, characterized by infiltrations of lymphocytes, plasma cells, and monocytes (Fig. 3.139), diminish caudally and may be absent in the caudal fossa and spinal cord. These infiltrates breach the pial barrier and destroy the superficial cortex to an extent and severity that is unusual. The evidence of

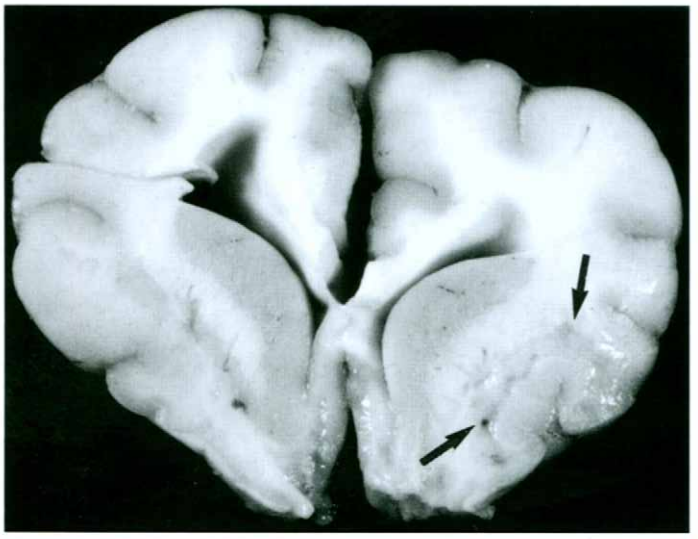

Figure 3.138 Malacic focus in ventrolateral cerebral hemisphere (arrows) in **Canine necrotizing meningoencephalitis**. (Reprinted with permission from Bradley GA. Vet Pathol 1991;28:91.)

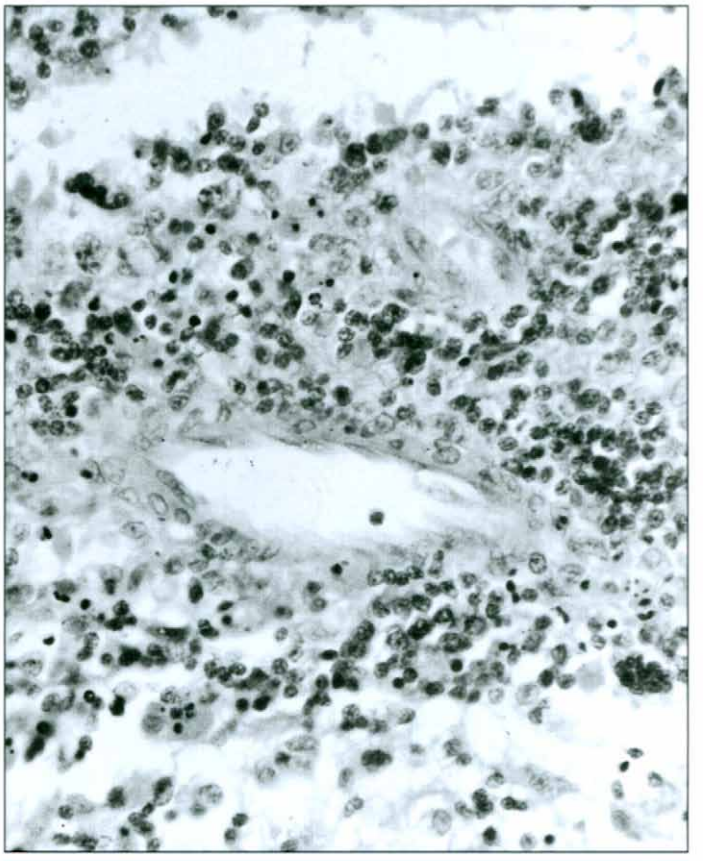

Figure 3.139 Meningeal arteriole surrounded by mixed mononuclear infiltrate in **Canine necrotizing meningoencephalitis**.

cerebral necrosis extends from selective neuronal necrosis to areas of malacia, the latter especially in chronic cases. Vascular endothelium in the cortex is reactive and associated with edema, occasional petechiae, and diffuse accumulation of mononuclear cells in parenchyma and vascular cuffs.

