In: **Clinical Neurology in Small Animals - Localization, Diagnosis and Treatment**, K. G. Braund (Ed.)
Publisher: International Veterinary Information Service (www.ivis.org), Ithaca, New York, USA.

Inflammatory Diseases of the Central Nervous System (5-Nov-2001)

K. G. Braund

Veterinary Neurological Consulting Services, Dadeville, Alabama, USA.

Inflammatory diseases form an important core of diseases of the Central Nervous System. By definition, neurological diseases of dogs and cats are characterized by central nervous system (CNS) inflammation. The one exception is feline spongiform encephalopathy, caused by an atypical infectious agent, a scrapie-like, transmissible prion protein. The hallmark of CNS inflammation is infiltration of peripheral blood leukocytes into the neuroparenchyma and its coverings, resulting in various types of encephalitis and/or meningitis, and sometimes associated with altered vascular integrity that leads to edema [1]. Miscellaneous inflammatory disorders such as diskospondylitis and otitis media-interna (both typically bacterial in nature) are discussed under Degenerative and Compressive Structural Disorders, and Peripheral Nerve Disorders, respectively.

The inflammatory diseases of the CNS have been divided into the following categories:

Algal Disorders
- Protothecosis

Bacterial Disorders
- Abscessation
- Bacterial Meningitis

Idiopathic Inflammatory Disorders
- Eosinophilic Meningoencephalitis
- Feline Polioencephalomyelitis
- Granulomatous Meningoencephalomyelitis
- Meningitis
- - Steroid Responsive Meningitis-arteritis
- Pug Dog Encephalitis
- Pyogranulomatous Meningoencephalomyelitis
- Shaker Dog Disease

Mycotic Diseases of the CNS

Parasitic Encephalomyelitis

Prion Protein
- Feline Spongiform Encephalopathy

Protozoal Encephalitis-encephalomyelitis
- Toxoplasmosis
- Neosporosis
- Sarcocystosis
- Encephalitozoonosis
- Trypanosomiasis
- Acanthamebiasis
- Babesiosis

Rickettsial Disorders
- Rocky Mountain Spotted Fever
- Canine Ehrlichiosis
- Salmon Poisoning

Viral Disorders
- Aujeszky's Disease
- Canine Herpes Virus Encephalomyelitis
- Canine Distemper Encephalomyelitis
- - Canine Distemper Encephalomyelitis in Immature Animals
- - Multifocal Distemper Encephalomyelitis in Mature Animals
- - Old Dog Encephalitis
- - Chronic Relapsing Encephalomyelitis
- - Post-vaccinal Canine Distemper Encephalitis
- Feline Immunodeficiency Virus
- Feline Infectious Peritonitis
- Feline Leukemia Virus
- Infectious Canine Hepatitis
- Rabies
- - Post-vaccinal Rabies

Abscessation of the Central Nervous System

Abscesses within the CNS are uncommon in dogs and cats but may arise as a result of either metastasis from distant foci of infection (e.g., lung abscesses and bacterial endocarditis), by direct extension from sinuses, ears, and eyes, as a result of trauma (e.g., bite wound), or from contaminated surgical instruments (e.g., spinal needle) [1-11]. Brain abscess may also result from penetration of the cranial cavity and brain substances by an exopharyngeal foreign body (e.g., sewing needle). Several instances of epidural infection in the cat have followed tail fracture or a purulent granulomatous dermatitis involving the tail [5,12]. The common sites for direct extension are the cribriform plate and the inner ear, resulting in abscess formation in the frontal lobe and the cerebellopontine angle, respectively (see otitis-media-interna). Abscesses of hematogenous origin, such as those that spread from pulmonary infection, bacterial endocarditis, or congenital heart disease with right to left

shunting, appear to have a predilection for the CNS parenchyma, especially in the hypothalamus and cerebral cortex, and particularly in less vascularized areas such as white matter and junctions of gray and white matter [1]. It is thought that neuraxial abscessation occurs preferentially in areas of focal ischemia or necrosis [13]. CNS abscesses are usually associated with bacteria, but are occasionally caused by fungi [9].
Aerobic bacteria such as *Streptococcus*, *Staphylococcus*, *Pasteurella*, and *Nocardia* may be more common than anaerobic bacteria as causes of CNS infection in dogs and cats [14]. Nevertheless, anaerobic bacteria such as *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, *Actinomyces*, and *Eubacterium* are reported to be important pathogens in animals that can cause either brain abscesses or subdural empyema [5,8,15]. *Actinomyces* typically spreads by direct extension, although brain and possibly vertebral abscesses may result from hematogenous dissemination [15].

The neuropathological progression of brain abscess (alpha-*Streptococcus*) formation has been studied experimentally at sequential stages in dogs, and the findings correlated with the appearance on CT brain scans [16]. The evolution of brain-abscess formation was divided into four stages based on histological criteria: early cerebritis (days 1 to 3); late cerebritis (days 4 to 9); early capsule formation (days 10 to 13); and late capsule formation (days 14 and later). The cerebritis stage was characterized by prominent perivascular cuffing by inflammatory cells (e.g., neutrophils, macrophages and lymphocytes) in the area adjacent to the developing necrotic center. However, the early elements of capsule formation appeared with the presence of fibroblasts by day 5. The CT scans showed ring-shaped contrast enhancement by day 3. Delayed scans at 30 minutes revealed diffusion of the contrast material into the developing necrotic center, forming a solid lesion. In lesions that were well encapsulated (14 days and older), five distinct histological zones were apparent:

1. a well formed necrotic center;
2. a peripheral zone of inflammatory cells, macrophages, and fibroblasts;
3. the dense collagenous capsule;
4. a layer of neovascularity associated with continuing cerebritis; and
5. reactive astrocytes, gliosis, and cerebral edema (vasogenic) external to the capsule.

The CT appearance of well encapsulated abscesses showed a typical ring-shaped contrast-enhancing lesion. The diameter of the ring correlated best with the presence of cerebritis (perivascular infiltrates in the adventitial sheaths of vessels surrounding the abscess). Brain abscesses can be an important complication in immunosuppressed patients. Experimental studies in immunosuppressed dogs suggested an initial reduction in mass effect from the brain abscess due to decreased inflammatory response and edema formation but that the eventual size and area of the abscess became larger than in controls due to the less effective host response and to delayed collagen formation and capsulation [17]. It should be noted that more virulent organism such as *Staphylococcus aureus* can produce larger CNS abscesses, earlier ependymitis, delayed progress toward healing, greater white matter destruction, and cause areas of inflammatory escape outside the collagen capsule [18]. In spontaneous CNS abscesses, organisms are often found in chains or small colonies, often within leukocytes [1]. A diffuse leptomeningitis may accompany a brain or spinal cord abscess. In addition, CNS embolization may occur during an acute septicemic infection [1].

Abscesses are life threatening due to systemic and local toxicity (in early stages of cerebritis) and increased intracranial pressure (during/after capsule formation) [19]. Capsules may rupture into the ventricle or subarachnoid space resulting in the formation of multiple abscesses [20]. Capsule formation may be rudimentary unless the abscess is close to the meningeal surface [1]. When abscesses are multiple, death occurs after a short clinical course. Prolonged survival may occur when abscesses are isolated; however, with brainstem abscesses, the clinical course is usually short because of interference with vital centers. Clinical signs will usually reflect a focal syndrome (e.g., cerebral, pontomedullary, or spinal cord) suggesting a space occupying lesion, or a multifocal syndrome associated with many small microabscesses. External fistulae have been observed in animals with vertebral actinomycosis [15].
Antemortem diagnosis is difficult. Leukocytosis, with or without left shift, and hyperglobulinemia may be found in blood analysis [15]. Fever is an inconsistent finding. Imaging techniques, such as CT and MRI scans, may facilitate early detection of CNS abscesses [21-23]. It should be noted that when an abscess becomes encapsulated there might be no evidence of infection and no systemic reaction. Accordingly, CSF evaluation may be of little value in excluding an abscess from the differential diagnosis. Indeed, CSF collection may be contraindicated because of the risk of brain herniation. It has been suggested that CSF should only be collected after a CT or MRI has ruled out the presence of a mass lesion or after reducing intracranial pressure using such techniques as hyperventilation, administration of mannitol, etc [8]. In some animals in which CSF has been collected, marked increase in both leukocyte numbers (especially neutrophils) and protein has been found [8,9], and raised intracranial pressure is to be anticipated. CSF analysis may be normal in animals with intraspinal abscessation [24]. In a dog with a subvertebral mass, associated with actinomycosis, that spread to compress the spinal cord,

radiography revealed productive and destructive bony changes on the ventral surfaces of the first three thoracic vertebrae and adjacent ribs [15].

Treatment of abscesses centers around antibiotic therapy, often for long periods, based on culture and drug sensitivity testing of organisms isolated from the abscess. When cultures cannot be obtained, a broad-spectrum antibiotic, such as penicillin (e.g., ampicillin at 5 - 22 mg/kg, IV, qid) in conjunction with chloramphenicol (at 10 - 15 mg/kg, PO, qid) or metronidazole (10 - 15 mg/kg, PO, tid), should be used [8,25,26]. Prognosis is guarded, especially if the mass lesion is large and encapsulated which may make it refractory to antibiotic therapy. Surgical decompression by craniotomy, burr holes, or laminectomy may be indicated in cases of subdural empyema [8,12].

Aujeszky's Disease

This disease, also known as pseudorabies, mad itch, and infectious bulbar paralysis, affects most species of wild and domestic animals except horses. Swine are the natural host of this virus (*Herpesvirus suis*), and adult pigs (domestic and feral) may serve as inapparent carriers of infection and shed virus. Aujeszky's disease in dogs and cats may be the first indication that the disease is present in swine on a farm. Aujeszky's disease in species other than swine, namely cattle, dogs, cats and wildlife, is usually fatal, seemingly associated with the enhanced virulence and neurotropism seen in nonporcine species [1]. The virus reaches the CNS by traveling centripetally (retrograde) in the peripheral nerves, probably in the axoplasm of motor and sensory nerves [27-29]. Experimentally, anterograde transport (slower than retrograde transport), transneuronal, and trans-synaptic transport have also been shown [29,30]. The mode of transmission to dogs and cats is usually via the consumption of virus-contaminated tissues of swine, cattle, rats, mice or raccoons. The virus may also gain entrance to the body via scratches or abrasions from contaminated objects. In cats, experimental studies suggest the tonsils are a portal of entry with the virus subsequently moving along the pathways of the sensory branches of the ninth and tenth cranial nerves, the tractus and nucleus solitarius and the area postrema in the medulla [28]. Dogs with Aujeszky's disease apparently do not shed sufficient virus to infect other dogs housed with them.

The incubation period in the dog and cat ranges from 2 to 10 days. Death usually occurs within 24 to 48 hours after onset of clinical signs [31]. Classically, the most characteristic clinical manifestations are intense localized pruritis of face or limbs, with scratching or chewing to the point of self-mutilation. However, pruritis may not always be a constant feature [31,32]. Early in the course of the disease, excessive salivation, fever, restlessness, anorexia, emesis, and dyspnea may be noted, followed by incoordination, vocalization, anisocoria, ptosis, trismus, cervical rigidity, and muscle spasms. In one report encompassing 25 confirmed cases of canine Aujeszky's disease, 36% of the dogs showed signs of aggression [31]. Convulsions, coma, and death quickly ensue. The course of the disease can be so rapid in dogs and cats that death may occur without any clinical signs [33].

The virus is highly neurotropic, especially for CNS gray matter, and the most extensive brain changes in the dog and cat occur in the medulla, followed by the pons, thalamus, cerebellum, and cerebral cortex. Microscopically, a moderate meningoencephalomyelitis and nonsuppurative ganglionitis is observed, with perivascular mononuclear infiltrations, proliferation of neuroglia, microabscessation, as well as Cowdry type A intranuclear inclusions in glial cells, ganglia and neurons [34]. Neuronal degeneration and neuronophagia have been reported in spinal and myenteric ganglia, spinal cord gray matter, medulla, and pons [35,36]. A ganglioneuritis of the stellate ganglia and autonomic ganglia within the heart has been noted in experimental dog studies, associated with fatal arrhythmias [37]. Karyorrhexis of the inflammatory cells and microglia is commonly found in dogs and cats [1].

Diagnosis may be suggested by clinical and neuropathological findings and confirmed by fluorescent antibody test of brain tissue, by laboratory animal (usually rabbit) inoculation with tissue extracts, or by virus isolation in cell culture. In addition, immunohistochemistry and *in situ* hybridization techniques are now available to confirm presence of Aujeszky's disease virus infection in paraffin-embedded tissues [38]. Eliminating consumption of infected tissues can prevent the disease. All offal fed to dogs should be cooked. A safe, reliable, effective vaccine for dogs and cats remains to be marketed. Treatment does not alter the course of the disease.

Canine Herpesvirus Encephalitis

Fatal herpes virus encephalitis has been seen in young puppies [39-41]. Transmission occurs *in utero*, by direct contact with diseased littermates, or by inhalation or ingestion of infected material. The virus is believed to spread to the CNS via the hematogenous route, after initial replication in the oronasopharynx. However, ganglioneuritis of the trigeminal nerve is also reported to be a frequent lesion in puppies infected by oronasal exposure, and the virus may travel to the CNS via the

peripheral nerve [42]. The high susceptibility of newborn puppies to disseminated canine herpesvirus (CHV) infection is related to their relatively low body temperature and immune status [43]. The infection is self-limiting beyond 3 weeks of age and puppies at 6 weeks of age are resistant to experimental infection [44]. Older puppies appear to be resistant to the virus and can serve as asymptomatic carriers of CHV. Experimental studies indicate that active infections, with viral shedding, may occur repeatedly for prolonged periods following immunosuppressive doses of prednisolone [45,46].
The syndrome is characterized by acute onset of signs including crying, diarrhea, dyspnea, and abdominal tenderness. Terminal depression and death usually occur 1 to 3 days after the onset of clinical signs. Diagnosis is based on age, clinical signs and pathological findings. At necropsy, ecchymoses and foci of necrosis are found in lung, liver, and kidney, along with diffuse pulmonary congestion, and splenomegaly [47]. In the CNS, acute encephalitis is a feature of this disease [40]. The main lesions are focal or laminar areas of necrosis involving mainly the Purkinje cell and granular layers of the cerebellum. Focal gliosis and perivascular cuffing by lymphocytes and macrophages are often seen in cerebrum, thalamus, and pons. Intranuclear inclusions may be observed occasionally in neurons and glial cells adjacent to the malacic areas. Meningitis, with necrosis of capillary walls, may be found. Perivascular edema and hemorrhages occur in many visceral organs. Puppies surviving acute disease may develop cerebellar dysplasia [48]. Polyneuritis and ganglionitis of craniospinal and sympathetic ganglia have been reported [41].

Canine Distemper Encephalomyelitis

Canine distemper encephalomyelitis (CDE) is caused by a paramyxovirus (genus Moribillivirus) closely related to measles virus of man, to Rinderpest virus of cattle, and to pestes des petits ruminants virus of sheep and goats [1,49]. The suggested link between dogs with canine distemper virus (CDV) and multiple sclerosis in people [50] has not been substantiated [51-53]. Although the incidence is decreasing, CDE is still a common CNS disorder in the dog, primarily in unvaccinated dogs but also occasionally in those dogs with a vaccinal history [1]. Young dogs are especially susceptible to infection, although older dogs are also at risk. While there are several different strains of the virus, there is only one serotype which means that exposure to one strain protects dogs against any subsequent challenge [1]. The virus is most commonly spread by aerosol exposure, although rarely, the virus may be spread transplacentally [54]. Dogs that are not immunized regularly may lose their protection and become infected following stress, immunosuppression, or contact with diseased animals [55]. Fifty to 75% of susceptible dogs are subclinically infected but clear the virus from the body, probably through antiviral antibodies, natural killer cells, and antibody-dependent cell mediated cytotoxicity [1]. Factors predisposing to development of clinical disease are multifactorial, including age, vaccination status, breed, and viral virulence (e.g., Snyder Hill and R252 strains are highly virulent and neurotropic) [55]. In addition, the clinical course, severity of the disease, and neuropathology have been shown experimentally to vary with the virus strain [56]. While the different strains all produced an encephalomyelitis, infection with Snyder Hill strain of CDV was consistently acute; dogs either succumbed 14 to 19 days post-inoculation or recovered. Lesions in the neuraxis were those of a polioencephalomyelitis. In contrast, CDV strain A75 - 17 produced subacute to chronic disease in which demyelination was the predominant finding. Some dogs succumbed, generally around 28 to 42 days post-inoculation, while others recovered. Some dogs developed persistent CNS infection but remained clinically stable until electively euthanized, up to 62 days post-inoculation. CDV strain R252 also induced delayed, predominantly white matter disease with a mixed pattern of mortalities, persistent infections and recoveries, similar to A75 - 17. Neutralizing antibody responses correlated with the disease course. Dogs which died had low serum titers or lacked serum antibody. Recovering dogs had the earliest and highest titers. A few dogs with persistent CNS infection had antibody in the cerebrospinal fluid also.

Virus replication initially begins in lymphoid tissues. The initial systemic phase of infection by this virus is marked by immunosuppression [57]. Virus reaches the CNS approximately 1 week after infection by virus-infected lymphocytes, monocytes, and platelets associated with immune complexes [58-60]. Spread of virus through cerebrospinal fluid pathways may explain the frequent distribution in subependymal areas throughout the CNS [61]. A rapid and high-titered viral antibody response to CDV is crucial for recovery from viral infection with minimal or no clinical signs. Dogs unable to mount an adequate response develop a rapidly progressive disease and die [62]. Dogs that mount a delayed or intermediate response tend to develop chronic neurological disease.

Lesions may be found in gray and white matter. The earliest changes seen in the CNS are degenerative and appear to be the result of viral replication in glial cells, especially astrocytes [63], followed by viral-induced demyelination [61], while a non-suppurative inflammatory component occurs later, perhaps as viral immunosuppression is declining, and becomes superimposed on the degenerative lesion, although both may be seen together [1,64]. The role of T cells, which have been found at lesion sites, in the development of acute demyelination remains uncertain [65]. Vandevelde and colleagues have reported that this early, acute demyelination in distemper is also associated with a restricted CDV infection of oligodendrocytes which down-regulates the expression of a variety of cellular genes, in particular those coding for myelin

proteins [66,67]. The degree of myelin destruction has been correlated with the amount of viral antigen in the tissue [61]. Inflammation during the latter stages of the infection appeared to be associated with viral clearance from the CNS in most dogs [61] but may lead to further damage of the white matter [68]. Ultrastructural findings include evidence of segmental demyelination with stripping of compact myelin by macrophages, ballooned myelin sheaths that are split at the intraperiod line, and numerous naked axons [1,69]. Oligodendrocytes numbers decline in areas of white matter injury, partly due to restricted CDV infection, but approximately one third remain even in chronic demyelinating lesions, even though it has been reported that CDV has no obvious tropism for oligodendrocytes [70]. At this time, the mechanism(s) leading to alteration and depletion of oligodendrocytes remains unexplained [71]. Whether progressive demyelination in chronic disease is immune-mediated [72] or associated with some other mechanism, such as macrophage-mediated bystander demyelination [73], remains an area of active research. It has been reported that viral persistence in the CNS is associated with decreased expression of viral surface proteins [74]. Dogs with chronic disease produce systemic and intrathecal IgG, anti-CDV antibodies, and antimyelin antibodies, especially against myelin basic protein [1,75,76]. These systemic humoral and cellular responses show little correlation with the disease course, are not necessarily protective, and can be accompanied by persistent viral presence within the CNS [68,74,75,77]. Restricted virus infection in the gray matter might represent a mechanism for viral persistence in distemper polioencephalitis [78]. Experimentally, the presence of interferon in CSF is considered a valuable marker for persistent CNS infection [79].

Several clinical syndromes associated with distemper have been recognized in dogs [80-82]. These are discussed below.

Canine Distemper Encephalomyelitis in Immature Dogs - This is the most common form of distemper virus infection and is often initially characterized by systemic evidence of gastrointestinal and respiratory disturbances: vomiting, diarrhea, coughing, and seromucopurulent oculonasal discharges. Hyperkeratosis of the footpad may be seen. Additionally, many animals have conjunctivitis and chorioretinitis. However, in one clinical report, only one third of the canine distemper cases had extraneural involvement [83]. These systemic signs may precede, or occur simultaneously with, neurological signs. Neurological signs are quite varied, often asymmetrical, and usually suggest a multifocal distribution of lesions [77,83]. Cortical and subcortical signs include generalized seizures and sometimes personality changes, such as depression and disorientation. Signs of localization in the brain stem include incoordination, hypermetria, falling, head tilt, and nystagmus. Occasionally, monoplegia and paraplegia are observed. A sign that is characteristic of distemper encephalitis is myoclonus, or more correctly, flexor spasm [84]. Appendicular flexor muscles, abdominal muscles, and the cervical musculature are most frequently involved. Sometimes the masseteric, temporalis, and periorbital muscles are affected. These rhythmic contractions are not necessarily associated with limb paresis or paralysis and usually persist during sleep. The movements are temporarily abolished by intravenous injection of local anesthetic agents. An abnormality in the motor neuron-interneuron pool in the spinal cord is thought to cause the muscle contractions. Contractions are not dependent on sensory nerves or descending pathways from the brain. Acute visual impairment (optic neuritis), typically accompanied by dilated, unresponsive pupils, may be the only clinical sign in some dogs. Canine distemper virus is a common cause of convulsions in dogs less than six months of age. Olfactory dysfunction has been reported in affected dogs [85,86]. Neonatal infection prior to eruption of permanent dentition can cause enamel hypoplasia. Cell-mediated immunosuppression can occur with CDV, predisposing affected animals to other infectious agents, including *Toxoplasma gondii* and *Neospora caninum* [83,87]. Increased levels of antibodies to canine distemper virus have been found in serum and synovial fluid of dogs with rheumatoid arthritis [88,89].