The differential features of this meningoencephalitis, in addition to its nonsuppurative nature, are the malacic degenerations and predilection for the cerebral cortex. This condition must be differentiated also from granulomatous meningoencephalomyelitis (GME). The inflammatory infiltrate in GME contains more histiocytes, which in the chronic stage transform to epithelioid cells that can form discrete cohesive sheets or granuloma-like lesions. Also, in GME, the reaction is predominantly in the white matter and is distributed in almost all parts of the CNS. In contrast, the reaction in NME is mostly in the cortical gray matter.

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Granulomatous meningoencephalomyelitis

Granulomatous meningoencephalomyelitis (GME) is a sporadic disease of the CNS of dogs. GME appears to have a worldwide distribution and to occur mostly in *young to middle-aged dogs of small breeds*, e.g., terriers and toy breeds, however the disease can occur in any breed and in an age range of 6 months to 12 years. The cause of GME is unknown; several infectious causes have been suggested but not confirmed to be the cause of this condition. Based on the predominance of CD3+ T cells and MHC class II antigen-positive macrophages, an immune-mediated mechanism has been proposed.

Variations in the distribution and extent of the lesions result in a variety of clinical signs. Spinal lesions may be associated with ataxia, paresis, or paralysis (Fig. 3.140). Lesions in the brain stem frequently produce signs of vestibular dysfunction. Changes of behavior, forced movement and circling, depression and convulsions occur with supratentorial lesions. Macroscopic lesions, if evident, consist of gray-white discoloration of the white matter of the brain or spinal cord, and in those cases in which the cellular aggregations become confluent, there may be irregular areas of malacia (Fig. 3.141).

The histologic changes are patchy in distribution. There may be very few foci, or they may be disseminated, or they may be localized to one area and confluent, or there may, in the same animal, be both confluent and disseminated distributions. *The essential histologic feature is perivascular aggregation of cells rather selectively in the white matter.* The minimal lesion is cuffing of vessels by lymphocytes and plasma cells with small eccentric clumps of macrophages. The macrophages increase in number and may come to comprise the cuff, appearing as discrete granulomas, which, depending on the plane of section, may appear to be in the parenchyma. Occasional mitoses are present in these cells. Transformation to epithelioid cells occurs later. The perivascular aggregates expand in concentric arrangements and displace surrounding parenchyma (Fig. 3.142). Where the cuffing response is severe, edema and necrosis may occur in the adjacent white matter leading to a spillover of mononuclear cells into the parenchyma and to the usual reactive changes. Large malacic foci are unusual. In cases of prolonged duration, confluence of lesions occurs and reparative responses include the deposition of abundant reticulin and collagen in perivascular arrangements. Involvement of meninges is patchy and often related to lesions of white matter directly underlying.

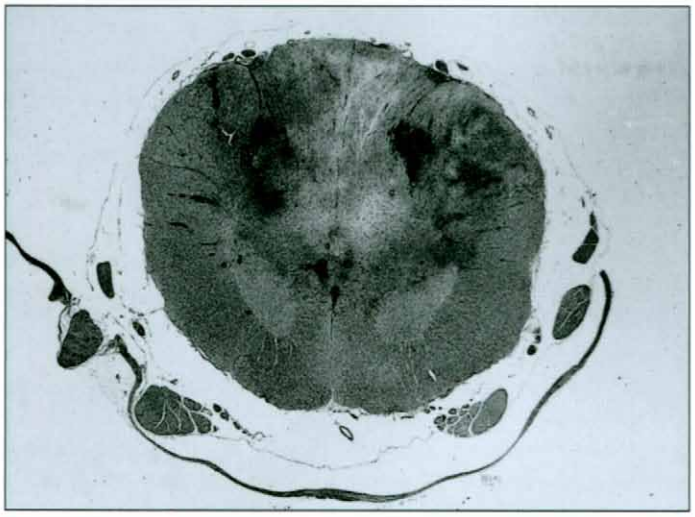

Figure 3.140 Focal lesions in the spinal cord of a dog with **granulomatous encephalitis**. (Courtesy of JB Thomas.)