Softening, brownish discoloration and sometimes hemorrhage may be found macroscopically in the CNS [1]. Microscopic lesions may be found in many of the visceral organs including the bladder, kidney, gastrointestinal tract, bronchioles, and tonsils. Lesions in the CNS may involve both white and gray matter. Summers and colleagues state that pure gray matter disease (polioencephalitis or polioencephalomyelitis) is rare but when observed usually occurs in young puppies [1]. Overall, pathological findings may be characterized by mononuclear perivascular cuffing, gliosis, microglial proliferation, and inflammatory cell infiltration of the pia-arachnoid membrane. Adventitial cell proliferation and endothelial swelling are commonly seen. Neuronal changes including nuclear pyknosis and shrunken cells, chromatolysis, and neuronophagia are found in the cerebral cortex, pontomedullary nuclei, Purkinje cells, and gray matter of the spinal cord. In some dogs, hippocampal cells can be selectively involved [90]. Intranuclear and intracytoplasmic inclusions bodies may be present in neuronal cells, astrocytes, histiocytes, meningeal cells, and ependymal cells. The distribution of inclusion bodies in distemper virus encephalitis is erratic and their presence is not an indication of the severity of the disease process. Changes in the white matter vary according to the duration and intensity of the infection. There is an apparent predilection for the central white matter of the cerebellum, the cerebellar peduncles, the optic nerves and tracts, rostral medullary velum, hippocampal fornix, and the spinal cord [1]. Demyelinating lesions can be focal or disseminated, isolated or confluent. Nerve fibers may undergo degeneration, resulting in the formation of swollen axonal ovoids. Pronounced gliosis may be evident in association with these changes. In many severe lesions, there is evidence of tissue necrosis, edema, and macrophage infiltration. These lesions

are often situated in the cerebellar peduncles or central white matter. Dogs with persistent CNS infection and chronic distemper encephalomyelitis harbor virus persistently in the uvea [91]. Recent studies suggest that restricted virus infection in the gray matter might represent a mechanism for viral persistence in distemper polioencephalitis [78]. Note that the pathological findings are often mild making accurate clinicopathological correlations difficult or impossible [1,83]. The distemper virus has been incriminated as a cause of bilateral polioencephalomalacia in dogs [92-94], although the relationship of malacic lesions to seizure-induced hypoxia-ischemia remains a possibility.

Multifocal Distemper Encephalomyelitis in Mature Dogs - In mature dogs between the ages of 4 and 8 years, canine distemper virus can produce a type of multifocal encephalomyelitis (MDE) that is characterized by a chronic course [80,81]. It is not unusual for an animal to be presented with a history of neurological signs that have been present for 12 months or more. The incidence of this disease is relatively low and does not appear to be related to breed or sex. Animals that have received vaccinations against distemper virus may be affected. This disease is not preceded by, nor is it coincident with, the systemic signs that are seen in younger dogs. Furthermore, it is not unusual for this slowly progressive disease to remain clinically and pathologically static. The initial neurological signs that are commonly seen in mature dogs with MDE include weakness of the pelvic limbs, generalized incoordination, and occasional falling. These signs frequently progress to tetraplegia. Generalized seizures or personality changes are not features of this disease and affected animals maintain a normal mental state. Many dogs will have unilateral or bilateral menace deficits, with normal or abnormal pupillary reflexes. Some animals will have signs of facial paralysis, head tilt, and nystagmus. Although head tremors may be seen, myoclonic movements or flexor spasms are usually not observed. Fecal and urinary incontinence and priapism have been reported in a 4 year old dog with multifocal distemper encephalomyelitis [95].
The pathological findings that occur in mature dogs with MDE are usually restricted to the CNS. The lesions tend to be multifocal and necrotizing and are frequently found in the cerebellopontine angle adjacent to the fourth ventricle, in the cerebellar and cerebral peduncles, in the central cerebellar white matter, in the optic tracts, and in spinal cord white matter. Cystic lesions may be noted along with a loss of the original architecture of the tissues and strong fibrillary astrogliosis. The focal lesions may be associated with thick, perivascular, mononuclear cuffs. Small, plaque-like demyelinative lesions may be found in the capsula interna and corona radiata. Inclusion bodies are rarely found and, when present, are usually located within astrocytic nuclei. Lesions generally are not found in the cerebral cortex.

Old Dog Encephalitis - Old dog encephalitis (ODE), in which canine distemper virus has been incriminated as the etiologic agent, is a subacute or chronic progressive panencephalitis that occurs rarely in mature dogs. ODE is also known as disseminated encephalomyelitis in mature dogs, subacute diffuse sclerosing encephalitis, and chronic dementional distemper. Affected animals are usually over six years of age; however, younger dogs may be affected. There are no related systemic signs, nor is there any apparent predisposition according to breed or sex. There is some speculation that this form of distemper no longer exists since no spontaneous cases have been observed at several institutions over the past decade. The most common initial neurological sign is visual impairment. ODE is an invariably progressive disorder and is accompanied by the development of increasing mental depression, compulsive circling, hyperkinesia, and head-pressing against objects (obstinate progression) [96]. A bilateral menace deficit of a central or peripheral nature is also a common sign. An affected animal may manifest a personality change and fail to recognize its owners. Signs of involvement of the brainstem are rare. Pathological findings associated with the disorder are restricted to the CNS and are characterized by disseminated perivascular infiltration with lymphocytes and plasma cells, diffuse microglial proliferation, astrogliosis, neuronal degeneration, and neuronophagia. The lesions have a diffuse distribution throughout all divisions of the cerebral cortex. Similar lesions are usually found throughout the basal nuclei, thalamus, hypothalamus, and midbrain. The perivascular mononuclear cuffs often extend beyond the Virchow-Robin space and infiltrate the nervous parenchyma. Diffuse demyelination is seen in subcortical areas, internal capsule, and cerebral peduncles, and often is observed in the pontine area and middle cerebellar peduncles. Large eosinophilic inclusion bodies are seen in the nuclei and cytoplasm of neuronal and glial cells. Necrotizing lesions may be present in the cerebral cortex, characterized by diffuse loss of neuronal cells with replacement by fibrillary astrocytes.

ODE is clinically and pathologically different from MDE in mature dogs. The nature of the lesions (diffuse sclerosis versus multifocal necrosis) and their topographic localization (cerebral cortex and upper brain stem versus lower brain stem and spinal cord) are quite distinct in ODE and MDE, respectively. In contrast to MDE, the cerebellum is mostly spared in ODE. Clinical differentiation between the two diseases is facilitated by the development of progressive cortical and subcortical signs (mental depression, unresponsiveness, obstinate progression) in old dog encephalitis. Also, experimental transmission of distemper encephalitis from young dogs and from dogs with MDE has been relatively easy [97], but is more difficult in dogs with ODE [98]. The interest generated by ODE is related to its clinical, pathological, and immunological similarities with subacute sclerosing panencephalitis in man [99,100] even though there appears to be different mechanisms operating in

the maintenance of persistent infection and pathogenesis of these two chronic viral diseases [101]. Recently, experimental infection of a gnotobiotic Beagle dog with the neurovirulent R252 strain of CDV resulted in long-term CNS infection in which cerebral and brain stem lesions were consistent with ODE [102].

Chronic Relapsing Encephalomyelitis - There have been occasional reports of dogs with a chronic relapsing course [82,83]. In one case, an 18 month old mixed-breed male dog with spontaneous canine distemper virus infection associated with chronic progressive multiphasic neurological disease, initial neurological deficits in the pelvic limbs progressed rapidly to paraplegia with almost complete remission after 9 weeks [82]. This was followed by another acute episode with severe, progressive thoracic limb weakness, muscle atrophy and proprioceptive deficits, coarse head tremors, and neck myoclonus over the ensuing 3 months, along with rising serum neutralizing anti-CDV titers in the serum and CSF. Three distinct CNS lesions were identified: spinal cystic necrosis, chronic demyelination in the cerebellum, and acute demyelination in the pons. Persistent CDV antigen was demonstrated immunocytochemically only in acute lesions and was restricted to neurons. The immunological mechanism associated with the distinct remissions and exacerbations and CDV antigen clearance from chronic demyelinating lesions but persistence in acute lesions, despite a vigorous anti-CDV serologic response, was not defined.

The diagnosis of canine distemper encephalomyelitis (in young dogs, especially) is usually based on history and clinical signs. The index of suspicion is higher in affected dogs that have not been vaccinated. Positive diagnosis may be made through use of immunofluorescent or immunocytochemical techniques to detect canine distemper viral antigen in brain sections and other tissues (e.g., mononuclear cells in blood smears, conjunctival or tracheal washes, or footpad biopsies) [77,103-106]. In one study, immunostaining was prominent in early and subacute and reduced in chronic demyelinating lesions [106]. These techniques are considered superior to the demonstration of inclusion bodies or syncytial cells for the confirmation of CDE [107]. Ophthalmoscopic examinations may detect a chorioretinitis [108] characterized by areas of hyperreflectivity and bright colored "medallion" lesions, indicative of past or latent infection. Hematological and biochemical data are non-specific, although many affected dogs will be lymphopenic during the acute phase of illness [77,83], and electroencephalographic traces may indicate presence of inflammatory disease. CSF analysis may reveal a moderate pleocytosis (15 to 60 WBCs/μl) of mononuclear cells (lymphocytes and macrophages), and elevated gamma globulins [109], although during the acute demyelinating stage of the disease, inflammatory reactions may be limited or lacking and CSF protein/cell count may be normal [76]. Eosinophilic intracytoplasmic inclusion bodies have been reported in CSF mononuclear cells [110], although their detection is rare. Increased β-glucuronidase levels have been reported in serum and CSF [111]. Specific neutralizing antibody in CSF occurs 2 to 3 weeks after onset of disease and is the most definite evidence for canine distemper. It is normally not present in the CSF of vaccinated dogs, dogs that develop circulating antibody quickly and remain asymptomatic after exposure, or dogs that die from acute CDV infection [103]. A competitive enzyme-linked immunosorbent assay (cELISA) has been described as a screening test for suspect CDV in sera from dogs [112]. The IgG index (a calculated quotient using IgG and albumin contents of CSF and serum to detect intrathecal IgG synthesis) has been reported to be elevated in most dogs with distemper (with the exception of dogs with acute non-inflammatory distemper), even in cases in which no significant pleocytosis is found [83,113]. This index, however, is not specific for distemper [114]. Detection of CDV in urine using polymerase chain reaction (PCR) amplification has been recently reported as a useful routine screen for dogs with suspected distemper encephalomyelitis [529].
Prognosis is guarded. Seizures are an unfavorable prognostic sign [83]. Curiously, dogs with impetiginous dermatitis rarely develop CNS disease [55]. Dogs with low CSF IgG titers (< 1:100), low CSF cell counts, low gamma-globulin levels, and high CSF albumin levels usually develop acute, fatal disease; whereas, dogs with high CSF IgG titers (> 1:100), high CSF cell counts, and sustained increase in gamma-globulin levels with normal or transient increase in albumin concentration may have a better prognosis for recovery [110,115,116].
There is no treatment for CDE, except supportive, and dogs with progressive neurological signs leading to incapacitation need to be euthanized. The prognosis is better in dogs with non-progressive neurological complications, such as intermittent seizures, myoclonus, and visual impairment, although only seizures may respond to medication.

Post-vaccinal Canine Distemper Encephalitis - Post-vaccinal canine distemper encephalitis occurs in young animals, especially those less than six months of age. It has been recognized as a disease entity for a number of years and is believed to be associated with vaccination using live virus [117-119]. The pathogenesis of this disease is unclear. It may result from:

a. insufficient attenuation of the vaccine virus which causes subsequent infection of the CNS,
b. the triggering of a latent distemper infection by vaccination,
c. other vaccine components, or
d. an enhanced susceptibility of the animal (e.g., animals that are immunosuppressed).

There is one report of post-vaccinal distemper in puppies immunosuppressed as a result of canine parvovirus infection [120]. Clinical signs are usually seen within one to two weeks after vaccination. They include anorexia, listlessness, and slight pyrexia. Neurological signs occur one to three days after the onset of these nonspecific signs. Sudden changes in temperament, viciousness (attacking owners, other animals, and inanimate objects), aimless wandering, howling, incoordination, and terminal convulsions may be seen in acute cases of approximately 24 hours' duration. In subacute cases (a disease course of 2 to 3 days), pelvic limb incoordination, circling, depression, and visual impairment are frequently observed. Clinical signs dominated by narcolepsy-cataplexy have also been reported in a 10 month old dog with presumed post-vaccinal distemper [121]. Cerebrospinal fluid analysis may reveal elevated protein levels and a mononuclear pleocytosis. Pathological findings in the brain are dominated by gray matter lesions including multifocal neuronal degeneration, neuronophagia, axonal degeneration, perivascular cuffing, and mild to moderate gliosis. The lesions are seen at all levels but tend to be most severe in the ventral pontine area, where malacia may also be present. Purkinje cells frequently remain unaffected. Intranuclear and intracytoplasmic inclusions bodies are present in many neuronal cells. Ultrastructural examination of the inclusion bodies reveals the presence of nucleocapsids having paramyxovirus features [118,119].

This disorder differs clinically from spontaneous distemper infection in young dogs by an altered personality (viciousness) that is very similar in nature and clinical course to that seen in the furious form of rabies encephalitis. Pathologically, post-vaccinal distemper encephalitis is distinguished from spontaneous distemper infection by the virtual absence of both visceral inclusions and demyelination in the area of cerebellopontine angle, the presence of many neuronal inclusions, diffuse pontine tegmental malacia, and large numbers of degenerating axonal ovoids. Prognosis is guarded and treatment is symptomatic. There has been a report of the transmission of vaccinal virus to "in-contact" animals [122]. A 5 year old Labrador Retriever bitch, which had whelped 10 puppies three days previously, was given booster vaccination against distemper, adenovirus, parvovirus, parainfluenza virus and leptospirosis. Eighteen days later, neurological signs (including seizures, crying/screaming, twisting of head/neck) were noted in some puppies, five of which were euthanized. Pathological findings in brain were similar to those described above, and, together with serological findings, suggested that vaccinal rather than field distemper virus was the cause of the encephalitis. The vaccination of pregnant bitches with attenuated live distemper virus vaccines is not recommended and vaccination of recently whelped bitches should be postponed until after puppies have been weaned.

Eosinophilic Meningoencephalitis

A neurological disorder termed idiopathic eosinophilic meningoencephalitis has been reported in six male dogs, 4 months to 5.5 years of age, in North America [123], and in 3 young male Rottweiler type dogs (between 12 and 17 months of age) in New Zealand [124]. Clinical signs included episodic collapsing into sternal or lateral recumbency without loss of consciousness, depression or somnolence, behavioral abnormalities, loss of learned behavior, circling, pacing, head pressing, blindness, facial palsy, absent gag reflex, reduced menace and pupillary light reflexes, torticollis, incoordination, and generalized or partial seizures. One dog had reduced myotatic reflexes [124]. CSF analysis revealed variable pleocytosis (from 11 to 8,200 WBCs /µl) with an eosinophil percentage ranging from 21 to 98. CSF protein content was elevated (range: 19 to 1,430 mg/dl). Three of the six dogs from the initial report were Golden Retrievers. Mild to moderate transient blood eosinophilia was observed in 7 dogs from these two reports. The etiology and pathogenesis of this condition are not known at this time. Pathological studies are limited. In one dog, the cerebral cortex was atrophied bilaterally, the sulci contained opaque, white exudate, and the meninges over the pyriform lobes were green [123]. Thickening and green discoloration of the meninges was also noted in one of the Rottweilers [124]. Microscopic lesions in the 2 dogs necropsied were almost identical. Severe eosinophilic and granulomatous meningitis, particularly over the cerebral hemispheres, was present, with vacuolation of the underlying neural parenchyma. Other microscopic changes included neuronal pyknosis, mild to severe demyelination of cerebral white matter, and diffuse gliosis and astrocytosis of the cerebral gray matter. Perivascular cuffing was confined to the superficial surface of the cerebral hemispheres. No organisms have so far been seen or cultured. In the original report of this condition, 1 dog recovered with antibiotic treatment (chloramphenicol) and 3 dogs were corticosteroid-responsive [123]. In the Rottweilers, 2 dogs were steroid responsive (1 dog responded quickly while the second responded slowly over a 4 month period and had a relapse) while the third dog showed no improvement and was euthanized [124]. The etiology of this disorder remains unknown, although the presence of eosinophils and the response to corticosteroids suggests an immune-mediated pathogenesis [124]. A similar disorder has been reported in a cat [125]. Clinical signs included nystagmus, facial muscle fasciculations, disorientation, and inability to stand, impaired vision and hearing, brief tonic-clonic seizures, and periodic hypersalivation and facial pawing. CSF revealed a mild pleocytosis (17 WBCs /µl), with 81% eosinophils, and mild protein elevation (24 mg/dl). The cat recovered following several weeks of corticosteroid therapy. A type I hypersensitivity reaction was considered as possible cause.

Feline Immunodeficiency Virus Encephalitis

Feline immunodeficiency virus (FIV) (formerly, feline T-lymphotropic lentivirus) is a lentivirus with certain morphological similarities to the human immunodeficiency virus [126]. The neurotropism of this virus has been documented [127] and FIV is considered a useful model for study of human immune deficiency virus infection of the human CNS (neuroAIDS) [128]. It is commonly found in cats with chronic oral cavity infections, chronic upper respiratory tract disease, chronic enteritis, and chronic conjunctivitis [129]. The literature to date suggests that spontaneously occurring FIV causes neurological signs in only about 30% of cats, and the signs tend to be mild or subtle [129-133]. Behavioral changes such as depression, social withdrawal, loss of "toilet-training", unusual aggression, seizures, episodic staring into space, restlessness, disorientation, frequent licking movements, and hypersthesia are the dominant signs [132,134]. Focal neurological signs, such as head tilt, anisocoria, circling, and spinal cord dysfunction, such as hindlimb ataxia and falling, are infrequently observed, occur late in the disease, and may be associated with secondary opportunistic CNS infections, such as toxoplasmosis and feline infectious peritonitis [132,135]. Histopathological changes in the brain in spontaneously occurring FIV infection include perivascular lymphocytic cuffing, gliosis, and white matter vacuolation [134]. In this report, lesions were most severe in the cerebrum, affecting the white matter and the deep laminae of the gray matter, but were also present in the medulla, and cervical spinal cord. Gemistocytes were prominent, and many bizarre cells with large, sometimes multinucleate, hyperchromatic nuclei were evident. Immunostaining with antibody specific for FIV p24 nucleocapsid protein produced staining in the gemistocytes and glial cells of the white matter. *In situ* hybridization produced staining that was most intense in the white matter and gemistocytes of the deep laminae of the gray matter, thus confirming the infection as active [134].

In experimentally infected cats, subclinical encephalitis has been reported [136], although behavioral changes, anisocoria, delayed righting and pupillary reflexes, as well as delayed visual and auditory evoked potentials, decreased spinal and peripheral nerve conduction velocities, and marked alterations in sleep patterns have been seen [137]. Neurological disease has been observed in both acute and chronic stages of experimental FIV infection [138]. Pathological findings in experimentally infected cats have included diffuse gliosis, glial nodules, occasional perivascular infiltrates, white matter pallor, meningitis, and perivascular leptomeningeal calcification. These changes were seen especially in cerebrocortical white matter and in periventricular locations [136], although early lesions are reportedly located in the basal ganglia and brainstem [132]. A marked increase of glial fibrillary acid protein (GFAP) reactivity has also been noted [131,139]. Experimental studies indicate that the virus targets astrocytes and macrophages [132], may induce microglial activation/proliferation [140], results in delayed neuron loss and axon reorganization, especially in the hippocampus [139,141], and impairs astrocyte homeostasis [142]. Systemic immune suppression is also considered an important determinant of FIV-induced neurovirulence [143].

Common hematological abnormalities in cats with naturally occurring FIV infection include anemia, lymphopenia, and monocytosis, along with serum hyperproteinemia, and hyperglobulinemia [130,133]. In spontaneous disease, a mild mononuclear pleocytosis and mild protein increase in CSF may be found [134]. Experimentally, a mild CSF pleocytosis and intrathecal IgG production has been reported [127,144].

A definitive diagnosis of FIV infection can be made by detection of FIV-specific antibodies in blood or saliva. Serodiagnosis for detecting FIV-specific antibodies in serum, plasma, or whole blood presently can be made using a commercial enzyme-linked immunosorbent assay (ELISA), immunofluorescent antibody assay, and a FIV Western blot assay [145]. Prognosis is poor. Safe and effective treatment strategies are presently unavailable [145,146]. Infected cats pose no public health hazard [146].

Feline Infectious Peritonitis

Feline infectious peritonitis (FIP) is a fatal, systemic Arthus-type immunopathological disease caused by feline coronavirus (FCoV) [147-149] Two biotypes of FCoV exist, feline infectious peritonitis virus (FIPV) that causes FIP, and feline enteric coronavirus (FECV) that induces mild enteritis from which cats typically recover [150]. FIPV has been shown to be a mutation of FECV [151] and this virus has the ability to replicate in macrophages, perhaps facilitated *in vivo* by the concept of antibody-dependent enhancement in which presence of antibody to FCoV increases the uptake of virus into macrophages through binding of the antibody-virus complex to the Fc receptor [152,153]. Deposition of virus-infected mononuclear cells and virus-antibody immune complexes within blood vessel walls results in severe vasculitis, with complement-dependent vessel damage and release of cytokines [154,155] leading to serum leakage. There are two clinical forms of FIP:

a. an effusive ("wet") form resulting from diffuse fibrinous peritonitis accompanied by excessive abdominal fluid [156,157] and
b. a noneffusive ("dry") form characterized by perivascular granulomas around small blood vessels in various sites, especially meninges, brain and uvea [158].

The effusive form is about four times more common than the non-effusive form. Lesions appear when affected cats mount a vigorous humoral antibody response with very little, if any, cellular immunity [159]. The non-effusive form develops in cats with humoral immunity, but with partial cell-mediated immunity [160]. In other words, this form may represent an intermediate stage of immunity, sufficient to induce granulomatous inflammatory reaction around virus present in macrophages, but not quite adequate to eliminate the infection. Cats who develop a strong cell-mediated and local immune response have the best chance of restricting the virus to intestinal mucosa and mesenteric lymph nodes leading to viral elimination and eventual recovery [161]. Note that in a small proportion of cats there is an overlap of the two forms of FIP [150].