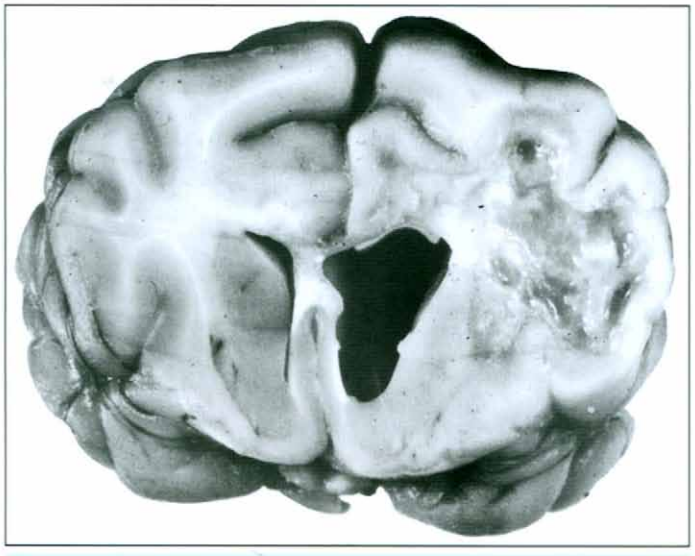

Figure 3.141 Malacia of cerebrum and hydrocephalus secondary to infarction in a dog with **granulomatous encephalitis**.

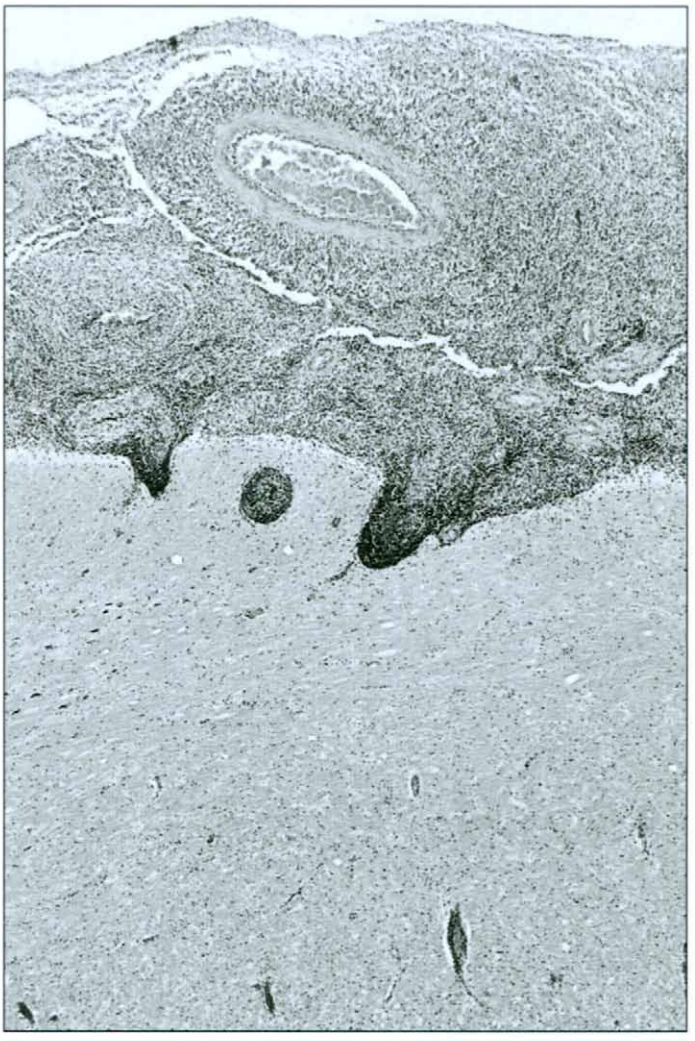

Figure 3.142 Dense perivascular meningeal infiltrate in **granulomatous encephalitis** in a dog.