FIP infection has a low morbidity but a high mortality (approaching 100%) [162]. The main route of infection with FCoV is oronasal from contact with infected feces [150]. Asymptomatic carriers are not common [163]. Up to 50% of cats with clinical FIP also test positive for feline leukemia virus [163]. The incidence of FIP is highest in cats 6 months to 2 years of age, although it has been reported in animals as young as 12-weeks of age [164]; lowest in cats from five to 13 years of age; and slightly higher in cats older than 14 years of age [162]. There is no breed predisposition, although results of a recent epidemiologic study indicated that sexually intact male cats may be at increased risk, and spayed females at reduced risk, for FIP [165]. Cats in closed colonies are at highest risk [150,165]. Up to 30% of cats with clinical FIP have CNS involvement [166-168]. The CNS lesions appear to result from an immune-complex-mediated vasculitis. In addition, failure of cellular immunity to destroy the virus results in multiple granulomas, surrounding virus-laden macrophages, within the CNS. Neurological signs and CNS pathology are more often observed in the dry form of FIP [156-158,[167,169] however; cats without neurological deficits still may have microscopic CNS involvement [166]. The clinical and neurological vagaries of FIP are recognized in earlier reports and include pelvic limb paresis, generalized ataxia, dorsal thoracolumbar hyperesthesia, nystagmus, anisocoria, behavioral changes, seizures, tetraparesis and intention tremors [166,170]. Multifocal or diffuse CNS involvement is common [171,172]. Animals may show evidence of iritis, anterior uveitis, and chorioretinitis [150].

The pathological findings typical of feline coronavirus disease in the CNS include a pyogranulomatous inflammatory cell infiltration of leptomeninges, choroid plexus, ependyma, and brain parenchyma, although the intensity of the lesions is greatest at the inner and outer surfaces of the CNS [1,158]. Perivascular cuffing and fibrin deposition are prominent. Subependymal periventricular necrosis is commonly observed, as is the infiltration of macrophages, lymphocytes, neutrophils, and plasma cells. Inflammatory ependymal lesions in the aqueduct and central canal may lead to obstructive ventricular dilatation and hydromyelia, respectively [1]. Inflammatory or degenerative vascular changes and thrombosis are sometimes present and many animals have associated panophthalmitis. Several cases of FIP-associated hydrocephalus have been reported [158,166,169,173,174].

Premortem diagnosis, especially in noneffusive FIP, is difficult. It is suggested by clinical signs, including ocular changes (anterior uveitis), laboratory evidence of CSF protein concentration of greater than 2 g/L and a white cell count of over 100 cells/μL (predominantly neutrophils), positive anti-coronavirus IgG titer in CSF, plasma hypergammaglobulinemia, and increased serum fibrinogen levels, and findings on MRI or CT suggesting periventricular contrast enhancement, ventricular dilatation, and hydrocephalus [149,171,172]. High serial serum titers of FCoV antibody may support the diagnosis; however, there is considerable overlap in titers in cats with and without FIP [175,176] (some cats with FIP have low titers, while many cats with high titers never develop FIP). Furthermore, they have no prognostic value, as they do not appear to be protective [150]. Confirmation generally is made by histopathological examination, either at biopsy or at necropsy. Postmortem diagnosis is facilitated by FIP monoclonal antibody staining of affected tissue and coronavirus-specific polymerase chain reaction [149,177,178]. Hydrocephalus is reported to be a common postmortem finding [172].
The prognosis for clinically affected cats is very poor since most animals die within a few weeks or months [161]. There is no satisfactory treatment and most therapy is based on supportive care, including fluid replacement and nutritional support [150]. The mainstay of palliative therapy is topical or systemic corticosteroids or both [179]. Vaccination using conventional and recombinant vaccines remains controversial since protection is often unpredictable and antibody-dependent enhancement may be seen after challenge [150,153,180]. Results of a recent field trial using modified live virus vaccine suggested that vaccination can protect cats with no or low FCoV antibody titers and that in some cats vaccine failure was probably due to pre-existing infection [181].

Feline Leukemia Virus
A degenerative myelopathy has recently been reported as a complication of chronic feline leukemia virus (FeLV) infection [532]. Affected cats were FeLV antigenemic for more than 3 years. Clinical signs consisted of nonpainful paraparesis progressing to spastic paralysis that sometimes was accompanied by abnormal vocalization and hyperesthesia. No hematological or CSF abnormalities were found and imaging studies (radiography, myelography, or MRI) were negative for

spinal cord compressive lesions. Microscopic lesions were found in the spinal cord (especially thoracolumbar) and brainstem and consisted of diffuse white matter degeneration in the absence of inflammation. FeLV antigen was identified immunocytochemically in spinal cord of affected cats, while proviral DNA was amplified from sections of spinal cord, intestine, spleen, and lymph nodes. Neuronal and glial infection by FeLV with subsequent axonal degeneration was suggested as the underlying pathogenesis of the CNS lesions in some chronically infected cats.

Feline Polioencephalomyelitis

This is a subacute to chronic, usually progressive neurological disease that has been described in immature and mature cats, of either sex and of different breeds, throughout the world [1,182-184]. The condition known as "staggering disease", a non-suppurative encephalomyelitis with a predilection for gray matter [185,186] may also be included in this group [187]. Overall, clinical signs from various reports have included ataxia with a tendency to stumbling and falling, hypermetria, nystagmus, paresis, circling, opisthotonus, and tonic-clonic seizures. Intention tremors may be seen involving the head. Affected cats are usually mentally alert but some manifest personality changes. Cranial nerve function is normal except for depressed direct and consensual pupillary reflexes in some animals. Postural reactions and segmental spinal reflexes may be noticeably depressed. Occasionally, a localized area of apparent thoracic or lumbar spinal hyperesthesia is evident. In some cases, a psychomotor-like pattern of seizures that is characterized by hallucinations, wild stares, clawing, and hissing and biting at imaginary objects has been reported by owners when cats are asleep. Some cats have fever, leukopenia, myeloid hypoplasia, and non-regenerative anemia. CSF analysis reveals a moderate protein increase and mild mononuclear pleocytosis [187].

Pathological findings are usually restricted to the CNS and are characterized by a disseminated meningoencephalomyelitis. Lesions have a predilection for gray matter and include severe neuronal degeneration and loss with nodular and diffuse astroglial sclerosis, especially in dorsal and ventral horns of the thoracic and/or cervical spinal cord segments, and in the medulla oblongata. Less severe lesions are found in the cerebral cortex, basal and diencephalic nuclei, midbrain, periaqueductal gray matter, and oculomotor and pontomedullary nuclei. Multifocal areas of Purkinje cell degeneration and isomorphic gliosis in the molecular layer of the cerebellar cortex are seen in some cats. Gray matter lesions are accompanied by mild to moderate perivascular cuffing with lymphocytes, focal areas of mononuclear meningitis consisting of multifocal accumulations of lymphocytes, monocytes, and occasionally, plasma cells, and gliosis. Diffuse Wallerian degeneration of white matter (demyelination and axonal necrosis) is usually present in ventral and lateral columns of the spinal cord, as well as along dorsal midline and ventrolateral areas of the medullar oblongata.

The cause of feline polioencephalomyelitis is unknown, although histopathological findings suggest a neurotropic viral infection. Viral inclusions have not been described and attempts at virus isolation have been unsuccessful [182]. The presence of leukemia, myeloid hypoplasia and non-regenerative anemia in some cats suggests possible feline panleukopenia virus infection, which has been known to cause leukodystrophic lesions [188], inflammatory lesions of the brain, and spinal cord demyelination in cats without the characteristic cerebellar lesions [189]. Serological studies have been negative for feline immunodeficiency virus and feline leukemia virus [187]. Another candidate is Borna virus. In one study involving 24 cats with ‘staggering disease’, Lundgren and colleagues reported that 44% had Borna disease virus (BDV)- specific antibodies [185,186]. A BDV-like agent was subsequently isolated from the CNS of affected cats [190]. Immunohistochemical studies indicated that T lymphocytes were the predominating inflammatory cells within the adventitial space, with CD4+ T cells being more abundant than CD8+ T cells [191]. Scattered IgG-, IgA- and IgM-containing cells were found in the adventitial space and surrounding neuropil, often adjacent to neurons. In several cats, BDV-specific antigen was detected in a few cells thought to be macrophages. The successful induction of neurological signs and encephalitis in cats infected with feline BDV, together with the detection of BDV-specific antigen and nucleic acid in the brain of each cat with encephalitis, is strong evidence that BDV is the etiological agent associated with this meningoencephalitis [192]. BDV-specific antibodies have also been detected in German, Austrian, and Japanese cats [193,194].
Prognosis is guarded. Data on treatment are lacking except for the Borna disease cats where supportive treatment, including use of corticosteroids early in the condition (prednisolone at 1 - 2 mg/kg PO divided in 2 doses for 7 days, then gradual reduction over 6 - 8 weeks until 0.125 mg/kg on alternate days) may produce short-term remissions or clinical stabilization [194]. Addition studies should help clarify if other cats in this polioencephalomyelitis grouping belong to the Borna disease group or if they form a subset of non-suppurative meningoencephalomyelitis.

Feline Spongiform Encephalopathy

An encephalopathic neurological disease, termed feline spongiform encephalopathy (FSE), was first reported in 1990 in the United Kingdom [195]. Single cases have been identified in Norway, Ireland, and Lichtenstein [530]. The disease occurs in older cats from 14 months to 14 years of age, with a mean age around 7 years [531]. It does not appear to be related to breed

or sex. The condition appears to be related to other transmissible spongiform encephalopathies (or scrapie-like encephalopathies, or prion diseases), such as bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep, and Creutzfeldt-Jacob disease (CJD) in people. Recent studies suggest that the cases in cats are consistent with oral exposure from consumption of foodstuffs derived from cattle contaminated with the BSE agent which in turn was spread to cattle through animal protein concentrates (e.g., meat and bone-meal) processed from scrapie-infected sheep carcasses [196-200]. There is evidence that the new variant CJD seen in Britain is due to further species-jumping transmission to humans from ingestion of BSE-contaminated beef products [201,202]. The infectious agent in these spongiform encephalopathies is a protease resistant prion protein (PrP), a product of nerve cells, and considered to be an abnormal post-translational modification of a host-encoded membrane-bound cellular glycoprotein produced by infection with scrapie and similar agents that accumulates in the affected brain [196]. The prions are inseparable from infectivity [203]. PrP is also the major protein component of abnormal fibrils (known as scrapie-associated fibrils) that are visualized by electron microscopy [204,205]. These fibrils are found in extracellular deposition of amyloid, seen as plaques or perivascular deposits in sheep with scrapie, which immunostains positively with antisera to PrP [206]. Disease is thought to appear when infectivity and neuropathology have reached a high enough level [201]. The length of the incubation period between the infecting event and the onset of clinical signs may be several years, thus accounting for the disease being observed in older animals. Recent studies indicate that the nature of the BSE agent remains unchanged when passaged through a range of species, irrespective of their genetic make up, demonstrating that variations in the host PrP gene are not a major factor in the susceptibility to the BSE agent [207].

Neurological signs in cats with FSE are usually insidious in onset and develop progressively over several weeks to months. Signs include muscle tremors, ataxia (especially of the pelvic limbs), dilated unresponsive pupils, jaw champing, salivation, behavioral abnormalities such as uncharacteristic aggression, biting, hyperesthesia, scratching when stroked, creeping about the house and hiding, vacant staring, excessive grooming, and being easily startled by noise. Signs may progress to severe ataxia, dysmetria-hypermetria, sometimes resulting in kangaroo-like movements, and intention tremors of the head. The clinical signs in cats are similar to those described in cats with experimentally-induced Creutzfeldt-Jacob disease [533]. Apart from a moderate leukopenia reported in some cats, laboratory findings are usually within normal limits. Testing for feline leukemia virus, feline immunodeficiency virus, and feline coronavirus is negative.

Microscopic changes in this non-inflammatory degenerative disorder include diffuse vacuolation (single or multiple vacuoles) of gray matter neuropil and neurons throughout the brain, particularly in cerebral cortex, corpus striatum, thalamus, medial geniculate body, and in nuclei of the central gray matter around the mesencephalic aqueduct [195,196,208-210]. Similar lesions occur in the spinal cord. In some instances, neuronal vacuoles are large and extend into axonal processes. These changes are accompanied by moderate to severe gliosis [530]. Perivascular cuffing and/or meningitis are not seen. Vacuolation of the white matter is sometimes seen, especially in the medulla where it is thought to be associated with axonal degeneration in the pyramidal tracts. PrP has been demonstrated in the brains of affected cats (commonly in the gray matter neuropil of the head of the caudate nucleus, putamen, and cerebral cortex [211]) both by immunostaining using the mouse monoclonal anti-hamster PrP antibody [211], immunoblotting, and by detection of abnormal fibrils equivalent to scrapie-associated fibrils using negative stain electron microscopy [209,212]. PrP has also been detected in the myenteric plexus, kidney, spleen, and Peyer's patches of affected cats [213].

There is no treatment. Prognosis is poor, since all spongiform encephalopathy cases are fatal [214]. At this time, there is no antemortem diagnostic test available. Postmortem diagnosis is made by histopathological examination of the brain. Prevention of exposure to contaminated foods is the most strategic measure. The slaughter of cattle in the UK and the ban on feeding of animal proteins to ruminant species should see the end of the BSE epidemic and also, the 1990s epidemic in cats of transmissible spongiform encephalopathy. There is no direct transmission of the agent between humans and cats. The first case of FSE in a domestic cat outside the UK was reported in Norway that had been fed several imported commercial dry cat food products [211].

Granulomatous Meningoencephalomyelitis

Granulomatous meningoencephalomyelitis (GME) is a sporadic, idiopathic, inflammatory disease of the CNS of dogs and, rarely, cats. This disease appears to have a worldwide distribution, with recent reports coming from the USA, Australia, New Zealand, and Europe [215-223]. GME is thought to account for the majority of lesions previously called reticulosis or inflammatory reticulosis [1,214,224].

The cause of GME is unknown. Bacteriological/mycological cultures of blood and cerebrospinal fluid (CSF) have been negative, as have special agent tissue stains including Gram, Giemsa, Ziehl-Neelsen, periodic acid-Schiff, methenamine silver, and Young's fungal stain. That the lesion resembles experimental allergic encephalomyelitis supports a possible

immunological basis for the disease. Immunohistological studies have indicated that many lymphocytic/lymphoblastic cells are immunoglobulin-bearing [215]. The recent report of IgE positive cells (coated mast cells or IgE-producing plasma cells) in perivascular cuffs in 2 dogs with GME lends credence to a possible underlying immunopathological perturbation [225]. In this same study, tryptase-positive mast cells were observed in all 20 dogs with GME and the authors suggested that release of histamine and other bioactive substances by degranulating mast cells may alter vascular permeability and facilitate CNS entry of lymphocytes, thereby contributing to the dynamics of the lesion and to rapid clinical deterioration [225]. Results of an immunomorphologic study further suggested a T cell-mediated delayed-type hypersensitivity of an organ-specific autoimmune disease as a possible pathogenic mechanism for this unique canine brain lesion [226]. It is also possible that GME represents an altered host response to an infectious agent. It is of interest that the onset of signs of GME in two dogs appeared to be related to administration of the anthelmintic drug levamisole, a known immunostimulant [227]. This observation, together with the reported occurrence of CNS lesions in normal dogs after levamisole administration [228], suggested that levamisole might have activated an immune response against latent or incomplete antigens present in nervous tissue. The unusual occurrence of GME in two related Afghan hounds also raised the possibility of common exposure to an infectious agent or genetic predisposition [229]. Summers and colleagues posed the possibility of a retrovirus causing GME, perhaps through vaccine contamination [1]. Distemper and rabies-like inclusion bodies and toxoplasma-like organisms have been described sporadically in CNS lesions of some dogs with GME. However, most GME dogs have been vaccinated against canine distemper and rabies and no correlation has been noted between onset of signs and the time of previous vaccination. Furthermore, canine distemper viral antigen has not been detected in dogs with GME using immunohistochemical techniques [107,225,226,230] and GME occurs in rabies-free countries such as Australia and New Zealand [1].

Most cases of GME occur in small breed dogs, and commonly in terrier and toy breeds and Poodles, although any breed may be affected [216,225,231]. The majority of confirmed cases occur in young to middle-aged dogs, with a mean age around 5 years (ranging from 6 months to 12 years) [231]. GME occurs in both sexes; however, there appears to be a higher prevalence in females [225,231]. The onset of disseminated GME is usually acute, with a progressive course over a 1 to 8 week period [219,220], and dogs with focal GME tend to have a longer clinical course [231]. As a caveat, a lack of obvious correlation between clinical signs and the course of the disease has been reported [225]. Clinical signs usually reflect several (i.e. multifocal) syndromes, e.g., cerebral, brain stem, and spinal cord syndromes, as a result of the scattered distribution of lesions. However, focal signs have been reported in up to 50% of cases [231]. Common signs include incoordination, ataxia and falling, cervical hyperesthesia, head tilt, nystagmus, facial and/or trigeminal nerve paralysis, circling, visual deficits, seizures, depression, and tetanic spasms [221,222]. Occasionally, fever, peripheral neutrophilia, and excess non-segmented neutrophils will accompany the clinical neurological signs [219,232]. An infrequently reported ocular form of GME appears to be related to lesions localized in optic nerves and optic chiasm resulting in visual impairment and abnormal pupillary reflexes [233]. A hyperemic and edematous optic disk may be seen on ophthalmic examination, vessels may be dilated, and focal hemorrhage may be present [234,235]. Occasionally, ocular and neurological signs may be found together in affected animals.

A tentative diagnosis of GME may be suggested by signalment data, the clinical course of the disease, and clinical signs. Hematology, serum chemistry, and urinalysis studies are usually normal and electroencephalographic recordings are frequently non-specific [225]. Rarely, an intrathecal filling-defect may be detected myelographically in dogs possibly due to focal cord swelling or subarachnoid granulomas [229,230,236]. The most useful diagnostic aid is CSF analysis [220,237]. In most dogs, CSF is abnormal with mild to pronounced pleocytosis, ranging from 50 to 900 WBCs/μl. Cells are predominantly mononuclear, including lymphocytes (60 - 90%), monocytes (10 - 20%), and variable numbers of large anaplastic mononuclear cells with abundant lacy cytoplasm. While neutrophils typically comprise from 1 - 20% of the cell type differential, they may be the predominant cell type on rare occasions. A marked decrease in CSF cellularity after glucocorticoid administration has been reported by some workers [216,225], but not by others [237]. Protein in CSF is usually mildly or moderately elevated, ranging from 40 to 400 mg/dl. Occasionally, protein is elevated without pleocytosis. In one retrospective study of dogs with GME, lumbar-derived CSF contained fewer cells and less protein than CSF derived from cisternal puncture [237]. CSF protein and cellularity is not necessarily influenced by the degree of meningeal involvement or the extent of necrosis within the granulomatous lesions. Results of CSF electrophoresis from dogs with acute GME have shown the presence of α-1-globulin and an increase in albumin/α-1-globulin ratio, suggesting blood-brain-barrier disruption [232]. In chronic cases, an increase in β-gamma globulin values suggests intrathecal production of immunoglobulin [232,238,239]. In addition to an elevated IgG production, evidence of intrathecal IgM and IgA production has been described in several encephalitides, including GME [114]. CSF pressure may be normal or increased. Although infrequently performed, brain biopsy can be a very useful diagnostic test in animals with focal lesions [231].
Lesions associated with GME are restricted to the CNS. In brain and/or spinal cord, soft, gray, oval lesions with irregular or

well-defined margins occasionally can be discerned on gross sectioning, especially with large focal lesions (see below) [218,225,240]. Sometimes, the cut surface of the CNS has a granular, mottled appearance with finger-like projections. Meninges may appear thickened and cloudy, and occasionally, optic nerves are grossly enlarged. Internal hydrocephalus may be present in some dogs. Microscopic lesions are usually widely distributed throughout the CNS, but primarily in white matter of cerebrum, caudal brain stem, cerebellum, and cervical spinal cord. Comparable lesions may be found in gray matter and in leptomeningeal and choroid plexus vasculature. The lesions are characterized by dense aggregations of mesenchymal cells arranged in a whorling perivascular pattern. The perivascular cuffs are composed of histiocytes (a heterogeneous population of MHC class II antigen-positive macrophages) and varying numbers of predominantly CD3 antigen-positive lymphocytes, monocytes, and plasma cells set in nets of reticulin fibers [219]. In some areas, the perivascular cells are predominantly lymphocytic, while in other regions, histiocytic cells are most numerous. Neutrophils and multinucleate giant cells are sometimes present in small numbers. Aggregates of histiocytic cells (granulomatous nodules), sometimes with an apparent epitheloid differentiation [1] appear to develop eccentrically from a previously formed lymphocytic cuff and may also be seen at the center of the most severe lesions. Granulomatous lesions may compress and invade adjacent CNS parenchyma, resulting in necrosis, glial cell reaction, and edema.

Coalescence of granulomatous lesions from a large number of adjacent blood vessels may produce a true space-occupying mass, referred to as the neoplastic form of reticulosis [224]. The dominant reticulohistiocytic cells of this mass may have neoplastic features, such as variable mitotic index and varying degrees of pleomorphism. Focal lesions are usually single and most commonly occur in brain stem, especially in the pontomedullary region, and cerebral white matter. Note that animals with large coalescing granulomatous lesions may also have accompanying disseminated GME lesions [240]. The nature and classification of these so-called "neoplastic reticulosis" lesions remains uncertain. Some cases may be examples of primary CNS lymphosarcomas [215], while other are now thought to be true histiocytic tumors [214]. Large, focal lesions usually produce signs suggestive of a single, space-occupying mass, with signs varying according to the location of the lesion. These lesions can usually be detected using CT or MRI imaging techniques [241].

Prognosis for permanent recovery is poor. Some dogs die from inhalation pneumonia secondary to megaesophagus [230]. Shortest survival periods, ranging from several days to weeks, are seen with the disseminated and ocular forms. Longer survival periods of from 3 to 6 months, or longer, are more suggestive of a focal lesion. In one retrospective study of 42 dogs with GME [231], median survival time for dogs with focal versus disseminated disease was 114 and 14 days, respectively, and dogs with focal forebrain signs (e.g., seizures) had significantly longer survival times (>395 days) than did dogs with focal signs in other areas of the CNS (59 days). Long-term therapy is generally unsatisfactory, although temporary remission of signs is often achieved with corticosteroid administration, such as oral prednisone, 1 to 2 mg/kg/day initially for several days, then reducing the dosage to 2.5 - 5 mg on alternate days. Most dogs will require continued therapy to prevent recurrences of signs. Improvement may last for several days, weeks or months, although most will eventually succumb to the disease [225,231]. Part of the temporary improvement may be related to a reduction of mast cell function in dogs receiving glucocorticoid medication [225]. Cessation of glucocorticoid therapy is invariably associated with rapid and dramatic clinical deterioration. The ocular form of GME may be treated initially with repositol retrobulbar glucocorticoid (betamethasone, 2.5 mg) in conjunction with oral prednisone therapy. Results of a recent retrospective study suggested that radiation therapy (e.g., total doses ranging from 40 to 49.5 Gy, divided in 2.4- to 4.0-Gy fractions) may be an effective treatment for dogs with GME, particularly those with clinical signs suggesting focal involvement [231].

Infectious Canine Hepatitis

Infectious canine hepatitis is an adenovirus (CAV-1) infection that is a highly contagious systemic disease of young dogs, unvaccinated dogs, and foxes [242,243]. The virus is antigenically and genetically distinct from canine adenovirus 2 (CAV-2), which produces respiratory disease in the dog. The CAV-1 virus is transmitted by direct contact with infected animals (saliva, respiratory secretions, urine, or feces) or by contact with contaminated objects. The virus may also be disseminated by contaminated hands. The virus spreads to local lymph nodes, via the oropharynx, and is disseminated throughout the body by the hematogenous route. There is special predilection for vascular endothelium of liver, kidney, and lymph nodes. The virus may enter the aqueous humor from the blood with subsequent replication in corneal endothelial cells leading to corneal clouding ("blue eye"). As the liver is a primary site of viral injury, signs of acute or chronic hepatitis may be observed. Hepatic insufficiency and hepatic encephalopathy may induce a semicomatose state and death. Signs of encephalitis due to damage of vascular endothelium are rare in the dog; but may include rapidly progressive tetraparesis, coma, seizures and death. These signs may be accompanied by vomiting, abdominal pain, fever and jaundice. Multiple hemorrhages may be present in the CNS, especially in brainstem and caudate nucleus [1]. Perivascular mononuclear inflammatory cells may be seen around capillaries and venules. Characteristic large, amphophilic (Cowdry type A) intranuclear inclusions are present in many tissues, including vascular endothelial cells, and are abundant in liver. Analysis of CSF may show a mild increase in

mononuclear cells and protein. Antemortem diagnosis can be obtained by serological testing (e.g., indirect hemagglutination, complement fixation, immunodiffusion, and ELISA), and by virus isolation (e.g., from urine). Prognosis is guarded. Peracutely affected dogs may die within hours of infection. Clinical signs of uncomplicated infectious canine hepatitis frequently last 5 to 7 days prior to improvement [243]. Treatment is symptomatic and supportive.

Lyme Borreliosis

Borreliosis or Lyme disease is caused by the spirochete *Borrelia burgdorferi* which is transmitted to humans and animals by ticks belonging to the *Ixodes ricinus* complex whose distribution is associated with the prevalence of disease, e.g., *I. pacificus* (West coast) and *I. scapularis* (Northeast, Midwest, and Southeast) [244,245]. *Ixodes scapularis* in the Northeast has been previously called *I. dammini*. The tick *Amblyomma americanum* has also been incriminated as a vector. The majority of canine and feline lyme borreliosis cases have been based upon serodiagnosis. In cats, the disease has not been described as a clinical entity [245]. Anorexia, depression, fever, stiffness, joint pain and swelling, and renal disease have been reported in cases of canine lyme borreliosis [246]. Definitive clinicopathological evidence that this organism induces neurological disease in dogs or cats is presently lacking [245], although it has been reported that antibodies against *B. burgdorferi* were found in serum and/or CSF in dogs with undefined neurological disease [247,248]. Intrathecal production of *Borrelia burgdorferi*-specific antibodies by ELISA and Western blot analysis has also been reported in a dog with behavioral changes and seizures [249], but no significant abnormalities were found at necropsy. Further data are needed to clarify the incidence and prevalence of lyme neuroborreliosis in dogs. The organism is sensitive to tetracycline, doxycycline, amoxicillin, ceftriaxone, and imipenem.

Meningitis

Meningitis in dogs and cats is being more commonly diagnosed today compared to the situation 10 to 15 years ago. Several forms of meningitis are recognized.

Steroid Responsive Meningitis-Arteritis

A severe form of steroid responsive meningitis-arteritis (SRMA) has been reported in Beagles, Bernese Mountain Dogs, Boxers, German Short-Haired Pointers, and sporadically in other breeds. This condition has a worldwide distribution and represents one of the most important inflammatory diseases of the canine CNS [250,251]. Beagles, especially but not exclusively those in laboratory-bred colonies, appear at risk [252-255]. In the Beagles, the condition has been termed Beagle pain syndrome [256], necrotizing vasculitis [257], polyarteritis [258] panarteritis [259], juvenile polyarteritis syndrome [252], and primary periarteritis [260]. In other breeds, this condition previously appears under the terms necrotizing vasculitis [261], corticosteroid-responsive meningitis [262], aseptic suppurative meningitis [263], and corticosteroid-responsive meningomyelitis [264]. This plethora of terminology reflects not only the dearth of knowledge about this condition but also highlights important clinical signs such as pain, improvement following corticosteroid medication, and histologic involvement of the meninges and blood vessels [251].

Affected animals usually are most commonly young adults between 8 and 18 months of age, although the age range may extend from 4 months to 7 years [251]. The clinical course is typically acute with recurrences. A more protracted form of the disease may be seen following relapses and inadequate treatment [264,265]. Signs include recurring fever, hyperesthesia, cervical rigidity, and anorexia. There may be a creeping gait, arching of the back with head held down, and crouched posture [254]. Some dogs with protracted disease may show clinical signs of parenchymal involvement such as ataxia, paresis, tetraparesis or paraplegia. Hematological studies often reveal a peripheral neutrophilia with a left shift, increased erythrocyte sedimentation rate, and in some cases, an elevated α2-globulin fraction [251]. CSF studies indicate increased protein and neutrophilic pleocytosis (in some dogs as high as 12,600 WBCs/μm). Dogs with chronic disease may have a normal or mildly increased CSF protein content and a mild to moderate, mixed cell pleocytosis [251]. In acute and chronic forms of the disease, the majority of affected dogs show elevated IgA levels in CSF [265] and serum [252,265], presumably as a result of dysregulation of the immune system. This finding appears to be relatively specific for this disease and is not found in other inflammatory or infectious diseases of the CNS (it may be present in animals with lymphoma, myeloma, or histiocytosis) [251]. Increased CSF levels of IgG and/or IgM have also been noted [266]. Recent studies suggest that the cytokine transforming growth factor–β1 (TGF–β1), does not appear to be correlated with the IgA production [267]. CT imaging may help localize changes in the CNS (meninges, spinal cord, and brain) and assist in the efficacy of therapy [268].

Grossly, subarachnoid hemorrhages may be seen extending over the entire spinal cord and brainstem [1]. Microscopic lesions are characterized by fibrinoid necrosis of the tunica media and vascular thrombosis of vessel walls and periarteritis in the meninges (especially of the cervical spinal cord), cranial mediastinum, and heart [269]. Meningeal fibrosis in some cases may lead to obstruction of CSF flow and hydrocephalus [265]. Partial and complete vessel occlusion by the inflammatory process or thrombi may lead to ischemia. Small and large muscular arteries can be affected. Organization and recanalization of

thrombi may be present in chronic lesions [251]. There is extensive perivascular and leptomeningeal infiltration by mononuclear cells (severe lymphoplasmacytic and moderate histiocytic infiltration) plus smaller numbers of neutrophils. In some cases, neutrophils predominate [258,270]. In Beagles, numerous IgG-and/or IgM-containing cells are seen in the leptomeninges and in the adventitia, media, or intima of affected vessels [258,259]. It has been demonstrated that B and T lymphocytes occurred in meningeal lesions, while only T cells were found around inflamed arteries [271]. In animals with parenchymal signs, pathological findings might include subpial wallerian degeneration, nerve root degenerative changes, and rarely, spinal cord infarction or compression secondary to occlusion or rupture and hemorrhage of structurally weakened vessels [270]. In chronic disease, the leptomeninges tend to be thickened with focal mineralization but with milder inflammatory cell infiltration. Amyloidosis (splenic, hepatic, and renal), lymphocytic thyroiditis, and generalize systemic vasculitis are present in some affected Beagles [258,269].

The cause of SRMA remains unknown. To date, no bacterial or viral infectious agents have been identified, although activated T cells have been found in some dogs indicating these cells have had contact with some unidentified antigen [272]. SRMA has the pathological features of an immune-mediated vasculitis [269]. Although deposition of immunoglobulins in blood vessels has not been seen in most studies [1,251,258-260], focal deposits of IgA were found in the vascular wall of one chronic case [266]. It has been reported that in SRMA chemotactic factors are generated in the CNS, including interleukin-8 [273]. The intensity of this production appears to correlate with IgA levels in the CSF suggesting either a causal link or reflecting the severity of the inflammation.

The prognosis is guarded to favorable, especially in dogs with acute disease that are treated promptly using immunosuppressive doses of corticosteroids. Untreated dogs tend to have a remitting and relapsing course [257]. Tipold [251] recommends the following long-term therapy (e.g., for at least 6 months), especially in any dog that has had a relapse: prednisolone at 4 mg/kg/day, PO or IV initially. After 2 days, the dose is reduced to 2 mg/kg daily for 1 to 2 weeks, followed by 1 mg/kg daily. Dogs are re-examined, including CSF analysis and hematology, every 4 to 6 weeks. When signs and CSF are normal, the dose can be reduced to half of the previous dosage until a dosage of 0.5 mg/kg every 48 to 72 hours is attained. Treatment is stopped 6 months after clinical examination, CSF, and blood profiles are normal. In refractory cases, other immunosuppressive drugs such as azathioprine (at 1.5 mg/kg PO every 48 hours) may be used in combination with steroids (e.g., alternating each drug every other day). Antibiotics are ineffective. Results of a long-term treatment protocol (up to 20 months) involving 10 dogs with SRMA have been recently published [274]. Eight of the 10 dogs were without clinical signs up to 29 months after the treatment was terminated. Long-term glucocorticosteroid treatment resulted only in mild clinical side effects, such as polyuria/polydipsia, polyphagia and weight gain, which were reversible after the therapy was discontinued. It was noted that elevated serum and CSF IgA levels did not decrease to normal values during prednisolone treatment and were still slightly increased after the therapy was discontinued. Monitoring of CSF cell count in dogs with this condition was a sensitive indicator of success of treatment. In addition, older dogs with high IgA levels in the CSF and frequent relapses seemed to require a longer duration of therapy and had a less favorable prognosis long term.
Note that Akitas with immune-mediated polyarthritis may show similar clinical signs as animals with SRMA and have concurrent meningitis [275].

A case of compressive, cervical, pyogranulomatous inflammation of undetermined cause affecting the dura mater (i.e., pachymeningitis), accompanied by fever and neck pain, right forelimb weakness that progressed to nonweight-bearing lameness and muscle atrophy and proprioceptive deficit has been reported in a 3 year old English Springer Spaniel [276]. Neutrophilia with a left shift was present, along with moderate neutrophilic pleocytosis (43 WBCs/µl) and elevated protein (106 mg/dl) in CSF. Cervical myelography demonstrated extradural cord compression at C4 - C5. Biopsy of the mass revealed marked dural thickening associated with an intense inflammatory cell infiltrate composed of sheets of macrophages and moderate numbers of neutrophils, plasma cells, and lymphocytes. There were also multifocal areas of necrosis and hemorrhage. No organisms were demonstrated. The pachymeningitis ultimately regressed with long-term (over a 30-week period) immunosuppressive therapy that included prednisolone and azathioprine. The authors considered that this case shared features with hypertrophic spinal pachymeningitis of humans, an uncommon, frequently idiopathic, chronic inflammatory disorder causing dural hypertrophy, radiculopathy, and spinal cord compression. It is also possible that the case represents a pathological variant of chronic SRMA.

Bacterial Meningitis
Bacterial meningitis is a rarely reported condition in dogs and cats [1,277]. Animals of any age may be affected, although most affected dogs are adult, with a mean age around 5 years [278]. Bacterial infections of the CNS most often occur via hematogenous spread from distant foci within the body (e.g., lung or splenic abscess, vegetative endocarditis, pleuritis, and urinary tract infections), by direct extension from sinuses, ears and eyes, as a result of trauma (e.g., bite wound), meningeal

spread with entry along nerve roots, or from contaminated surgical instruments (e.g., spinal needle) [80,278-283]. Organisms usually disseminate via CSF pathways and produce cerebrospinal meningitis, often associated with microabscess formation of brain and spinal cord. A plethora of organisms have been cultured from dogs with bacterial meningitis including *Pasteurella* sp (e.g., *P. multocida*), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus albus*, *Actinomyces* sp, *Nocardia* sp, *Escherichia coli*, *Streptococcus* sp (e.g., *S. pneumoniae*) and *Klebsiella* sp.

Bacteria that survive in the circulation enter the CSF from the bloodstream through the choroid plexus of the lateral ventricles and other areas of altered blood-brain barrier (BBB) permeability [284]. Normal CSF contains no phagocytic cells, has a low protein concentration, contains no IgM and is inadequately prepared to counter invading bacteria due to insufficient numbers of complement components and immunoglobulins for bacterial opsonization [285]. The rapid multiplication of bacteria leads to release of bacterial cell wall components and induction of formation of inflammatory cytokines, interleukin-1 and tumor necrosis factor by monocytes, macrophages, brain astrocytes, and microglial cells which leads to further alteration of the BBB permeability, recruitment of polymorphonuclear leukocytes, and formation of a purulent exudate in the subarachnoid space [284]. The permeability of blood vessels increases through the adherence of leukocytes to cerebral capillary endothelial cells, which allows entry of plasma proteins and leads to vasogenic brain edema. Cytotoxic brain edema results from toxic oxygen metabolites released from degranulating leukocytes which have been stimulated by the inflammatory cytokines [286]. Interleukin –1 is thought to play a role in altering the level of consciousness and in fever production by its effect on the hypothalamus. The purulent exudate in the subarachnoid space can interfere with resorptive function of the arachnoid granulations and its presence in the basal cisterns may obstruct outflow of CSF through the ventricles leading to transependymal fluid movement into brain parenchyma and interstitial edema [284]. These mechanism lead to an increase in intracranial pressure and impaired cerebral perfusion pressure (see cranial trauma).

Irrespective of the etiologic agent, bacterial meningitis usually is acute in onset and tends to be characterized by a group of clinical signs that include hyperesthesia, fever, cervical pain, and frequently, cervical rigidity. In addition, vomiting, bradycardia, anorexia, occasional cranial nerve deficits, and seizures may be observed. Seizures may be caused by high fever, hypoglycemia, brain edema, or inflammation, while vomiting may result from increased intracranial pressure or from direct effects on the vomiting center [287]. In some animals, clinical signs may develop that suggest parenchymal involvement. The clinical diagnosis of bacterial meningitis is supported by the finding of highly pleocytic CSF (500 to 1000+ WBCs/µl) with a high proportion of neutrophil cells [288]. The protein content of the CSF is usually increased as well (100 to 1000+ mg/dl). Low CSF glucose, relative to plasma glucose values, are typical. Organisms may be seen on CSF cytology [289]. Neutrophilia may be present in blood samples and there may be evidence of shock, hypotension, and disseminated intravascular coagulation Thrombocytopenia, abnormal liver enzymes, electrolyte imbalance, abnormal anion gap, and uremia have been reported in some cases [278]. Electroencephalographic traces may demonstrate high voltage (30 - 70µv), fast (20 - 35 Hz) or slow (5 - 10 Hz) wave activity. Definitive diagnosis is made by bacterial culture of CSF (both aerobic and anaerobic) [289]. Blood and urine cultures may incriminate a pathogenic organism when CSF cultures are negative (which is usually the case in our experience). Meningeal inflammation, ventriculitis, and possibly brain edema can be detected using MRI or CT scans [278,290].
Pathological findings that are characteristic of bacterial meningitis include diffuse infiltration of inflammatory cells (by both polymorphonuclear and mononuclear cells) into the leptomeninges. Frequently, inflammation is found throughout the entire subarachnoid space of the brain and spinal cord. Vasculitis is often pronounced. Bacterial invasion of CNS parenchyma is characterized by mononuclear and polymorphonuclear inflammatory infiltration and extensive perivascular cuffing. Necrosis of gray and white matter, sometimes associated with vascular thrombosis, may be observed with infiltration of macrophages, neutrophils and plasma cells.

Prognosis is guarded since death is common even if appropriate therapy is administered, and relapses are frequently encountered [291]. Appropriate use of antibiotics, according to the culture results, is basic to successful therapy of bacterial meningitis (encephalomyelitis). Antibiotic therapy should be maintained for several weeks after clinical signs have resolved [277]. Chloramphenicol (up to 50 mg/kg, IV, IM, or SC, bid), metronidazole (10 - 15 mg/kg, PO, tid), trimethoprim-sulfonamide (from 30 to 60 mg/kg, PO, daily; note that complications may include sulfonamide urolithiasis in dogs and nephrotoxicity in cats) penetrate the CNS in therapeutic concentration. Ampicillin and penicillin enter the CNS only with meningeal irritation. Aminoglycosides and cephalosporins reportedly do not adequately penetrate the CNS, even when inflammation exists. Intrathecal administration of antibiotics should only be considered in refractory cases. Corticosteroids, in general, are contraindicated in the treatment of bacterial meningitis [277,291]. It has been suggested that *Staphylococcus* sp. should be assumed when the organism involved is not known [277]. Ampicillin, 5 - 10 mg/kg, IV, every 6 hours is recommended. Diazepam or other anticonvulsants can be used for seizures if they occur. Osmotic diuretics may be useful for treating increased intracranial pressure secondary to brain edema.

Note that it may be very difficult to differentiate between bacterial meningitis and steroid responsive meningitis-arteritis (SRMA). The latter is more common and probably should be at the top of the differential list. Analysis of CSF for elevated levels of IgA should be diagnostic for SRMA.

Miscellaneous Meningitis

Different forms of encephalitis may have an associated meningitis (see Pug dog encephalitis). In general, viruses typically do not produce a pure meningitis. Rickettsial infections (Rocky Mountain Spotted Fever or Ehrlichia) might be considered in dogs with evidence of meningitis and negative cultures (see Rickettsial Disorders). Also, parasitic migration through the CNS can result in aseptic, suppurative meningitis. An eosinophilic CSF pleocytosis may accompany parasitic migration, protothecal infections (see Protothecosis) and some forms of meningoencephalitis in dogs and cats (see Eosinophilic Meningoencephalitis). Trypanosomiasis occasionally may involve the CNS producing a severe chronic meningoencephalitis in dogs. Fungal meningitis may be severe, but it is usually associated with granulomatous encephalitis and clinical evidence of parenchymal disease (see Mycotic Diseases). A subclinical encephalopathy associated with feline immunodeficiency virus has a meningitic component (see Feline Immunodeficiency Virus Encephalopathy). Subclinical meningitis or meningoencephalitis may occur in young Akita dogs with polyarthritis [275].

Mycotic Diseases of the CNS

Mycotic agents sporadically produce a granulomatous meningoencephalomyelitis in dogs and cats. The more common mycotic infections of the CNS are caused by *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidioides immitis*. Each agent has a particular geographic distribution in the USA. The pathogenesis is similar for blastomycosis, histoplasmosis and coccidioidomycosis. The organism is present in the soil, producing mycelia and airborne spores. The coccidia of spores are probably inhaled, deposited in the alveoli, phagocytosed and converted into the spherical parasitic, yeast form. This form is disseminated via lymphatics producing local hilar lymphadenopathy and there is hematogenous spread to other organs. The fate of the infected host is believed to be dependent upon time and ability to develop cellular immunity to fungal antigens. Unlike other mycotic diseases, *C. neoformans* exists only in the yeast form and has a worldwide distribution. Endemic areas have not been identified. Infection is probably acquired from the environment rather than from animals. Cryptococcosis infection often occurs in mature dogs and cats that are immunodepressed (e.g., cats with feline leukemia virus or feline immunodeficiency virus, or dogs with ehrlichiosis), and infection may be accelerated or worsened by glucocorticoid therapy [292]. Cats contract the disease more frequently than dogs. The natural route of infection is generally believed to be the respiratory tract, with subsequent hematogenous and lymphogenous dissemination to other areas of the body. As with bacteria, mycotic infections also may reach brain and spinal cord by direct spread from an adjacent infection, e.g., from the nasal chambers, tooth alveolus and sinuses, outer ear, eustachian tube, middle/inner ear, petrous temporal bone, and basilar bone.