Cytological characterization of the cell aggregates can be difficult. In many, and perhaps most, cases, the cells are easy to classify, being well differentiated as lymphocytes, monocytes, plasma cells, and histiocytes (Fig. 3.143). Granulocytes may be present but are not numerous, and histiocytes often show epithelioid transformation and may form small syncytial masses. There may also be in some cases large immature cells of reticulohistiocytic type in which mitoses may be few or many. Differentiation between GME and brain malignant histiocytosis (BMH) can be problematic occasionally; BMH is frequently part of a multisystemic tumor and rarely occurs in isolation. Also, the absence of cellular atypia and the predominance of perivascular orientation should favor the diagnosis of GME.

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Acute polyradiculoneuritis (coonhound paralysis)

Acute polyradiculoneuritis, or polyradiculoneuropathy, affects primarily dogs, occasionally cats, and rarely horses, and has many similarities to Guillain-Barré syndrome in humans. The condition was named coonhound paralysis to reflect the fact that some affected dogs had been bitten or scratched by raccoons, although cases may have no known exposure to raccoons. Within 7–10 days, ascending flaccid paralysis, starting in the hindlimbs and progressing cranially to involve the forelimbs, leads to quadriplegia and rapid atrophy of muscle. There are no cerebral signs. Some dogs die of respiratory paralysis, but most will recover slowly if nursing is adequate. Dogs that have

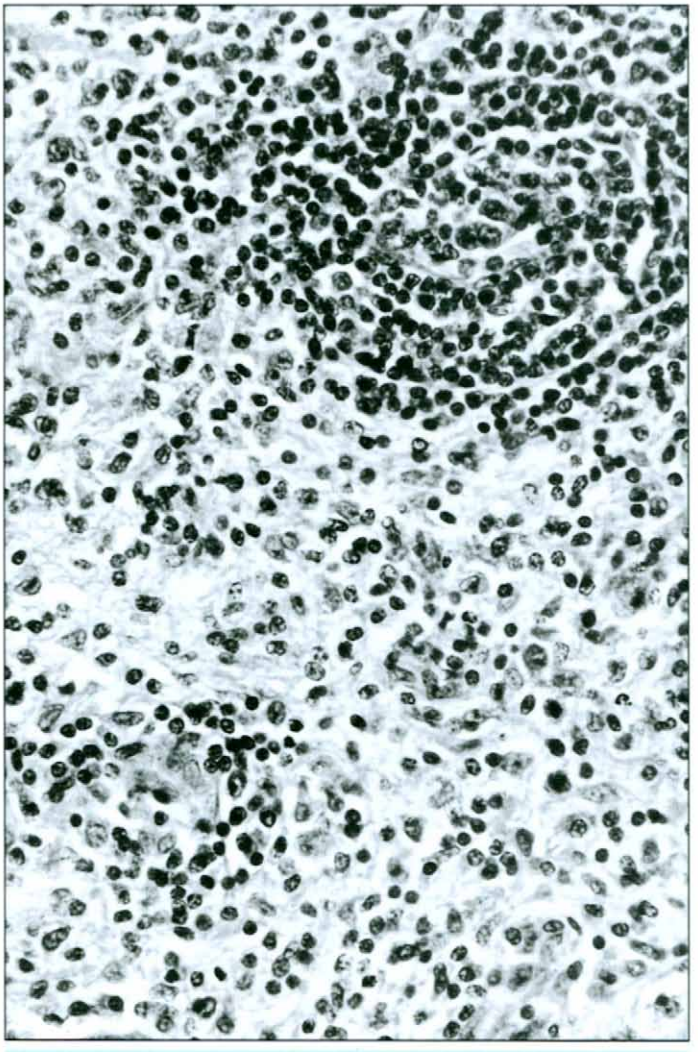

Figure 3.143 Detail of cellular infiltrate in brain in **granulomatous encephalitis** in a dog.

recovered appear to have increased sensitivity to subsequent exposure but may survive several bouts of paralysis. The disease has been transmitted using pooled saliva of raccoons, but the cause has not been identified; an autoimmune mechanism is suspected. Lesions are found in the *ventral roots of spinal nerves and in peripheral nerves*. Mononuclear and plasma cells infiltrate around venules, but the extent of the infiltrate is variable and not correlated with the course of the illness or the severity of nerve degeneration. There is primary and Wallerian degeneration afflicting ventral roots in particular, with axonal reaction in motor neurons and atrophy of denervation in muscle. This idiopathic polyradiculoneuritis is the most common inflammatory condition of peripheral nerves in dogs.