While the overall incidence of CNS involvement by mycotic diseases is low, *C. neoformans* may be more likely to be incriminated than the other organisms in dogs [293-299] and cats [300-303]. Neurological signs will vary according to lesion location and severity [303]. The signs may reflect either a focal mass lesion or a diffuse multifocal disease process. Neurological signs may include seizures, depression, disorientation, circling, ataxia, falling, pelvic limb paresis, paraplegia, anisocoria, pupillary dilatation and blindness. Deficits of one or several of cranial nerves 5 to 12 are often present. Note that these signs may be seen with any of the mycotic infections. Radiographic evidence of diffuse miliary to nodular interstitial pulmonary infiltrates may be seen with blastomycosis, histoplasmosis, and coccidioidomycosis. Gross lesions may include thickening of the meninges, which sometimes have a gelatinous, cloudy appearance [302]. On sectioning of the brain, cystic spaces may be seen within the parenchyma. These spaces reflect expanded perivascular spaces and are frequently filled with crytococcal organisms having a round/ovoid cell body and surrounded by a halo-like capsule that stains strongly with PAS or Mayer's mucicarmine [1]. In cats, only a minimal or mild nonsuppurative inflammatory response may be present. In affected dogs, the cellular response is more granulomatous with epithelioid macrophages, lymphocytes, and plasma cells [295]. The organism may be found as free hyphae or yeast form some of which may be budding. The yeast form is often present within macrophages. Ocular lesions associated with a cell-mediated chorioretinitis may also be observed [304]. Pyogranulomatous encephalitis has been reported occasionally in dogs and cats in association with blastomycosis [305-307]. Neurological disease associated with histoplasmosis and coccidioidomycosis is rare or quite uncommon [1,304,308,309], although granulomatous meningitis attributable to *C. immitis* was diagnosed on postmortem examination in a 4 year old Border Collie by demonstration of coccidioides endospores in brain tissue [310]. There are a few reports of CNS infection in dogs and cats associated with uncommon opportunistic fungi, such as phaeohyphomycoses, in which the agents involved are almost always Cladosporidium species, and usually *C. bantianum* [9,311-313]. CNS disease is usually due to localized brain abscess or to multiple large pyogranulomatous lesions in the cerebrum and meninges, sometimes with multifocal malacic foci, and is invariably fatal [314]. Brown, branching hyphae and/or budding yeasts are seen in the areas of pyogranulomatous

inflammation [1]. There have been sporadic reports of other fungal infections involving the CNS, including *Geotrichum candidum* (cerebral granulomas, choriomeningitis) [315], *Aspergillus* sp. (cerebral granulomas) [316], and *Paecilomyces* (brain abscess or multifocal perivascular granulomas) [317,318].

Diagnosis of mycotic infection is based on demonstration of the organisms in tissue sections using immunofluorescent procedures or in material taken from aspirates or impression smears, culture, and serology. A commercial latex agglutination test is available for detecting cryptococcal capsular antigen in serum, urine, or cerebrospinal fluid [319]. In dogs, common strains isolated are *C. neoformans var. neoformans* and *C. neoformans var. gattii* [298]. In one affected cat with cryptococcosis, detailed typing of the strain indicated that it belonged to serotype AD and *Filobasidiella neoformans var. neoformans* mating type "alpha" [300]. The agar-gel immunodiffusion test is a useful serological test for diagnosis of blastomycosis. Histoplasma organisms may be found in neutrophils or monocytes of buffy coat or bone marrow smears [320]. Fungal organisms may be observed in CSF (staining is facilitated by using India ink), which usually will be pleocytic (increase in numbers of mononuclear and polymorphonuclear cells) and will have elevated protein levels. Inflammatory lesions may be detected using MRI (Gadolinium-enhanced T1-weighted images showed multiple, focal contrast enhancing areas in frontal cortex and diffuse meningeal enhancement) [299]. In one report involving an 8 year old Chow Chow dog in which an antemortem diagnosis of *C. bantianum* was made using a stereotaxic CT-guided brain biopsy, MRI scans revealed the presence of a large hypointense, irregular lesion corresponding to the location of a phaeohyphomycotic fungal granuloma and pronounced shift of structures toward the midline [313]. Antemortem diagnosis of paecilomycosis in a 3 year old Vizsla was made from a bone-marrow culture [318].

Prognosis of mycotic infection is always guarded, especially in the disseminated form and with CNS involvement. Most of the organisms are sensitive to treatment with amphotericin B (AMB), e.g., using a dosage of 0.1 to 0.5 mg/kg body weight, IV, three times weekly, in dogs and cats [292]. The treatment of choice for cryptococcosis still appears to be AMB and flucytosine (FCY), although toxic epidermal necrolysis may sometimes be seen as a side-effect [296]. A recommended dosage for FCY is 120 mg/kg body weight, divided into 4 equal doses daily [292]. Due to the inability of AMB and FCY to cross the blood-CNS barrier, it is recommended that these drugs be used in combination with other antifungal agents such as itraconazole (ITZ, at 5 - 10 mg/kg, PO, bid) or fluconazole (FCZ, at 5 - 15 mg/kg, PO, bid) [292] in animals with CNS disease. It would seem that the same recommendation would apply to other fungal diseases having CNS involvement, e.g., ITZ at 10 mg/kg, PO, daily is suggested for dogs with blastomycosis/brain involvement [321]. In a recent report of cryptococcosis in 19 cats, treatment with ketoconazole (KTZ), was unrewarding in cases with CNS involvement [303], although KTZ and ITZ (both at 10 mg/kg, PO, daily) successfully treated a small number of experimentally-infected cats, including some with CNS disease [301]. FCZ therapy has been used successfully in a dog for a period of 1 year (before progression of signs and clinical deterioration led to euthanasia) with disseminated CNS cryptococcosis [299] and in cats without CNS disease [322]. FCZ as a sole agent successfully treated an extradural compressive cryptococcal cervical lesion in a 6 year old Doberman [534]. A combination of AMB and KTZ failed to stem the progression of neurological signs (deafness and bilateral vestibular syndrome) in a dog with disseminated paecilomycosis [318].

Parasitic Encephalomyelitis

In contrast with large domestic animals, myiasis and/or helminthiasis involving the CNS in dogs and cats is infrequently encountered clinically [1]. Most instances of parasitic encephalomyelitis in small animals are the consequence of aberrant migration of parasites that normally reside in dogs and cats, such as *Dirofilaria immitis* or canine *Angiostrongylus vasorum* infestation, although infestation of an aberrant host may also occur, such as the rat metastrongylid *Angiostrongylus cantonensis* which causes paraparesis and ataxia in dogs [323,324]. In general, little is known of the route of migration of parasites that invade the brain, with the exception of hematogenous-borne *Dirofilaria immitis* (heartworm). In Cuterebriasis, caused by the dipteran (fly) parasite *Cuterebra*, larvae possibly gain entry to the cranium by migration through skull foramina, penetration of ethmoid bone and cribriform plate, hematogenous spread after penetrating a large vessel, or via the external-middle ear with direct extension to the meninges and venous sinuses [1,325-327]. Apart from dirofilariasis, which occurs sporadically in mature dogs and cats, CNS parasitic invasion usually takes place in immature and young adult animals that have exposure to the external environment. Some species of *Cuterebra* and some nematodes, such as *Angiostrongylus* sp., may have a selective affinity for the neuraxis and it has been proposed that aberrant cuterebral larval migration in the brain is the cause of feline ischemic encephalopathy [328]. Cysticercosis is another cause of parasitic encephalomyelitis in dogs with sporadic reports coming from Africa, Mexico City, and the United States [329-332]. The larval stage is *Cysticercus cellulosae*, the metacestode of the human tapeworm *Taenia solium* and pigs are the most common hosts. Neurocysticercosis is considered the most common parasitic disease of the CNS in humans [284]. *Toxocara canis*, the common roundworm in the dog, can cause "visceral larva migrans" syndrome in dogs and humans, which may include generalized illness, eosinophilia, and symptoms arising from larval invasion of different organs. Of these, the clinically most important in

humans are liver, lungs, eyes and CNS [333]. *Baylisascaris* infection, usually associated with *Baylisascaris procyonis*, the common roundworm of raccoons, sporadically causes cerebrospinal nematodiasis in dogs [334,335]. The epidemiology of this infection appears related to exposure to soil or fecal debris containing contaminated embryonated eggs from caged raccoons shedding large numbers of roundworms in their feces [335]. The larvae may migrate throughout the body, including the CNS. Cerebral coenurus cysts are sporadically reported in cats. These cysts are associated with the larval stages (coenuri) of certain dog tapeworms belonging to the genus *Taenia*, and most reports implicate *Taenia serialis* [336-339]. *Taenia serialis* has a canid-lagomorph life cycle, with cats being accidental intermediate hosts.

Aberrant migration and growth of parasites can result in extensive damage to neural parenchyma which appears to be largely mechanical, although toxic larval excretory products resulting in vascular compromise and ischemia are thought to be important factors in *Cuterebra* infestation [328]. Gross CNS changes in the CNS resulting from parasitic migration may include palpable softening and discoloration of focal areas of the cerebral hemispheres or spinal cord and multifocal presence of small hemorrhages in the cerebrospinal meninges and CNS parenchyma. Microscopic changes are commonly characterized by multiple tracts of necrotic debris, gitter cells, gliosis, vascular rupture with hemorrhage, malacia, and proliferative (granulomatous) changes. The margins of the tracts may have many eosinophilic axonal spheroids, ballooned myelin sheaths, and myelin loss [1]. There may be perivascular cuffs of macrophages, lymphocytes, plasma cells and variable numbers of eosinophils. Parasitic granulomas within the ventricular system, inflammatory changes in the periventricular brain tissue, and stenosis of the mesencephalic aqueduct can lead to obstructive hydrocephalus [340]. Note that it is not uncommon to find parasites in lesion-free areas in paraffin sections, presumably reflecting parasite migration following death of the host [1].

Adult parasites of *Dirofilaria immitis* in dogs and cats usually are found in the right side of the heart and the pulmonary arteries, but aberrant migration to the CNS occurs occasionally and may cause focal or multifocal cerebral infarction secondary to arterial occlusion, malacic tracts, granulomatous and eosinophilic encephalomyelitis, and parenchymal compression if worms are in CSF pathways [1,341-343]. Aberrant adult heartworm infection resulted in thrombosis of the femoral artery and multiple muscular branches, with subsequent muscle necrosis and inflammation in one hindlimb of a 2 year old Boston Terrier [344]. Additionally, an unusual larval-tissue interaction to microfilariae resulted in a multifocal encephalomyelitis in the brain and spinal cord. In one report of dogs with heartworm microfilarial infection treated with ivermectin, microgranulomas containing microfilariae were found seen in many organs, including skeletal and cardiac muscles, while small glial nodules were seen in the CNS [345]. Angiostrongylosis due to *Angiostrongylus vasorum* occurs in dogs in Europe, especially South West France and the United Kingdom. This worm parasitizes the pulmonary artery and right ventricle of dogs. Just as for *Dirofilaria immitis*, aberrant migration through the CNS by this worm, as well as thromboembolic disease associated with adults or first-stage nematode larvae, may result in neurological disease [346-348]. A rare, aberrant infection with *Ancylostoma caninum* has been reported in a 12-week-old puppy [349], in whom a young adult female parasite was found in the cervical spinal cord in association with severe meningeal and deep tissue hemorrhage. Hemorrhagic and necrotic tracts led from the subarachnoid space to the central gray matter. A granulomatous encephalomyelitis associated with nematode larvae occurs in puppies with neural angiostrongylosis (*A. cantonensis*), with lesion most severe through all levels of the spinal cord, but also extending up to the brainstem [350]. Immature adult worms of *A. cantonensis* have also been identified in brain and spinal cord. In a report of 10 cats with cerebrospinal cuterebriasis, superficial laminar cerebrocortical necrosis, cerebral infarction, subependymal rarefaction and astrogliosis with or without ependymal cell loss, and subpial astrogliosis were seen in addition to the parasitic track lesions [328]. The larvae were recovered most commonly in the region of the olfactory bulbs and peduncles, optic nerves, and cribriform plate, suggesting entry from the nasal cavity. In dogs with cysticercosis, multiple cysticerci (consisting of a fluid-filled cyst in which the invaginated cestode scolex develops) are commonly found in subarachnoid spaces, cerebral cortex, white matter, and ventricles of the brain [329,330]. A chronic inflammatory exudate comprising lymphocytes and macrophages was observed in host tissues surrounding the parasites. In dogs, larvae of *Toxocara canis* may also wander widely through various tissues, including the CNS. Damage may arise from the tracts or from granulomas that develop around larvae whose migration has been arrested. Granulomas comprising inflammatory cells, including eosinophils, and calcified and uncalcified nematodal fragments, have been reported in pituitary gland, brain, and cauda equina of dogs [351]. In one dog, a 2.5 year-old Great Dane, a granuloma consisting of lymphocytes, plasma cells, and occasional eosinophils had destroyed much of the caudal median eminence and adjoining pars tuberalis of the hypothalamus and extended dorsally to involve the ependyma of the third ventricle [352]. In dogs with *Baylisascaris* infection, extensive multifocal necrotizing, granulomatous and eosinophilic encephalomyelitis occurs often with intralesional ascarid larvae [334,335]. Larvae may measure 50 to 70 µm in diameter and often have prominent lateral alae. These larvae are much larger than those of other ascarids, including *Toxocara canis*, and the tissue damage is greater [1]. In cats with cerebral coenuriasis (*Coenurus serialis*, the intermediate stage of *Taenia serialis*), pathology is associated with a fluid-filled cerebral hemispheric coenural cyst (measuring up to 2 cm in diameter)

that results in compression of neural tissue with destruction and phagocytosis of neurons and myelin by macrophages (gitter cells), gliosis, and marked perivascular cuffing with lymphocytes and plasma cells [337]. Diffuse flattening of the cerebral hemispheric gyri and obstructive hydrocephalus may occur [339]. The damage from the cyst can be extensive leading to increased intracranial pressure and herniation of the cerebellar vermis into the foramen magnum, and compression of the brainstem and cerebellum [337,339,353].

In aniaged indoor-outdoor mals with parasitic encephalomyelitis, the clinical course may be rapid or chronic, usually progressive, and follows an acute or insidious onset of signs. Clinical signs are extremely variable depending on the location and nature of the lesion. The signs may reflect either a mass lesion in the brain or spinal cord or a multifocal disease process. In dogs and cats with dirofilarial encephalomyelitis, clinical signs may include seizures, visual impairment, constricted pupils, depression, incoordination, circling, paraparesis, or paraplegia [341,344,354,355]. Similar signs may be seen with *Angiostrongylus vasorum* encephalomyelitis [346-348]. Epidural migration of adult heartworms (*D. immitis*) has been reported in several dogs involving cervical and thoracolumbar spinal regions [356-358]. In one dog, signs of a recurring nonambulatory tetraparesis were observed [358]. A 12-week-old Cocker Spaniel puppy with spinal nematodiasis associated with *Ancyostoma caninum* showed signs of incoordination, loss of balance, posterior paresis that progressed to tetraplegia, torticollis, and cervical pain [349]. In a clinicopathological study involving 11 cats with *Cuterebra* larvae myiasis of the CNS, young to middle-aged indoor-outdoor Domestic Shorthaired cats frequently presented with acute neurologic signs that were progressive and most commonly consisted of depression, blindness, and behavior changes [328]. These signs typically occurred from July through September, and many cats had initial clinical signs consistent with upper respiratory disease [359]. In canine neural angiostrongylosis caused by *A. cantonensis*, neurological signs are commonly seen in puppies from 5 to 16 weeks of age and are characterized by a lumbosacral syndrome (paresis or paralysis of tail, pelvic limbs, bladder) that sometimes ascends to involve thoracic limbs, neck, and muscles of mastication [323,324]. Severely affected puppies may become depressed, show behavioral changes, and have seizures. Severe lumbar and/or generalized hyperesthesia is common [360,361]. Neurocysticercosis in a 2 year old Whippet was characterized by a chronic history of falling and circling, difficulty maintaining balance, an inabilty to walk in a straight line, and walking sideways [332]. Neurological signs may be minimal in dogs with visceral larval migrans associated with *T. canis* infestation [351], however, hypothalamic larva migrans has been reported in several dogs with diabetes insipidus and signs of polydipsia-polyuria and nocturia [352,362]. Acute signs of ataxia that progressed to recumbency within 48 hours were reported in a 10-week-old Walker hound puppy with *Baylisascaris* encephalomyelitis [335], while progressive weakness, dysphagia, and circling were noted in an affected 12-week-old Beagle [334]. Clinical signs in cats with cerebral coenuriasis are extremely variable and may be multifocal if brain herniation has occurred, e.g., ataxic wobbly gait, falling with episodes of extensor rigidity, lethargy, sudden aggression, visual impairment, and depression [337,338,353].

Clinical diagnosis of parasitic migration is difficult but may be suggested by presence of an eosinophilic pleocytosis in CSF (often with neutrophils and mononuclear cells); however, definitive diagnosis requires isolation and/or pathological demonstration of the parasite within the CNS [1]. Signs of ascending paresis/paralysis in young puppies with eosinophilic pleocytosis is considered characteristic of neural angiostrongylosis [323,324]. CSF may be normal in dogs with cysticercosis [332]. Eosinophilia in blood is not considered to be highly suggestive of CNS parasitic migration, since it may also be induced by intestinal worm populations. Epidural heartworms may be detected using myelographic and imaging techniques [356,358]. MRI has been used for the diagnosis of cysticercosis. T1- weighted, contrast-enhanced, 3-mm-thick axial, sagittal, and coronal views of the brain revealed multiple cyst-like lesions located in the subdural portion of the left occipital lobe and the dorsal midline and right dorsolateral aspect of the brain stem [332]. The cysts had high-signal-intensity and ring-like peripheral margins. CT scans have also been used to diagnose coenural cysts in cats [338]. Thrombocytopenia and bleeding episodes associated with chronic disseminated intravascular coagulation have been reported in some dogs with *Angiostrongylus vasorum* infestation [347,363].

Prognosis is guarded and treatment frequently ineffective with most instances of parasitic encephalomyelitis. However, surgical removal of mature heartworms has been successful in several cases of epidural dirofilariasis [356,358], and mildly affected puppies with neural angiostrongylosis (associated with *A. cantonensis*) usually recover with supportive care and corticosteroid therapy [323]. Anthelmintic treatment has been ineffective in this condition and may be contraindicated. In one study, levamisole and mebendazole treatment of dogs mildly affected with neural angiostrongylosis resulted in a 75% death rate [323]. *Angiostrongylus vasorum* in dogs has been successfully treated using ivermectin, fenbendazole, or mebendazole [347,363]; however, severe hypovolemic shock occurred in one dog following levamisole treatment [364], possibly caused by an anaphylactic reaction triggered by the rapid release of a large amount of worm antigen in the blood due to the rapid death of adult worms by levamisole. Treatment of cysticercosis in a 2 year old Whippet with albendazole and prednisone was successful with resolution of clinical signs over several weeks [332]. In endemic areas, environmental sanitation and public

education are necessary in order to reduce the incidence of cysticercosis in dogs [329].

Protothecosis

Protothecosis is a rare disease caused by an achlorophyllous genus of algae. Two species, *Prototheca wickerhamii* and *Prototheca zopfii*, have been shown to produce systemic disease in animals. CNS involvement has been reported in dogs (but not in cats, in which only cutaneous protothecosis has been observed) with both *Prototheca* sp. [365,366]. The pathogenesis of protothecosis is uncertain. An alimentary route of exposure has been suggested [367,368]. Failure of the host's immune competence (including cell-mediated immunity and impaired neutrophil function) may predispose to infection with this ubiquitous organism. A recent study suggested that either protothecal organisms inhibit the migration or proliferation of cellular inflammatory infiltrates or only dead protothecal organisms induce an effective local immune response [369]. Collie dogs seem to have a higher incidence of this disease compared with other breeds [370]. Infection can occur at any age. Most cases have been reported in female dogs [368]. It appears that the organism has a definite affinity for the eyes in dogs [371,372]. The most common clinical sign is bloody diarrhea. Draining ulcers have been reported only in a few dogs. Neurological signs are variable, reflecting a multifocal disease process, and include visual impairment, paresis, tetraplegia, deafness, head tilt, facial hypalgesia, anosmia and dementia [367,371,373,374]. CSF abnormalities may include marked pleocytosis (>100 cells/µl) with granulocytes and lymphocytes dominant, and increased protein (>100 mg/dl) [368]. A pronounced eosinophilic pleocytosis (>6,000 cells/µl) and elevated CSF protein (>830 mg/dl) was noted in one dog [366]. Pre-retinal hemorrhage, clouding of vitreous, and multiple white, raised foci or streaks in the retina, and exudative retinal separation have been noted ophthalmoscopically [371].

Organisms have been identified in CSF (e.g., using Gram's iodine stain), in fluid obtained by vitreous centesis, in urinary sediment, and in tissue sections using Gomori's methenamine silver or PAS stains, ultrastructural studies, and immunofluorescence [367,375]. Organisms and pyogranulomatous lesions with neutrophils, histiocytes, lymphocytes and plasma cells, have been described in eyes, brain, spinal cord, kidneys, skeletal muscle, heart, liver, spleen, colon, and lungs [365,366]. Gliosis may be prominent in and around areas of necrosis in the CNS, including gray and white matter. In the spinal cord, scattered demyelinated fibers and swollen axons may be seen, especially in dorsolateral funiculi in cervical and thoracic sections [366]. Small multifocal lesions have been seen in the meninges and ependymal cells lining the ventricles [366]. Organisms have a round to oval shape, range from 10 to 30µm in diameter, and have internal partitions and a birefringent capsule that is PAS positive. Histologically, myriads of protothecal organisms in different stages of development are found in the granulomatous lesions [367]. The prognosis is grave and treatment to date has been unrewarding in dogs with disseminated disease [371,376], although oral ketoconazole for six months resolved most of the clinical signs in one dog with systemic protothecosis and cutaneous lesions [377].

Protozoan Encephalitis-encephalomyelitis

Toxoplasma, *Neospora*, and *Sarcocystis* are three genera of the phylum Apicomplexa that cause encephalomyelitis in dogs and cats.

Toxoplasmosis and Neosporosis - Toxoplasmosis is an infectious condition caused by the protozoal parasite *Toxoplasma gondii* and occurs in acquired and congenital forms in man and animals [378]. Cats are the definitive host for this parasite. The three known infective stages of *Toxoplasma gondii* are bradyzoites, tachyzoites and sporozoites. The three modes of transmission are carnivorism (ingestion of encysted bradyzoites), fecal contamination, and in utero infection [378]. These modes of transmission involve the different infective stages as follows: carnivorous ingestion of encysted bradyzoites, tachyzoites or both; contamination with feline feces containing sporozoites of sporulated oocysts; transplacental infection of the fetus with tachyzoites after ingestion of encysted bradyzoites or sporulated oocysts by the mother. Humans, sheep, pigs, dogs and (rarely) cats are known to transmit *T. gondii* transplacentally. In humans, congenital infection occurs when a woman becomes infected during pregnancy [379,380]. *Toxoplasma* oocysts are shed in feline feces unsporulated and are not infective until sporulated (1 - 5 days). Sporulated oocysts can survive in soil for several months. Land snails, earthworms, flies and cockroaches may serve as transport hosts for oocysts. Most mammals become intermediate hosts through ingestion of oocysts. Following the acute systemic infection in intermediate hosts in which the organism can be disseminated to many body organs (this phase may be subclinical), tissue cysts form, most commonly in the CNS, skeletal muscle, and heart muscle. This conversion is related to development of the host humoral and cellular immune response [1]. The parasites are mainly intracellular and subclinical infection may persist for the life of the host. Activation of toxoplasmosis may occur in association with severe immunosuppressive disorders [378]. The condition is often associated with canine distemper or other infections such, as ehrlichiosis, or with glucocorticoid therapy [378,381]. Clinical toxoplasmosis is most commonly seen in young dogs less than 1 year of age or in immunocompromised older dogs.

Note that many disorders previously ascribed to toxoplasmosis in dogs have now been found to be cases of neosporosis caused by *Neospora caninum*, an apicomplexan protozoan parasite that can infect puppies in the neonatal period [382-384]. Dogs are the only proven definitive host for *N. caninum* [385,386]. Its life cycle is unknown, although transplacental

transmission has been shown in dogs [387-389]. It has a wide host range, but its zoonotic potential is unknown. Older dogs may also be affected [390]. Fatal neosporosis has been documented throughout the world and *Neospora caninum* has been isolated in the USA and in several European countries [391,392]. These isolates may have significant biological and genetic differences [393]. Because many cases of neurological disease previously diagnosed as toxoplasmosis are now turning out to be examples of neosporosis, the acronym TX-NS will be used in the following discussion to encompass both protozoa. Several clinical syndromes may be observed in dogs with TX-NS infection:

a. Encephalomyelitis - TX-NS in dogs resulting in a systemic infection will typically affect most organs, and the CNS, in particular [394]. Neurological signs associated with TX-NS encephalomyelitis are variable and may reflect a focal or multifocal disease process. In dogs, signs include hyperexcitability, depression, intention tremor, paresis, paralysis, head tilt, and seizures [395]. Clinically apparent encephalomyelitis associated with toxoplasmosis is uncommon in cats; however, pelvic limb paralysis, hypertonia, and hyperreflexia, were observed in a 10 year old, male Domestic Shorthaired cat secondary to myelitis reportedly caused by *Toxoplasma gondii* [396]. The cat was also seropositive for feline immunodeficiency virus, which has been shown to predispose cats to acute generalized toxoplasmosis [397]. Ophthalmic disease, respiratory disorders, muscle hyperesthesia, and fever are common findings in feline toxoplasmosis [398,399]. Note that naturally-occurring cases of neosporosis have not been documented in cats [400]. Pathologically, perivascular cuffing, diffuse and focal infiltration of meninges by lymphocytes, plasma cells and histiocytes, hemorrhage, edema, necrosis and neuronal degeneration have been described throughout the CNS [401,402]. Protozoan organisms may be found extracellularly and/or in cysts. In one study, tachyzoites (endozoites) within parasitophorous vacuoles were found in neurons, astrocytes, macrophages, and vascular pericytes, while cyst stages were only observed in cells showing features of neurons [402]. Proliferating tachyzoites were associated with lesions of a necrotic-granulomatous type. Activation of astrocytes and perivascular fibroblasts resulted in marked sclerosis. The gray matter was most seriously affected in the brain, while the white matter was most often the site of inflammation in the spinal cord [402]. Experimental infection of kittens with *Neospora caninum* has resulted in fatal encephalomyelitis/myositis [403], although natural infections have not been documented [378]. Congenitally infected children may have signs of retinochoroiditis, hydrocephalus, seizures and cerebral calcification.

b. Myositis-polyradiculoneuritis - This is probably the most commonly reported infectious myositis in dogs [390,404-408]. The disease tends to be more severe in young dogs, especially those less than 6 months of age. The exact pathogenesis of TX-NS protozoan myositis-polyradiculoneuritis is speculative. While the organisms' predilection for the neuromuscular system is accepted, their myotropism in congenital and chronic infections in dogs remains enigmatic. Protozoan myositis-polyradiculoneuritis in dogs results in progressive pelvic limb paresis, synchronous pelvic limb hopping gait, and bilateral rigidity of the pelvic limbs. Rigid pelvic limb muscles are non-painful on palpation and slowly become atrophic. A fulminating disease resulting in tetraplegia over several days has been observed in mature dogs with TX-NS infection [409]. Extremely severe myonecrosis and mononuclear cell infiltrations were found in all skeletal muscles and protozoan organisms were identified in muscle and CNS. Exacerbations of disease may reflect depression of immune mechanisms in animals with both toxoplasmosis and neosporosis [378]. Pathological changes include variation in fiber size as a result of pronounced fiber atrophy, severe multifocal or diffuse myonecrosis, and mononuclear granulomatous inflammation. Free protozoan organisms are frequently seen within muscle fibers. Interstitial fibrosis is pronounced in chronic cases. In addition, myositis is usually accompanied by nerve fiber degeneration, demyelination, and occasional presence of endoneurial cysts, in nerve roots and peripheral nerves.

In the diagnosis of TX-NS neurological disease, abnormal hematological parameters may include non-regenerative anemia, neutrophilic leukocytosis, lymphocyosis, and eosinophilia. Serum alanine aminotransferase and aspartate aminotransferase levels may be increased, especially in dogs with acute hepatic and muscle necrosis [378]. Results of CSF may be abnormal, with elevated protein content and a mixed monocytic-polymorphonuclear pleocytosis. An eosinophilic pleocytosis was found in 2 dogs with a granulomatous encephalomyelitis due to protozoan infection [123]. Xanthochromia will be present if hemorrhage has occurred. Electromyographic testing may reveal fibrillation potentials, positive sharp waves, bizarre high-frequency potentials, and myotonic-like discharges. Nerve conduction velocities may be decreased. Serum creatine kinase levels are often increased. Protozoan meningoencephalitis has been detected using MRI scans [410]. The close resemblance between *T. gondii* and *N. caninum* tachyzoites and tissue cysts prevents definitive diagnosis by histopathology [384,402], and the clinical syndromes appear to be identical [411]. Differentiation between the two protozoan organisms can be made using assays for circulating antibodies [378,412,413], by tissue immunocytochemistry [414], and ultrastructural studies [401,402]. Sensitive polymerase chain reaction assays have been reported for the detection of both *Neospora caninum* DNA [415,416] and *Toxoplasma gondii* DNA [417] in biological samples. Muscle biopsy of appropriate muscles (as suggested by the clinical

signs) may also provide the possibility of a definitive premortem diagnosis using the aforementioned techniques [394]. Prognosis is poor when signs of pelvic limb spasticity are observed [418] and is guarded in any animal with signs of CNS disease. In one study involving 27 cases of neosporosis, recovery was less likely in peracute cases with severe clinical signs, and when treatment was delayed [535]. Many animals with myositis-polyradiculoneuritis have concomitant lesions in the CNS. A 4 to 8 week regimen of trimethoprim-sulfonamide (at 15 - 20 mg/kg combined dose, PO, bid) and pyrimethamine (at 1 mg/kg, PO, daily) has successfully treated animals with TX-NS-induced encephalomyelitis and myositis-polyradiculoneuritis [378,411]. Clindamycin is considered to be the drug of choice for treating canine and feline toxoplasmosis, at a dose of 10 to 40 mg/kg/day, PO or IM, divided bid to tid [378,419]. This dose can also be used for treating dogs with neosporosis [378]. Clindamycin crosses the blood-brain barrier. Oral and parenteral dosages are similar because of the good intestinal absorption of clindamycin [378]. Oral clindamycin can cause anorexia, vomiting, or diarrhea in dogs and cats.

Sarcocystosis - *Sarcocystis canis* has been proposed for the apicomplexan protozoan parasite associated with encephalitis, hepatitis, and generalized coccidiosis in young dogs between 3 and 10 months of age [420,421] in which fatal visceral and neural sarcocystosis has been described [422]. This protozoan parasite is related to *Toxoplasma gondii* and *Neospora caninum*. Only asexual stages of *Sarcocystis canis* are known in macrophages, neurons, dermal, and other cells of the body. The parasite is located free in the host cell cytoplasm without a parasitophorous vacuole. The parasite is PAS-negative and reacts with *Sarcocystis cruzi* antiserum but not with *Toxoplasma gondii* or *Neospora caninum* antisera, although tachyzoites of these coccidians appear similar in routine HE-stained sections (these organisms can be differentiated ultrastructurally) [420]. In one dog in which there was concurrent canine distemper infection, *S. canis* schizonts and merozoites stained weakly with Sarcocystis neurona antiserum [422]. Neurological signs may include depression, generalized weakness, recumbency, nystagmus, periodic seizures, and status epilepticus [420,422]. Microscopic lesions in the brain consist of a subacute or chronic granulomatous meningoencephalitis characterized by vasculitis, malacia, neovascularization, perivascular cuffings, and infiltrations of mononuclear cells and neutrophils [420,422]. *S. canis* schizonts and merozoites may be found in the lesions, commonly within neutrophils and histiocytes. The organisms may also be found in other tissues outside of the CNS. A Sarcocystis-associated meningoencephalomyelitis has been reported in a 13-week-old Burmese kitten with clinical signs of depression, lethargy, crying as if in pain, knuckling of one forelimb that progressed to tetraparesis and a left-sided hemiparesis [400]. Microscopic lesions were confined to the CNS, where a severe meningoencephalomyelitis was characterized by perivascular infiltrates composed of mixed mononuclear inflammatory cells, necrosis of the neuropil, and vasculitis. The most severe lesions were found in the cerebral cortex and caudate nucleus, with multifocal areas of inflammation and associated necrosis, edema, and gemistocytic astrocytosis in the underlying subcortical white matter. Lesions throughout the spinal cord and the medulla oblongata consisted of marked perivascular cuffings of lymphocytes, plasma cells, and mononuclear cells in gray and white matter, with mild inflammatory cell infiltrates in the neuropil. Schizonts and merozoites were found in neurons and in unidentified cells in the neuropil of one spinal cord section. In one neuron, merozoites were seen without a parasitophorous vacuole. The protozoa did not react with antisera to *T. gondii* and *N. caninum* but did react weakly to *S. cruzi* antiserum [400]. In a subsequent report, these organisms were found to react positively to *Sarcocystis neurona*-specific antibodies [423]. Muscular sarcocystiasis has been reported as an incidental finding in a 9 year old cat [424].

Encephalitozoonosis - Encephalitozoonosis (nosematosis) is a rare disease caused by the opportunistic, obligate intracellular protozoal parasite *Encephalitozoon cuniculi*. This protozoan disease has been reported from many mammals including man, dogs, cats, foxes and laboratory animals [425,426]. It has been reported in Africa, England and in the USA [427-431]. *E. cuniculi* and the related mammalian microsporidia are emerging as significant opportunistic pathogens of immunocompromised individuals [426]. Molecular studies have identified *E. cuniculi* strain III as the cause of encephalitozoonosis in both humans and dogs [432].

Infection occurs by ingestion or inhalation of spores from contaminated urine or feces that are shed by infected hosts, as well as via the transplacental route [433,434]. The organism is shed in urine of affected animals. The condition is typically reported in young puppies, especially those 4 - 12 weeks of age. Bitches producing puppies with overt encephalitozoonosis can be subclinically infected [435]. Clinical signs of disease in young dogs with encephalitozoonosis vary considerably and range from no signs (especially in older dogs) to severe CNS disturbance, coma, and death [433]. Poor growth, ataxia, tremor, blindness, seizures, aggression, and abnormal vocalization have been reported in dogs. In cats, natural infections are rare, but severe muscle spasms, depression, paralysis, and death have been observed [433]. The clinical signs may be identical to those seen with distemper encephalitis in young dogs. Clinical diagnosis can be suggested by a combination of neurological and renal disease in young dogs. It has been stated that experimentally induced disease is invariably subclinical but the histopathological changes are similar although milder than those found in fatal natural disease [436].

Urinalysis can be an indicator of chronic renal disease [436]. Organisms have been identified in urine sediment [433]. In

chronic stages, affected animals may have palpably enlarged kidneys, renal anemia and mild to severe increases in creatinine and blood urea nitrogen [436,437]. Lymphocytosis and hypergammaglobulinemia may be present early in the disease. Results of CSF analysis from affected animals are frequently unremarkable, although mild protein increase and pleocytosis may be seen in some dogs, along with higher anti-*E. cuniculi* IgG levels in the CSF than in serum [434]. The prevalence of *Encephalitozoon* antibodies in domestic dogs in South Africa has been estimated at 18% in serological studies using the immunofluorescent antibody test [438]. Both humoral and cell-mediated immune responses develop in dogs experimentally infected with *E. cuniculi* [439]. Reciprocal IgG-immunofluorescent antibody titers >40, or an ELISA titer >1:800 are considered diagnostic of active canine encephalitozoonosis [433,434]. In experimental studies, infected dogs developed an antigen-specific blastogenic response to *E. cuniculi* spores, and lymphocyte blastogenic responses to the lectin phytohemagglutinin A were depressed compared to controls [437]. Definitive diagnosis of this rare disease is based on renal biopsy, routine histopathology, culturing, immunoperoxidase techniques, and electron microscopy [440,441]. Vasculitis is considered to be the basic lesion in canine encephalitozoonosis, frequently leading to thrombosis and encephalomalacia [427]. Vasculitis and fibrinoid necrosis of small to medium arteries are present in brain and viscera. A severe necrotizing nonsuppurative to granulomatous meningoencephalitis, multifocal interstitial nephritis, and glomerulonephritis have been seen in affected puppies [429]. Organisms may be found in neurons and endothelial cells, although viable organisms are present only within endothelial cells. Macrophages containing dead spores are usually seen around parasitized vessels and, less frequently, in the neuropil [427]. Focal hepatitis and interstitial pneumonitis may also be observed, especially in dogs [436]. In experimental studies, a large component of the inflammatory infiltrate consisted of plasma cells and lymphocytes, and hyperplasia of B-lymphocyte-dependent regions of lymph nodes and erythrophagocytosis were consistently seen in infected dogs [437]. Encephalitozoonosis has been reported in wild dogs in conjunction with intranuclear inclusion bodies in neurons and lesions resembling canine distemper [442]. Prognosis is poor. At present, there is no treatment [434].

Trypanosomiasis - American trypanosomiasis is caused by *Trypanosmona cruzi* (canine Chagas disease). This disease is infrequently reported in dogs, and usually in those living in the southern United States [443]. There are presently no reports of domestic feline trypanosomiasis from North America [444]. The main vector is the kissing bug (reduviid vector). Infection usually occurs when trypomastigotes are deposited in the insect vector's feces at bite sites. Oral ingestion of infected insects may also be a route of infection in dogs [444]. Transplacental or transmammary infection is also a possibility [445]. Principal sylvan reservoirs in the USA include opossums, raccoons, armadillos, mice, squirrels, and rats [444].
Clinical signs are most commonly seen with the acute form of the disease (especially in dogs less than 1 year of age) and include lymphadenomegaly, sudden collapse and death associated with acute myocarditis in previously normal young dogs. In some dogs, tachyarrhythmia may be present. More chronic signs include ascites and hepatomegaly associated with right-sided heart failure that will eventually lead to chronic myocarditis with cardiac dilatation [444]. Neurological signs may include weakness and ataxia. A well-studied case report of canine trypanosomiasis due to *Trypanosmona cruzi* involved a 13 month old Doberman Pinscher evaluated because of slowly progressive paraparesis and signs of depression [443]. The dog had temporal, supraspinatus and infraspinatus muscle atrophy, bilateral enophthalmos, superficial inguinal lymphadenopathy, tachycardia with pulse deficits, and lesions of active and inactive chorioretinitis. Neurologic abnormalities included hyperreflexic patellar reflexes, lack of conscious proprioception, and depressed hopping reflexes in the forelimbs. Cranial nerve abnormalities included decreased sensation in the left nostril and a delayed gag reflex [443]. Trypanosomiasis has been reported as an incidental finding in an older dog with laryngeal paralysis [446]. Distemper has been seen in acutely affected puppies [445], possibly as a result of immunosuppression [444]. In experimentally-infected dogs, diffuse granulomatous inflammation, degeneration, and necrosis were observed in the heart, a mild multifocal myositis (comprising mononuclear cells) was present in skeletal and smooth muscle, and a nonsuppurative, lymphohistocytic encephalitis was present along with pseudocysts in the cerebral cortex, cerebellum, and brain stem [447].
Diagnosis may be based on demonstration of trypomastigotes in blood smears from dogs with acute disease (organism are rarely found in animals with chronic disease) [444,446]. Serological tests include indirect immunofluorescent antibody, direct hemagglutination, and complement fixation, with titers becoming positive by 3 weeks post infection [444,448]. CSF analysis may suggest nonsuppurative inflammation [447]. Postmortem diagnosis has been made on identification of the amastigote form of the organism in sections of brain, spinal cord, and myocardium [447]. Organisms are not always present in the brain lesions [449]. The lack of granulomatous myositis and amastigotes in muscle of one affected dog suggested a strain variation in the behavior of *T. cruzi* [446]. Treatment of dogs may be effective using the investigational drug nifurtimox (at 2 - 7 mg/kg, PO, qid, for 3 to 5 months) in conjunction with antiinflammatory doses of corticosteroids [444]. Benznidazole may be effective at 5 mg/kg, PO, daily, for 2 months. Prognosis is guarded. The outcome is usually fatal in chronic cases. Oral cythioate (at 3 mg/kg, every other day) given to dogs housed outdoors will help reduce vector numbers in endemic areas [444].

Acanthamebiasis - *Acanthamoeba* is a genus of ubiquitous free-living amebas found in fresh and salt water, soil and sewage

[450]. The pathogenesis of acanthamebiasis is unclear, including routes of infection. Amebic meningoencephalitis was reported in a 4 month old female Akita with signs of lethargy, depression, and seizures [451]. The white blood cell count was 7,500/mm^3 and differential count revealed panleukopenia. Gross findings at necropsy included marked vascularity of the meninges and congestion and hemorrhage in the brain parenchyma. The pathologic diagnosis was acute, hemorrhagic, necrotizing and granulomatous meningoencephalitis associated with numerous amebic trophozoites and cysts. Indirect immunofluorescence tests indicated that the amebae were *Acanthamoeba castellanii*. Immunologic studies suggested that the dog was immunosuppressed or immunodeficient which allowed the amebic meningoencephalitis to develop. An outbreak of acanthamebiasis involving grayhounds from 8 to 13 months of age associated with trophozoite and occasional cyst forms of *Acanthamoeba* has been reported [452]. Neurological signs included incoordination, head tilt, ataxia-dysmetria, and seizures. Brain lesions comprised large areas of necrosis and granulomatous inflammation, along with thrombi, hemorrhage, necrosis, and a mixed inflammatory cell infiltrate in the subarachnoid space. Perivascular inflammatory infiltrates were seen in the neuropil mainly composed of macrophages, with a few neutrophils and plasma cells [452]. Contamination was considered to be from a common environmental source. *Acanthamoeba culbertsoni* was isolated from another outbreak of granulomatous amebic meningoencephalitis in a kennel of grayhounds, several of which were affected by a progressive fatal neurologic and respiratory disease [453]. In grayhounds, leukopenia is due to marked lymphopenia [450]. Antemortem diagnosis of acanthamebiasis in dogs is rare, and at present, there is no established treatment, although trimethoprim-sulfonamide at 30 mg/kg, bid, might be effective [450].

Babesiosis - Babesiosis is caused by species of the protozoan parasite *Babesia*. Dogs may be naturally infected with *B. canis* and *B. gibsoni,* while *B. felis*, *B. cati*, *B. herpailuri*, and *B. pantherae* are the agents that cause feline babesiosis [454,455]. Under natural conditions, all babesias are transmitted by ixodid ticks. *B. gibsoni* is endemic in the southwestern United States and its vector ticks may be *Haemaphysalis bispinosa* and *Rhipicephalus sanguineus*. Several strains of *B. canis* have been identified, including *Babesia canis vogeli*, the strain commonly found in the USA and in tropical and subtropical regions throughout the world that is transmitted by the brown dog tick, *R. sanguineus*; *B. canis canis*, the European and Asian strain transmitted by ticks of the *Dermacentor* genus, and *B. canis rossi*, the highly pathogenic strain transmitted by *Haemaphysalis leachi* that is found in southern Africa [455]. Transplacental transmission may also occur [455]. In the USA, babesiosis occurs most commonly along the Gulf Coast, and in the south, central, and southwestern states.
Babesiosis in dogs tends to be characterized either by hemolytic anemia or by hypotensive shock and/or multiple organ dysfunction [455]. Clinical signs may include sudden coma and death in hyperacute disease; lethargy, anorexia, fever, and hemolytic anemia, icterus, and splenomegaly, and hypotension in acute disease; and intermittent fever, depressed appetite, and marked loss of condition in chronic disease [454,456]. Fever and icterus are rarely observed in cats, in which signs typically include lethargy, anorexia, weakness, rough hair coat, or diarrhea [455,457]. In animals with babesiosis, CNS involvement is rare; however, seizures, weakness, ataxia, cerebellar signs (e.g., head bobbing, incoordination, head tremors, and variable menace deficits), transient blindness, tetraparesis, and sudden death have been reported sporadically in dogs [458-460]. Clinical signs may be mistaken for rabies. Rare, atypical presentations include *Babesia*-associated muscle tenderness, especially along the back and legs, hyperesthesia including masseteric myalgia which causes dogs to scream with pain if their heads are touched or their mouths opened, rhythmic ear movements, and sciatic nerve peripheral neuropathy [461]. Neurological manifestations may result from sludging of parasitized erythrocytes within capillaries of the CNS with subsequent tissue hypoxia [462]. The molecular mediators of multiple organ dysfunction, including cytokines, nitric oxide, and free oxygen radicals may also play a role [463]. Muscle pain and tremors have been observed in 2 dogs with *Babesia*-associated rhabdomyolysis [464], and muscle necrosis and hemorrhage were present at necropsy.
Primary hematological abnormalities in dogs with babesiosis include anemia, thrombocytopenia, and lymphocytosis. In dogs with rhabdomyolysis, caramel-colored urine and markedly elevated serum myoglobin and muscle enzymes were found [464]. Diagnosis of babesiosis is made by demonstrating the presence of *Babesia* organisms within infected erythrocytes or on positive serology (e.g., using the immunofluorescent antibody test, titers >80 on a single sample are considered positive) [454,455]. The drug of choice appears to be diminazine aceturate [455,460,465]; however, this drug, along with phenamidine isethionate, another very effective drug, is presently not approved for use in the USA. Other antibabesial drugs that are available include pentamidine isethionate (at 16.5 mg/kg, IM, daily for 2 days) and imidocarb dipropionate (at 7.5 mg/kg, IM or SC, single injection) [455]. Prognosis is usually favorable in dogs with uncomplicated babesiosis [455] and dogs with neurological signs may respond favorably to treatment [460]. Prevention measures include environmental control of the tick vector, frequent inspection of skin and hair coat for ticks, application of topical ascaricides (e.g., fipronil) and use of tick collars.