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Neuritis of the cauda equina

Neuritis of the cauda equina of horses is a polyneuritis in which the presenting signs are referable to the sacrococcygeal nerves and include perineal anesthesia, tail paralysis, urinary incontinence, fecal retention, weakness, atrophy of coccygeal muscles and, in longstanding cases, atrophy of the muscles of the hindlimbs. The neuritis is progressive. The cause is unknown, but the nature of the reaction suggests immune mediation, which may follow viral infection. The condition has been compared to experimental allergic neuritis in laboratory animals. *Halicephalobus gingivalis* is reported as a novel cause of cauda equina neuritis in one horse.

Although the pathologic changes emphasize the *sacral and caudal spinal nerve roots*, there may simultaneously be asymmetric pareses of other nerves producing isolated limb pareses, and paresis or paralysis referable to cranial nerves. The lesions in these other nerves are similar in character to, but much milder than, those in caudal nerve roots. Inflammatory changes are present in sensory and some autonomic ganglia, but changes in the spinal cord are limited to those that reflect peripheral nerve injury.

The gross changes affect in particular the extradural parts of the sacral and coccygeal nerves and may extend through the intervertebral foraminae into the adjacent muscle. The roots are thickened and fusiform and usually discolored by recent or old hemorrhage. The intradural segments of affected nerves are discolored but not usually enlarged.

Microscopically there is *granulomatous inflammation with extensive fibrosis*. The thickening and discoloration are attributable to hemorrhage, proliferation of epineural tissue, and inflammatory cell infiltrates. The infiltrating lymphocytes, plasma cells and macrophages are frequently disposed as to form granulomas, often with central epithelioid and giant cells; granulocytes do not feature in the infiltrates. Degenerative and regenerative changes are present in the myelin and axons of affected roots and appear to be more closely associated with endoneurial and perineurial fibroplasia than with leukocytic infiltrates.

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Steroid-responsive meningitis-arteritis (Beagle pain syndrome)

Steroid-responsive meningitis-arteritis (SRMA) is a *polyarteritis of possible immune-mediated origin affecting mainly small to medium-sized leptomeningeal and myocardial arteries*, but arteries in many organs can be affected. Beagles, especially those in laboratory-bred colonies, are at high risk, but the disease is reported in Boxers, German Shorthaired Pointers, Nova Scotia Duck-tolling Retrievers, and rarely in other breeds. Affected dogs have fever, hyperesthesia, severe pain on manipulation, cervical rigidity, and anorexia. The clinical course of SRMA is usually acute, but a chronic form exists. Gross lesions are minimal, but areas of subarachnoid hemorrhage may be present

along the brain stem and the spinal cord, especially the cervical part. Histologically, small to medium-sized leptomeningeal arteries, especially of the brain stem and spinal cord, and to a lesser extent heart and cranial mediastinum, have moderate to severe perivascular and transmural infiltrates of lymphocytes, plasma cells, histiocytes, and fewer neutrophils. Occasionally, neutrophils predominate. Also, there is severe fibrinoid necrosis, thrombosis, and occasionally periarterial fibrosis. Mild lymphocytic and histiocytic leptomeningitis is also a constant finding.

Distinct from SRMA, an unusual case of idiopathic vasculitis resembling "*isolated angiitis of the CNS*" in humans has been reported in a mixed-breed dog. The necrotizing vasculitis, with cuffs of mixed cell types including multinucleated giant cells, resulted in localized cerebral necrosis.

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Shaker dog disease

Shaker dog disease is an idiopathic condition characterized clinically by *tremors* that worsen after stress or excitement. The condition was described first affecting solely young adult white-haired small dogs (little white shakers), but now is recognized in dogs of any size or coat color. Histologically, *mild diffuse, nonsuppurative encephalomyelitis* is present. No myelin disease is present.