Pug Dog Encephalitis
A sporadic, necrotizing meningoencephalitis affecting juvenile, adolescent, and mature Pug dogs of either sex has been reported in the USA, Australasia, Southeast Asia, and Europe [1,466-471]. Dogs range in age from 6 months to 7 years and

many affected dogs are closely related and/or born in the same kennel [467]. Onset of signs is frequently acute. The course of the disease varies from several days to 6 months or more. Common clinical signs include seizures, depression, staring into space, circling, head-pressing, blindness with normal pupillary reflexes, strabismus, cervical rigidity, opisthotonus, and intermittent screaming. Death is often preceded by coma or status epilepticus. In a 2 year old dog, visual hemifield loss (homonymous hemianopia) preceded onset of neurological signs [472]. CSF shows moderate to marked mononuclear (usually lymphocytic) pleocytosis (70 to 600 WBCs/µl) and moderate protein increase (58 to 228 mg/dl). Results of hemograms, blood chemistries, and urinalysis are normal. MRI studies on one affected 3 year old dog revealed dilated cerebral ventricles and inflammatory lesions throughout the cerebral hemispheres [473].

Macroscopically, cerebral gyri may appear flattened and multiple variably sized (e.g., 0.2 - 0.5 cm in diameter) yellow-tan foci may be seen within the cerebral hemispheres involving both white and gray matter [474]. Cortical lesions are typically bilateral, asymmetrical, and often confluent. Subcortical white matter is frequently involved, especially areas in the centrum semiovale and corona radiata where there may be loss of distinction between gray and white matter [1]. In one report, the lesions were most extensive in the ventral cerebrum, especially in the parietal and occipital regions [474]. Lateral ventricular dilatation has been observed in one dog [475]. Microscopically, a non-suppurative meningoencephalitis is seen mainly restricted to the cortical leptomeninges (especially in sulci) and cerebral hemispheres and characterized by perivascular accumulations of lymphocytes, plasma cells, and macrophages, neuronal necrosis, and focal malacia, sometimes with cavitation. Hypertrophy and hyperplasia of endothelial cells may be prominent. Lesions in white matter include edema, glial necrosis, reactive astrogliosis, loss of myelin staining, perivascular cuffing, and axonal degeneration. Perivascular cuffs and radiculitis may be present in trigeminal ganglia. Minimal lesions are seen in brainstem or spinal cord. Myocardial necrosis has been reported in one affected Pug dog [474] while echocardiography and pathological examinations have identified a ventricular septal defect and double-chambered right ventricle in another Pug [476].

The etiology is presently unknown; although alpha type herpesvirus encephalitis has been suggested as a possible cause, based on the extensive necrosis and affinity for the cerebral hemispheres [467]. However, subsequent virus isolation attempts have been negative [1]. In one report, all 3 affected animals were females with clinical histories of pregnancy or pseudopregnancy 2 weeks or less before the onset of the clinical signs [468]. An autoantibody against GFAP (glial fibrillary acid protein)-positive astrocytes and their cytoplasmic projections has recently been identified in CSF and serum of several affected dogs [477]. While the role of this autoantibody for astrocytes remains to be defined, it may prove to be a useful clinical diagnostic marker and a key to the pathogenesis of this disease. Prognosis is poor. Seizures are often refractory to anticonvulsant drugs [475], and corticosteroids are ineffectual.
A similar condition has been reported in Maltese dogs in which the clinical course and pathologic changes are indistinguishable from necrotizing meningoencephalitis of Pug dogs, indicating that this lesion is probably not unique to Pug dogs [478]. In addition, similar histopathological lesions have been recently reported in a 4 year old male Pekingese dog with a history of recurrent seizures and progressive abnormal gait and behavior, which did not respond to treatment [479]. Multifocal non-suppurative necrotizing encephalitis has also been observed in Yorkshire terriers in Switzerland [480]. Clinically, the dogs presented primarily brainstem signs or evidence of cerebral involvement, including seizures. The course of the disease was mostly chronic and progressive. Protozoal, bacterial and mycotic organisms were not found on histopathological examinations. The morphology of the lesions was strongly suggestive of a viral etiology, however, immunocytochemistry and/or *in situ* hybridization failed to provide evidence for canine distemper virus or canine herpesvirus infection. Other known canine encephalitides were excluded on clinical and morphological grounds, although there were certain similarities to Pug dog encephalitis. Similar necrotizing encephalitis has been seen in a 10 year old spayed female Yorkshire terrier in the USA [481].

Pyogranulomatous Meningoencephalomyelitis
Pyogranulomatous meningoencephalomyelitis is an acute, rapidly progressive disease of two to three weeks' duration that (to date) has been recognized only in mature Pointers [80]. The cause of the meningoencephalomyelitis is unknown. Special histological stains for microorganisms, cultures of blood and cerebrospinal fluid (CSF), and studies of animal inoculations have all been negative. Clinical and pathological data suggest a bacterial etiology. Clinical signs include cervical rigidity, kyphosis, nose held close to the ground, reluctance to move, incoordination, head tilt, falling/rolling, spontaneous and positional nystagmus, and seizures. Occasionally atrophy of the cervical muscles, facial paralysis, Horner's syndrome, bradycardia, and vomiting are observed. Pathological findings are found throughout the brain and spinal cord, but are most severe in the upper segments of the cervical spinal cord and in the lower brain stem. These changes are characterized by extensive mononuclear (plasma and lymphocytic cells) and polymorphonuclear inflammatory infiltrations in the leptomeninges and parenchyma. Large perivascular cuffs are seen. In some cases, central necrosis of gray matter and edema are found in segments of the cervical cord along with infiltration of macrophages, monocytes, neutrophils, and plasma cells.

These changes are probably secondary to impaired spinal circulation from the meningeal reaction. An increased population of reticuloendothelial cells is occasionally observed among the perivascular cells. Focal ependymitis may be present along ventricular pathways. Marked, predominantly neutrophilic pleocytosis (500 to 1000 WBCs /µl) and an increased protein concentration (sometimes over 700 mg/dl) are found on CSF examination. In this small series of cases so far observed, prognosis has been poor. Temporary remission of signs has resulted following antibiotic therapy.

Rabies

All warm-blooded mammals are susceptible to rabies encephalitis and there is considerable interspecies susceptibility. Rabies is the most important zoonotic infection. Wildlife are the chief natural reservoir of rabies [482,483]. In most northern countries such as Continental Europe, Canada, Greenland, and the former Soviet Union, foxes are the main vectors and also reservoirs [484,485]. In other parts of the world, wolves (Iran); mongooses (the Caribbean); skunks and raccoons (USA); and bats (Latin America) play important roles in transmitting rabies [486]. The dog remains an important vector for transmitting rabies to humans in developing countries [487]. In the USA, dogs play a relatively small part in current epizootics. Vaccination of dogs helped to bring down cases of canine rabies in the USA from 5000 cases in 1946 to 338 cases in 1987, thus eliminating the major route of rabies transmission to people. Presently, rabid cats account for a greater proportion of human rabies post-exposure prophylaxis than do rabid dogs [488]. A recent report indicated that bat-associated rabies virus variants were not a common cause of rabies in dogs and cats in the USA [489]. In contrast, bats have been implicated in most recent cases of human rabies in the USA [490].

Rabies is caused by a rhabdovirus (genus *Lyssavirus*) that is destroyed by lipid solvents and low pH [491]. Transmission most often occurs through bite wounds from infected animals that are secreting virus in their saliva. Infection may also occur by wound/abrasion contamination from infected saliva or other infected material, or by airborne transmission (e.g., in bat caves where the density of virus particles is high) and infection through mucous membranes.

The incubation period is variable, depending on the amount of virus transmitted, site of inoculation (e.g., bites closer to the head have shorter incubation periods than those at the periphery), viral strain, immune status, and nature of the wound. In naturally occurring cases of rabies, incubation periods may range between 3 weeks to 6 months in dogs, 2 to 6 weeks in cats, and 3 weeks to 12 months in people before CNS signs are seen [492]. After an early replicative phase in striated muscle [493,494], rabies virus is highly neurotropic and reaches the CNS via passive centripetal movement in the axoplasmic compartment of motor and sensory peripheral nerves. Following the entry of the virus into CNS, usually spinal cord, its ascending course to the brain is rapid (possibly via CSF pathways). The virus has a significantly higher tropism for neurons than for glia [495]. The virus may also pass from neuron to neuron via synapses [1]. Once the CNS has become infected, virus spreads centrifugally via peripheral nerves (sensory, motor, and autonomic) to other organs, including the eyes, salivary glands, and skin. Salivary gland mucous epithelium is the major source of virus shed into secretions in species that maintain rabies in nature. These include the dog, fox, skunk, raccoon, and bat [496]. Presently, in cases of suspected rabies, a holding period of 10 days is recommended. However, results of experimental studies indicate that dogs can excrete rabies virus in the saliva up to 13 days before clinical signs are exhibited [497]. Thus, a longer observation period (e.g., 3 weeks) seems more appropriate.

Initial clinical signs tend to be nonspecific and include apprehension, restlessness, anorexia, and vomiting. A change in temperament may be noted at this stage and excessive salivation may occur. These signs, which may be present for 2 to 5 days, are followed either by the dumb or the furious form of the disease. Approximately 25 - 30% of affected animals exhibit the furious form, which is characterized by increased restlessness, wandering, viciousness (attacks on animals, people, or inanimate objects), howling, polypnea, drooling of saliva, and sometimes convulsions [498]. Furious rabies is associated with infection of limbic system neurons [499]. Death usually occurs between four and eight days after the onset of clinical signs. It is usually the furious form of rabies that occurs in cats. The dumb or paralytic form of rabies encephalomyelitis is more common in dogs and is characterized by progressive ascending spinal paresis or paralysis, paralysis of the lower jaw, pharyngeal and hypoglossal paralysis (resulting in difficulty in eating and drinking, and drooling of saliva), and facial paralysis. Biting is uncommon with this form of rabies. In dogs, a noticeable change in the character of the bark occurs as a result of laryngeal paralysis. Death from respiratory failure occurs between 3 and 6 days after the onset of clinical signs. A moderate mononuclear pleocytosis (40 - 60 WBCs/µl) and slight protein elevation (50 - 70 mg/dl) may be found on CSF analysis in dogs and cats.

Pathologically, rabies is characterized by a multifocal, mild, polioencephalomyelitis and craniospinal ganglionitis with mononuclear perivascular infiltrates, diffuse glial proliferation, regressive changes in neuronal cells, and glial nodules [1]. There is no apparent correlation between the severity of changes and the clinical signs observed. In people and animals, rabies virus is usually extremely widespread in the brain. There is a predilection for the brain stem, especially the substantia nigra, red nucleus, and periaqueductal gray matter of the midbrain; the pontine nuclei; the reticular formation; the floor of the

fourth ventricle; and the hypothalamus. Other areas commonly affected include the gray matter of the spinal cord, hippocampus, globus pallidus, and thalamic nuclei. Intracytoplasmic Negri bodies (viral antigen aggregates) are usually most numerous in hippocampal neurons and Purkinje cells. Many cells with inclusions remain morphologically normal. The frequency of Negri bodies is often inversely proportional to the severity of inflammation [1]. Not all rabid animals have inclusions, including animals killed early in the course of the disease [1]. The inclusions need to be differentiated from the pseudo-inclusions seen in neurons of the lateral geniculate nucleus and hippocampal pyramidal cells of cats [500] and neuronal cytoplasmic lamellar bodies seen in nonrabid dogs (especially in thalamic and cerebellar Purkinje neurons) [501,502]. The lamellar bodies are stacks of parallel cisternae derived from endoplasmic reticulum [502] and can be differentiated from Negri bodies using immunoperoxidase staining and/or fluorescent antibody staining techniques [501]. Ultrastructurally, rabies virus particles are characteristically bullet-shaped and embedded in an amorphous matrix [487].

It should be noted that clinical signs associated with rabies in dogs are often so variable that a distinction between the furious and dumb forms may be unjustified [503]. As a result, the diagnosis of rabies must be based on laboratory confirmation-histopathological examinations of brain sections/smears for presence of an acute meningoencephalitis and identification of Negri bodies; direct immunofluorescent antibody test on tactile facial hair follicles obtained by skin biopsy or on fresh or frozen brain samples, and mouse inoculation. Mouse inoculation has the disadvantage of a 3-week observation period to establish a negative diagnosis. The rabies immunofluorescent antibody test is widely used, for it is an extremely accurate and rapid technique. Also, a focus-forming inhibition assay to detect rabies antibodies in serum is available. Rabies viral antigen can be shown immunocytochemically as well as through use of the fluorescent antibody test in formalin-fixed, paraffin-embedded tissue [1,504]. Antigenic differences between rabies strains have been documented using monoclonal antibody studies [505,506]. A rapid diagnostic technique based on amplification of nucleic-acid sequences to detect rabies-specific RNA in the saliva and CSF has been reported in human patients with rabies [507]. In addition, single-tube, non-interrupted reverse transcription-polymerase chain reaction for the detection of rabies virus in brain tissue has been recently published [508].

There is no treatment. Animals exposed to rabies that have not been immunized should be euthanized. If the animal is current on rabies vaccination and exposed (and the owners do not want euthanasia), the animal should be revaccinated and closely confined under observation for at least 3 months. Administration of a potent vaccine, as a booster after exposure in previously immunized animals, results in rapid amplification of the antibody titer.
Note that **post-vaccinal rabies** occurs occasionally in dogs and cats [509,510], especially if vaccination is done at a time of stress, e.g., surgery. It has been reported that monoclonal antibodies can be used to confirm vaccine-induced rabies in dogs and cats [511]. There have been a few reports of animals recovering after street virus and vaccine virus-induced rabies [487,509,512]. These findings place an increased responsibility on the veterinarian in managing animals with encephalomyelitis.

Rickettsial Meningoencephalitis
Rickettsial diseases such as Rocky Mountain spotted fever (RMSF) caused by *Rickettsia rickettsii*, and canine ehrlichiosis caused by *Ehrlichia canis* (canine monocytic ehrlichiosis) sporadically involve the CNS of dogs, where they produce a meningoencephalitis [513-515]. Several other granulocytic ehrlichial species, in which the morula inclusions are primarily in neutrophils, such as human granulocytic ehrlichiosis (HGE), *E. equi* (equine granulocytic ehrlichiosis), and *E. ewingii*, may also cause CNS signs in dogs [515,516]. In contrast, a recent experimental study in which dogs infected with either *E. canis*, *E. ewingii*, *E. chaffeensis*, or HGE, indicated that ocular (uveitis) and brain lesions (meningitis) were observed only in dogs infected with *E. canis* [517]. Ehrlichiosis and RMSF are tick-borne disorders. *Dermacentor andersoni* and *Dermacentor variabilis* are the primary vectors for RMSF in North America. The arthropod vector and primary reservoir for *E. canis* is the brown dog tick, *Rhipicephalus sanguineus*. Canine RMSF occurs mainly in the spring and summer. In both diseases, vasculitis and perivascular inflammatory cell infiltrates may be observed in most body tissues. CNS lesions are characterized by a lymphoplasmacytic meningoencephalitis involving the meninges, cerebral cortex and brainstem. Both diseases are characterized by fever, depression, and lymphadenopathy. Edema may be seen on the lips, penile sheath, ears, and limbs. Neurological signs occur in about one third of dogs with either RMSF or ehrlichiosis and include seizures, depression, paraparesis or tetraparesis, vestibular dysfunction, generalized or localized hyperesthesia, cranial nerve deficits, intention tremors of the head, and coma [514,518,519]. Fundic lesions, including retinal hemorrhage, chorioretinal exudate, or retinal detachment can occur with either disease [520]. Hyporeflexia, tetraparesis, and muscle wasting associated with lymphoplasmacytic polymyositis were seen in 2 dogs seropositive for *E. canis* [521]. Analysis of cerebrospinal fluid (CSF) from dogs with either disease may reveal slight to moderate elevations in protein content (e.g., 40 to 160 mg/dl) and variable, predominantly mononuclear pleocytosis (10 to 130 WBCs/μl). Thrombocytopenia occurs with both diseases, often accompanied by anemia, hypoalbuminemia, leukopenia early in the disease followed by leukocytosis, and hyperproteinemia.

Coagulation abnormalities may be present [522]. Intracytoplasmic ehrlichial morulae may be observed in blood leukocytes, especially monocytes, and in CSF mononuclear cells. A four-fold rise in antibody titer to *R. rickettsii*, or a single *R. rickettsii* antibody titer of 1:1,024 or greater (when this initial titer is determined one week or more after the onset of clinical signs), or positive direct fluorescence for *R. rickettsii* in skin biopsy specimens will confirm a diagnosis of RMSF [523]. The latter technique can confirm the diagnosis as early as the 3rd or 4th day of disease on a single sample [524]. Recently, elevated platelet-associated immunoglobulin titers have been reported in dogs with RMSF [525]. A single positive serum titer, using the indirect FA test for *E. canis* is considered indicative of infection, since animals become seronegative within 3 to 9 months after effective treatment. Most laboratories measure IgG and a titer $\geq$ 20 is generally considered to be evidence of infection and/or exposure [515]. Note that there is some antigenic cross-reactivity between ehrlichial species [515].

The treatment of choice for both diseases used to be tetracycline, using a dosage of 22 - 30 mg/kg, PO, tid; although the newer semisynthetic, lipid-soluble tetracyclines, doxycycline (at 10 - 20 mg/kg, PO bid) and minocycline (at 3 mg/kg, PO, bid) are used more frequently now [515]. Chloramphenicol may also be used at 15 - 30 mg/kg, PO, tid. Traditionally, animals are treated for 14 to 21 days. Chloramphenicol is recommended for use in puppies less than 6 months of age to avoid tetracycline-induced discoloration of permanent dentition. Antibiotics are only effective in reducing the severity of infection if given early in the course of the disease [515,524]. While dogs without neurological disease can show a dramatic response to treatment, generally within 24 to 48 hours [526], the prognosis is guarded for those animals with neurological signs. Recovery may be prolonged with residual neurological deficits from irreversible brain damage. It has been reported that dogs with RMSF have a more rapid and consistent recovery than dogs with ehrlichiosis in the absence of neurologic deficits and when treated with tetracycline [514].
Prevention measures include environmental control of the tick vector, frequent inspection of skin and hair coat for ticks, application of topical ascaricides (e.g., fipronil) and use of tick collars [524]. Tetracycline at 6.6 mg/kg PO, daily, is an effective prophylactic drug against initial infection or reinfection with *E. canis* [515]. Note that RMSF is an important zoonotic disease [524]. It now seems that dogs and cats can be naturally infected with the granulocytic strains *E. equi* or *E. phagocytophilia* which may cause HGE in people, although the role, if any, of domestic animals in the human disease is yet to be determined [515,527]. Ehrlichiosis has been reported in cats [515] but the species have yet to be identified and, to the author's knowledge, signs of CNS disease have not been described.

Salmon Poisoning
Salmon poisoning, caused by *Neorickettsia heminthoeca*, is a lethal rickettsial disease of dogs on the Pacific West Coast. Infection is acquired by eating salmonoid fish, certain species of nonsalmanoid fish, or the Pacific giant salamander that contain metacercaria of the fluke *Nanophyetus samincola*, which harbors the rickettsiae throughout its life cycle stages from egg to adult. Snails and then fish serve as intermediate hosts for the flukes [528]. The infection in dogs results in a subclinical diffuse mononuclear leptomeningitis [1].

Shaker Dog Disease
This condition has been observed in the United States and Australia involving young, mature dogs of either sex. It has been noted particularly in Maltese and West Highland White Terriers, although the condition has also been seen sporadically in Bichon Frise, Spitz, Samoyed, Beagle, Dachshund, and Yorkshire Terrier dogs [536-539]. In a recent report of 24 dogs with generalized tremors (2 of which were associated with mycotoxin ingestion), most were young adults between 1 and 5 years old, more than half of the dogs were nonwhite mixed-breeds, and all weighed <15 kg [540]. Synonyms for this disease include idiopathic tremors of adult dogs, sporadic acquired tremors of adult dogs, and "little white shakers" since many dogs are white. The underlying pathogenesis remains unclear; however, an acquired autoimmune disorder affecting neurotransmitter synthesis (dopamine, epinephrine, and norepinephrine) has been hypothesized [536].

The tremors appear to be intentional and worsen with exercise, stress and excitement, and disappear with sleep. Signs may occur sporadically, progress over 1 to 3 days, and remain static. Occasional dogs have a history of spontaneous clinical improvement [538]. Tremors typically involve all four limbs and the head. The eyes may also be affected. Neurological examination is usually normal; however, absent menace response, nystagmus or dysconjugate eye movements, ataxia, head tilt, tetraparesis, and paraparesis were variably noted in a report of generalized tremors involving 7 Maltese dogs [539]. Mild to moderate hypermetria and body swaying may also be present. Rarely, seizures are seen. Results of hematological and serum biochemical testing and urinalysis are usually within normal limits, although peripheral eosinophilia was found in 3 dogs in one report [539]. CSF analysis often reveals a mild to moderate lymphocytic pleocytosis, usually with normal or mildly elevated protein levels. MRI scans have demonstrated symmetrical ventricular enlargement in some dogs [539]. In this report, abnormal electroencephalographic traces were characterized by either generalized low-frequency (6 to 9 Hz) high-amplitude (25 to 100 μV) activity or low-frequency (7 to 9 Hz) normal amplitude (10 to 25 μV) activity. Brainstem auditory

evoked response testing showed mildly increased I to V or I to Vn waveform latencies [539]. Histopathologically, a very mild diffuse, nonsuppurative encephalomyelitis, with perivascular cuffing by lymphoplasmacytic mononuclear cells, have been observed [541]. CNS myelin is normal.