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Sensory ganglioneuritis (sensory ganglioradiculitis)

Sensory ganglioneuritis (sensory neuronopathy) is a rare idiopathic disease of adult dogs characterized by *nonsuppurative inflammation of dorsal root (sensory) spinal ganglia and cranial sensory ganglia* with degeneration and necrosis of sensory neuronal cell bodies and proliferation of ganglionic satellite cells. The cause may be a cell-mediated immune mechanism. Secondary to sensory ganglion neuronal injury, Wallerian degeneration develops in the dorsal funiculi (fasciculus cuneatus and fasciculus gracilis) and the affected areas appear grossly as white V-shaped or triangular areas throughout the entire length of the spinal cord. Similar but milder lesions can be present in sympathetic ganglia, peripheral nerves, myenteric plexi, motor roots, and the spinal tract of the trigeminal nerve. Breed or sex predilection have not been observed. Clinical signs are variable and include generalized sensory ataxia, depression or absence of spinal reflexes, facial hypalgesia/paresthesia, megaesophagus, and dysphagia. Masticatory muscle atrophy is observed in a few dogs in association with this condition and is attributed to loss of motor fibers as they course through the trigeminal ganglion.

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Post-infectious encephalomyelitis

Neurological disease that follows, after a variable period, common viral infections or vaccination exposure is well known in children as post-infectious or post-vaccinal encephalitis, or acute disseminated encephalomyelitis. The common pathologic basis is a *demyelinating inflammatory process dominated by mononuclear inflammatory cells with a distinctive perivenous distribution*. Examples that meet the criteria have occurred in relation to rabies vaccination in dogs when such vaccines were prepared in neural tissue, and the pathologic process is the same as that in experimental allergic encephalomyelitis. The histologic changes are widely distributed in the brain and cord and affect mainly the white matter. Perivascular infiltrates of lymphocytes, plasma cells, and monocytes/macrophages widely distend the space and spread into the surrounding parenchyma. Proliferation of adventitial cells may be prominent. Although much descriptive emphasis has been given to demyelination, this is restricted to the perivascular areas of infiltration and to surrounding areas showing the usual degenerative and reactive changes.

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Eosinophilic meningoencephalitis

Recognized causes of eosinophilic meningoencephalitis include nematode and protozoan parasites. **Idiopathic eosinophilic meningoencephalitis** has been reported in dogs, with Rottweilers and Golden Retrievers over-represented, and one cat. The condition is characterized clinically by behavioral changes such as inappropriate urination and lack of response to commands. In severe cases, episodes of sternal or lateral recumbency without loss of consciousness are described. Clinical pathology findings are mild to moderate peripheral blood eosinophilia and CSF pleocytosis with predominance of eosinophils. Grossly, there is thickening and green discoloration of the meninges. Histologic changes are those of eosinophilic and granulomatous meningitis of the cortex and cerebellum, and the underlying neural parenchyma appears pallid, occasionally spongiotic, and has mild eosinophilic and histiocytic cuffing with rare areas of axonal swelling and neuronal degeneration. Spinal cord lesions are poorly documented. The condition is usually responsive to steroid treatment, suggesting an immune-mediated mechanism.

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Granulomatous radiculitis of the seventh and eighth cranial nerves of calves

This is a rare condition affecting young calves and characterized clinically by facial paralysis and pathologically by the presence of multifocal granulomas affecting mainly the roots of cranial nerves VII and VIII. The etiology is unknown; however, *Mycoplasma bovis* was suggested as a cause because some affected calves had concurrent mycoplasmal otitis media.

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NEOPLASTIC DISEASES OF THE NERVOUS SYSTEM

Primary neoplastic disease of the CNS of animals is rare in species other than the dog and cat. Neoplasms derived from virtually every cell type in the nervous system are recorded.

The tumors may be *congenital*, and these do not differ in their characteristics from similar tumors in adult animals with the possible exceptions of: medulloblastoma, which is thought to be derived from the residual cells of the external granular layer of the cerebellum; craniopharyngiomas, which are thought to arise from remnants of Rathke's pouch, which forms the adenohypophysis; chordoma, which is thought to arise from remnants of notochord; intracranial teratoma, which is probably derived from germ cells; and cystic epidermoid tumors, which are thought to result from the inclusion of surface ectodermal cells at the time of closure of the neural groove. The relatively high incidence of tumors in Boxers and Boston Terriers may indicate a hereditary predisposition, which these breeds also have for endocrine neoplasia. The introduction of computerized tomography (CT) and magnetic resonance imaging (MRI), in addition to the use of immunohistochemistry, have improved our understanding of CNS tumors in various domestic animals and have helped in reaching more accurate diagnoses. Neoplasms of the CNS rarely metastasize to extraneural tissue, and their clinical importance depends on their destructive effect on host neural tissue and the resulting neurologic deficits.

The conventional tumors of the CNS are discussed here and classified according to the current histological classification published by the Armed Forces Institute of Pathology (AFIP) in cooperation with the World Health Organization (WHO). Tumors of the pituitary and nonchromaffin paraganglia are discussed with the Endocrine system.

Tumors of neuroepithelial tissue

Astrocytoma

Astrocytoma is the most common primary intracranial tumor (Fig. 3.144A–E). Astrocytomas are found most commonly in dogs, but are reported also in cats and cattle, and may occur in the brain or cord but are more prevalent in cerebrum, thalamus, hypothalamus, and midbrain. In dogs, astrocytomas are common in brachycephalic breeds but can occur in any breed. Astrocytomas have no age predilection, but are more prevalent in middle-aged or older dogs. The gross appearance varies, depending largely on the degree of malignancy. These tumors can be very difficult to detect grossly, especially when they involve white matter or grow slowly. They are then white and, because of their firmness, may be more readily palpable than visible. Their presence may be suspected only by deviation of some architectural feature (Fig. 3.144B, D). Larger and more malignant tumors are prone to vascular accidents and necrosis, and they are then easy to see (Fig. 3.144E), but the margins are never discrete, especially not when they are surrounded by edematous tissue. The extent of the tumor is always much greater than can be appreciated grossly.

Histologically, these tumors are very diverse and are classified as *low-grade astrocytoma* (well differentiated), *medium-grade astrocytoma* (anaplastic), and *high-grade astrocytoma* (glioblastoma).

Low-grade astrocytoma appears as an unencapsulated expansile and subtly invasive mass that replaces pre-existing tissues and has low to moderate numbers of bland round to oval cells. In most cases, the neoplasm appears as an increased population of fibrous astrocytes that individually are not clearly malignant (Fig. 3.144A). Variants of this neoplasm include **fibrillary astrocytoma** (neoplastic cells have scant cytoplasm but abundant fibrillary processes and filaments), **protoplasmic astrocytoma** (neoplastic cells have scant cytoplasm and few short processes and filaments), **gemistocytic astrocytoma** (neoplastic cells have abundant acidophilic cytoplasm and eccentric oval to round nuclei; Fig. 3.144C). Another variant, the **pilocytic astrocytoma** (neoplastic cells are bipolar, elongated (piloid or hair-like) astrocytes and have few Rosenthal fibers), has been reported in both dogs and cats.

In **medium-grade astrocytoma**, the population is denser; the nuclei are a little larger and darker and show slight but definite variations in size and shape but no mitoses. The cells are recognizable as astrocytes. The walls of the vessels may be slightly thickened.

In **high-grade astrocytoma**, or *glioblastoma multiforme*, hemorrhage and necrosis are expected and the adventitial and endothelial cells of the vessels proliferate forming glomeruloid blood vessels. Generally, only a few cells are recognizable as astrocytes. Neoplastic cells have a tendency for pseudopalisading around necrotic areas. Pleomorphism, giant nuclei, and multinucleated giant cells are common. Mitotic figures are common and atypical.

Astrocytomas exhibit positive immunostaining for glial fibrillary acidic protein (GFAP), S-100 protein, and vimentin. The staining pattern for GFAP varies from sparse to abundant.

Oligodendroglioma

This is the easiest of the glial tumors to recognize even when growing rapidly. This tumor is reported in dogs especially in brachycephalic breeds and rarely in cats. Grossly, it usually appears well demarcated, being gray, soft, and almost fluctuating (Fig. 3.145A). Hemorrhage and necrosis occur but are unusual. The tumor is densely cellular with almost no stroma. The nuclei are remarkably uniform and like those of normal oligodendroglia in size and shape. The cytoplasm does not stain, but its membrane does, so that the nucleus seems to lie in a clear