Affected animals are usually responsive to immunosuppressive doses of corticosteroids (e.g., prednisolone at 2 to 4 mg/kg, PO, bid, until clinical remission, followed by the lowest dose that controls the clinical signs [539]. Duration of prednisolone treatment may range from 4 weeks to several months. In one report of steroid-responsive tremor syndrome in 22 dogs, 80% of the dogs responded to immunosuppressive treatment within 3 days [540]. For refractory cases, Parker reported using prednisolone in conjunction with benzodiazepines for maximal therapeutic effect - oral prednisolone (at 1 to 2 mg/kg once a day for 4 weeks; 0.5 to 1 mg/kg once a day for 2 weeks; 0.5 to 1 mg/kg every other day for 2 weeks; and 0.5 to 1 mg/kg every third day for 4 weeks) and oral diazepam (at 0.5 to 1 mg/kg repeated three times a day for 4 weeks; 0.5 to 1 mg/kg repeated twice a day for 4 weeks; and 0.5 to 1 mg/kg once a day for 4 weeks) [538]. Propranolol alone, at 1 mg/kg, PO, tid, improved signs in one dog but was ineffective in another [539]. Prognosis is usually favorable with tremors decreasing in most dogs by the end of the first week of therapy. Some dogs relapse at the end of the treatment, requiring continued medication. Occasionally, relapses may occur after several months or years. Relapses have been reported in some instances within a month of routine vaccination [538]. Anticonvulsant therapy is ineffective in controlling the tremors.

References

1. Summers B, Cummings J, de Lahunta A. Veterinary Neuropathology. St Louis: Mosby, 1995; 95-188.
2. Rhoades H, Reynolds H, Rahn D, et al. Nocardiosis in a dog with multiple lesions of the central nervous system. J Am Vet Med Assoc 1963; 142:278-281.
3. Palmer AC. Pathological changes in the brain associated with fits in dogs. Vet Rec 1972; 90:167-173.
4. Stowater J, Codner E, McCoy J. Actinomycosis in the spinal canal of a cat. Feline Pract 1978; 8:26-27.
5. Bestetti G, Buhlmann V, Nicolet J, et al. Paraplegia due to actinomyces viscosus infection in the cat. Acta Neuropathol (Berl) 1977; 39:231-235.
6. Heavner JE, Pierce M. Brain abscess in a dog. Vet Med Small Anim Clin 1976; 71:785-790, 793.
7. McCandlish IAP, Ormerod EJ. Brain abscess associated with a penetrating foreign body. Vet Rec 1978; 102:380-381.
8. Dow SW, LeCouteur RA, Henik RA, et al. Central nervous system infection associated with anaerobic bacteria in two dogs and two cats. J Vet Intern Med 1988; 2:171-176.
9. Dillehay DL, Ribas JL, Newton JC Jr., et al. Cerebral phaeohyphomycosis in two dogs and a cat. Vet Pathol 1987; 24:192-194.
10. Ndikuwera J, Knottenbelt DC, Lawrence J, et al. Spinal abscess in a dog. Vet Rec 1987; 120:554-555.
11. Dewey CW, Kortz GD, Bailey CS. Spinal epidural empyema in two dogs. J Am Anim Hosp Assoc 1998; 34:305-308.
12. Kraus KH, Butler LM, Pope ER. Paraparesis caused by epidural granuloma in a cat. J Am Vet Med Assoc 1989; 194:789-790.
13. Kaplan K. Brain abscess. Med Clin North Am 1985; 69:345-360.
14. Greene C. Infections of the central nervous sytem In: Greene CE, ed. Clinical microbiology and infectious diseases of the dog and cat. Philadelphia: WB Saunders, 1984; 284-297.
15. Edwards DF. Actinomycosis and nocardiosis In: Greene CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 303-313.
16. Britt RH, Enzmann DR, Yeager AS. Neuropathological and computerized tomographic findings in experimental brain abscess. J Neurosurg 1981; 55:590-603.
17. Obana WG, Britt RH, Placone RC, et al. Experimental brain abscess development in the chronically immunosuppressed host. Computerized tomographic and neuropathological correlations. J Neurosurg 1986; 65:382-391.
18. Enzmann DR, Britt RR, Obana WG, et al. Experimental Staphylococcus aureus brain abscess. AJNR Am J Neuroradiol 1986; 7:395-402.
19. Allen P, Speakman T. Brain abscess: an evaluation of current treatment. Can Med Assoc J 1962; 86:852-854.
20. Britt RH, Enzmann DR, Placone RC Jr., et al. Experimental anaerobic brain abscess. Computerized tomographic and neuropathological correlations. J Neurosurg 1984; 60:1148-1159.
21. Runge VM, Wells JW, Kirsch JE. Magnetization transfer and high-dose contrast in early brain infection on magnetic resonance. Invest Radiol 1995; 30:135-143.
22. Runge VM, Wells JW, Williams NM, et al. The use of gadolinium-BOPTA on magnetic resonance imaging in brain infection. Invest Radiol 1996; 31:294-299.
23. Klopp LS, Hathcock JT, Sorjonen DC. Magnetic resonance imaging features of brain stem abscessation in two cats. Vet Radiol Ultrasound 2000; 41:300-307.
24. Edwards DF, Nyland TG, Weigel JP. Thoracic, abdominal, and vertebral actinomycosis. Diagnosis and long- term

therapy in three dogs. J Vet Intern Med 1988; 2:184-191.
25. Dow SW. Management of anaerobic infections. Vet Clin North Am Small Anim Pract 1988; 18:1167-1182.
26. Fenner WR. Central nervous system infections In: Greene, CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 647-657.
27. McCracken RM, McFerran JB, Dow C. The neural spread of pseudorabies virus in calves. J Gen Virol 1973; 20:17-28.
28. Hagemoser WA, Kluge JP, Hill HT. Studies on the pathogenesis of pseudorabies in domestic cats following oral inoculation. Can J Comp Med 1980; 44:192-202.
29. Card JP, Rinaman L, Schwaber JS, et al. Neurotropic properties of pseudorabies virus: uptake and transneuronal passage in the rat central nervous system. J Neurosci 1990; 10:1974-1994.
30. Chien CH, Shieh JY, Liao MH, et al. Neuronal connections between the auricular skin and the sympathetic pre- and postganglionic neurons of the dog as studied by using pseudorabies virus. Neurosci Res 1998; 30:169-175.
31. Monroe WE. Clinical signs associated with pseudorabies in dogs. J Am Vet Med Assoc 1989; 195:599-602.
32. Murdoch RS. Aujeszky's disease in foxhounds. Vet Rec 1990; 126:226.
33. Hawkins B, Olson GR. Clinical signs of pseudorabies in the dog and cat: a review of 40 cases. Iowa State Univ Vet 1985; 47:116-119.
34. Fankhauser R, Fatzer R, Steck F, et al. Aujeszky's disease in dog and cat in Switzerland. Schweiz Arch Tierheilkd 1975; 117:623-629.
35. Dow C, McFerran JB. Aujeszky's disease in the dog and cat. Vet Rec 1963; 75:1099-1102.
36. Gore R, Osborne AD, Darke PG, et al. Aujeszky's disease in a pack of hounds. Vet Rec 1977; 101:93-95.
37. Olson GR, Miller LD. Studies on the pathogenesis of heart lesions in dogs infected with pseudorabies virus. Can J Vet Res 1986; 50:245-250.
38. Quiroga MI, Nieto JM, Sur J, et al. Diagnosis of Aujeszky's disease virus infection in dogs by use of immunohistochemistry and in-situ hybridization. Zentralbl Veterinarmed A 1998; 45:75-81.
39. Carmichael L, Squire R, Krook L. Clinical and pathological features of a fatal virus disease of new-born pups. Am J Vet Res 1965; 26:803-814.
40. Percy DH, Olander HJ, Carmichael LE. Encephalitis in the newborn pup due to a canine herpesvirus. Pathol Vet 1968; 5:135-145.
41. Percy DH, Munnel JF, Olander HJ, et al. Pathogenesis of canine herpesvirus encephalitis. Am J Vet Res 1970; 31:145-156.
42. Seo IB, Lim CH. Study on the pathogenesis of canine herpesvirus infection 1. Histopathological and electron microscopical observation. [Chinese]. Korean J Vet Res 1994; 34:569-581.
43. Carmichael LE, Barnes FD, Percy DH. Temperature as a factor in resistance of young puppies to canine herpesvirus. J Infect Dis 1969; 120:669-678.
44. Wright N, Cornwell H. The susceptibility of 6-week-old puppies to canine herpes virus. J Small Anim Pract 1970; 10:669-674.
45. Okuda Y, Ishida K, Hashimoto A, et al. Virus reactivation in bitches with a medical history of herpesvirus infection. Am J Vet Res 1993; 54:551-554.
46. Okuda Y, Hashimoto A, Yamaguchi T, et al. Repeated canine herpesvirus (CHV) reactivation in dogs by an immunosuppressive drug. Cornell Vet 1993; 83:291-302.
47. Love DN, Huxtable CRR. Naturally-occurring neonatal canine herpesvirus infection. Vet Rec 1976; 99:501-503.
48. Percy DH, Carmichael LE, Albert DM, et al. Lesions in puppies surviving infection with canine herpesvirus. Vet Pathol 1971; 8:37-53.
49. Imagaw D, Goret P, Adams J. Immunological relationships of measles distemper and rinderpest viruses. Proc Natl Acad Sci USA 1959; 46:1119-1123.
50. Cook SD, Natelson BH, Levin BE, et al. Further evidence of a possible association between house dogs and multiple sclerosis. Ann Neurol 1978; 3:141-143.
51. Appel MJ, Glickman LT, Raine CS, et al. Canine viruses and multiple sclerosis. Neurology 1981; 31:944-949.
52. Kurtzke JF, Priester WA. Dogs, distemper, and multiple sclerosis in the United States. Acta Neurol Scand 1979; 60:312-319.
53. Kurtzke JF, Hyllested K, Arbuckle JD, et al. Multiple sclerosis in the Faroe Islands. IV. The lack of a relationship between canine distemper and the epidemics of MS. Acta Neurol Scand 1988; 78:484-500.
54. Krakowka S, Hoover EA, Koestner A, et al. Experimental and naturally occurring transplacental transmission of canine distemper virus. Am J Vet Res 1977; 38:919-922.
55. Greene C, Appel M. Canine Distemper. In: Greene C, ed. Infectious Diseases of the Dog and Cat. Philadelphia: WB Saunders Co, 1990; 226-241.
56. Summers BA, Greisen HA, Appel MJ. Canine distemper encephalomyelitis: variation with virus strain. J Comp Pathol

1984; 94:65-75.
57. Krakowka S, Ringler SS, Lewis M, et al. Immunosuppression by canine distemper virus: modulation of in vitro immunoglobulin synthesis, interleukin release and prostaglandin E2 production. Vet Immunol Immunopathol 1987; 15:181-201.
58. Krakowka S, Cork LC, Winkelstein JA, et al. Establishment of central nervous system infection by canine distemper virus: breach of the blood-brain barrier and facilitation by antiviral antibody. Vet Immunol Immunopathol 1987; 17:471-482.
59. Axthelm MK, Krakowka S. Canine distemper virus: the early blood-brain barrier lesion. Acta Neuropathol 1987; 75:27-33.
60. Summers BA, Greisen HA, Appel MJ. Possible initiation of viral encephalomyelitis in dogs by migrating lymphocytes infected with distemper virus. Lancet 1978; 2:187-189.
61. Vandevelde M, Zurbriggen A, Higgins RJ, et al. Spread and distribution of viral antigen in nervous canine distemper. Acta Neuropathol 1985; 67:211-218.
62. Appel M, Gillespie J. Canine distemper virus. Virol Monogr 1972; 11:1-96.
63. Mutinelli F, Vandevelde M, Griot C, et al. Astrocytic infection in canine distemper virus-induced demyelination. Acta Neuropathol 1989; 77:333-335.
64. Summers BA, Greisen HA, Appel MJ. Early events in canine distemper demyelinating encephalomyelitis. Acta Neuropathol (Berl) 1979; 46:1-10.
65. Tipold A, Moore P, Zurbriggen A, et al. Early T cell response in the central nervous system in canine distemper virus infection. Acta Neuropathol (Berl) 1999; 97:45-56.
66. Graber HU, Muller CF, Vandevelde M, et al. Restricted infection with canine distemper virus leads to down- regulation of myelin gene transcription in cultured oligodendrocytes. Acta Neuropathol 1995; 90:312-318.
67. Zurbriggen A, Schmid I, Graber HU, et al. Oligodendroglial pathology in canine distemper. Acta Neuropathol (Berl) 1998; 95:71-77.
68. Bollo E, Zurbriggen A, Vandevelde M, et al. Canine distemper virus clearance in chronic inflammatory demyelination. Acta Neuropathol 1986; 72:69-73.
69. Higgins RJ, Krakowka SG, Metzler AE, et al. Primary demyelination in experimental canine distemper virus induced encephalomyelitis in gnotobiotic dogs. Sequential immunologic and morphologic findings. Acta Neuropathol 1982; 58:1-8.
70. Vandevelde M, Zurbriggen A, Dumas M, et al. Canine distemper virus does not infect oligodendrocytes in vitro. J Neurol Sci 1985; 69:133-137.
71. Schobesberger M, Zurbriggen A, Vandevelde M, et al. CNP-expressing oligodendrocytes are still present in demyelinating distemper lesions. In: Proceedings of the 14th Annu Symp, ESVN 2000; 36-37.
72. Wunschmann A, Alldinger S, Kremmer E, et al. Identification of CD4+ and CD8+ T cell subsets and B cells in the brain of dogs with spontaneous acute, subacute-, and chronic-demyelinating distemper encephalitis. Vet Immunol Immunopathol 1999; 67:101-116.
73. Griot C, Burge T, Vandevelde M, et al. Antibody-induced generation of reactive oxygen radicals by brain macrophages in canine distemper encephalitis: a mechanism for bystander demyelination. Acta Neuropathol 1989; 78:396-403.
74. Kimoto T. In vitro and in vivo properties of the virus causing natural canine distemper encephalitis. J Gen Virol 1986; 67:487-503.
75. Johnson GC, Fenner WR, Krakowka S. Production of immunoglobulin G and increased antiviral antibody in cerebrospinal fluid of dogs with delayed-onset canine distemper viral encephalitis. J Neuroimmunol 1988; 17:237-251.
76. Vandevelde M, Zurbriggen A, Steck A, et al. Studies on the intrathecal humoral immune response in canine distemper encephalitis. J Neuroimmunol 1986; 11:41-51.
77. Thomas W, Sorjonen DC, Steiss J. A retrospective evaluation of 38 cases of canine distemper encephalomyelitis. J Am Anim Hosp Assoc 1993; 29:129-133.
78. Nesseler A, Baumgartner W, Zurbriggen A, et al. Restricted virus protein translation in canine distemper virus inclusion body polioencephalitis. Vet Microbiol 1999; 69:23-28.
79. Tsai SC, Summers BA, Appel MJ. Interferon in cerebrospinal fluid. A marker for viral persistence of canine distemper encephalomyelitis. Arch Virol 1982; 72:257-265.
80. Braund KG. Encephalitis and meningitis. Vet Clin North Am Small Anim Pract 1980; 10:31-56.
81. Vandevelde M, Kristensen B, Braund KG, et al. Chronic canine distemper virus encephalitis in mature dogs. Vet Pathol 1980; 17:17-28.
82. Higgins RJ, Child G, Vandevelde M. Chronic relapsing demyelinating encephalomyelitis associated with persistent spontaneous canine distemper virus infection. Acta Neuropathol 1989; 77:441-444.
83. Tipold A, Vandevelde M, Jaggy A. Neurological manifestations of canine distemper virus infection. J Small Anim Pract 1992; 33:466-470.
84. McGovern V, Steel J, Wyke B, et al. Canine encephalitis causing a syndrome characterized by tremor. Aust J Exp Biol

Med Sci 1950; 28:433-447.
85. Myers LJ, Hanrahan LA, Swango LJ, et al. Anosmia associated with canine distemper. Am J Vet Res 1988; 49:1295-1297.
86. Simpson ST, Myers LJ. Dysosmia caused by encephalitis in a dog. J Am Vet Med Assoc 1987; 191:1593.
87. Turnwald GH, Barta O, Taylor HW, et al. Cryptosporidiosis associated with immunosuppression attributable to distemper in a pup. J Am Vet Med Assoc 1988; 192:79-81.
88. Bell SC, Carter SD, Bennett D. Canine distemper viral antigens and antibodies in dogs with rheumatoid arthritis. Res Vet Sci 1991; 50:64-68.
89. May C, Carter SD, Bell SC, et al. Immune responses to canine distemper virus in joint diseases of dogs. Br J Rheumatol 1994; 33:27-31.
90. Braund KG, Crawley RR, Speakmen C. Hippocampal necrosis associated with canine distemper virus infection. Vet Rec 1981; 109:122-123.
91. Summers BA, Greisen HA, Appel MJ. Does virus persist in the uvea in multiple sclerosis, as in canine distemper encephalomyelitis? Lancet 1983; 2:372-375.
92. Braund KG, Vandevelde M. Polioencephalomalacia in the dog. Vet Pathol 1979; 16:661-672.
93. Hartley WJ. Polioencephalomalacia in dogs. Acta Neuropathol (Berl) 1963; 2:271-281.
94. Lisiak JA, Vandevelde M. Polioencephalomalacia associated with canine distemper virus infection. Vet Pathol 1979; 16:650-660.
95. Guilford WG, Shaw DP, O'Brien DP, et al. Fecal incontinence, urinary incontinence, and priapism associated with multifocal distemper encephalomyelitis in a dog. J Am Vet Med Assoc 1990; 197:90-92.
96. Cordy D. Canine encephalomyelitis. Cornell Vet 1942; 32:11-28.
97. Koestner A, McCullough B, Krakowka G, et al. Canine distemper: a virus-induced demyelinating encephalomyelitis. In: Zeman W and Lenette E, eds. Slow Virus Diseases. Baltimore: Williams and Wilkins, 1974; 86-101.
98. Imagawa DT, Howard EB, Van Pelt LF, et al. Isolation of canine distemper virus from dogs with chronic neurological diseases. Proc Soc Exp Biol Med 1980; 164:355-362.
99. Koestner A. Animal model of human disease: subacute sclerosing panencephalitis, multiple sclerosis; animal model: distemper-associated demyelinating encephalomyelitis. Am J Pathol 1975; 78:361-364.
100. Adams JM, Brown WJ, Snow HD, et al. Old dog encephalitis and demyelinating diseases in man. Vet Pathol 1975; 12:220-226.
101. Hall WW, Imagawa DT, Choppin PW. Immunological evidence for the synthesis of all canine distemper virus polypeptides in chronic neurological diseases in dogs. Chronic distemper and old dog encephalitis differ from SSPE in man. Virology 1979; 98:283-287.
102. Axthelm MK, Krakowka S. Experimental old dog encephalitis (ODE) in a gnotobiotic dog. Vet Pathol 1998; 35:527-534.
103. Appel MJ. Pathogenesis of canine distemper. Am J Vet Res 1969; 30:1167-1182.
104. Kristensen B, Vandevelde M. Immunofluorescence studies of canine distemper encephalitis on paraffin- embedded tissue. Am J Vet Res 1978; 39:1017-1021.
105. Vandevelde M, Kristensen B. Observations on the distribution of canine distemper virus in the central nervous system of dogs with demyelinating encephalitis. Acta Neuropathol (Berl) 1977; 40:233-236.
106. Baumgartner W, Orvell C, Reinacher M. Naturally occurring canine distemper virus encephalitis: distribution and expression of viral polypeptides in nervous tissues. Acta Neuropathol 1989; 78:504-512.
107. Palmer DG, Huxtable CR, Thomas JB. Immunohistochemical demonstration of canine distemper virus antigen as an aid in the diagnosis of canine distemper encephalomyelitis. Res Vet Sci 1990; 49:177-181.
108. Fischer CA. Retinal and retinochoroidal lesions in early neuropathic canine distemper. J Am Vet Med Assoc 1971; 158:740-752.
109. Cutler RW, Averill DR Jr. Cerebrospinal fluid gamma globulins in canine distemper encephalitis. An immunoelectrophoretic study. Neurology 1969; 19:1111-1114.
110. Alleman AR, Christopher MM, Steiner DA, et al. Identification of intracytoplasmic inclusion bodies in mononuclear cells from the cerebrospinal fluid of a dog with canine distemper. Vet Pathol 1992; 29:84-85.
111. Long JF, Jacoby RO, Olson M, et al. Beta-glucuronidase activity, and levels of protein and protein fractions in serum and cerebrospinal fluid of dogs with distemper associated demyelinating encephalopathy. Acta Neuropathol 1973; 25:179-187.
112. Saliki JT, Lehenbauer TW. Monoclonal antibody-based competitive enzyme-linked immunosorbent assay for detection of morbillivirus antibody in marine mammal sera. J Clin Microbiol 2001; 39:1877-1881.
113. Tipold A, Pfister H, Vandevelde M. Determination of the IgG index for the detection of intrathecal immunoglobulin synthesis in dogs using an ELISA. Res Vet Sci 1993; 54:40-44.

114. Tipold A, Pfister H, Zurbriggen A, et al. Intrathecal synthesis of major immunoglobulin classes in inflammatory diseases of the canine CNS. Vet Immunol Immunopathol 1994; 42:149-159.
115. Johnson GC, Krakowka S, Axthelm MK. Albumin leakage into cerebrospinal fluid of dogs lethally infected with R252 canine distemper virus. J Neuroimmunol 1987; 14:61-74.
116. Sorjonen DC, Cox NR, Swango LJ. Electrophoretic determination of albumin and gamma globulin concentrations in the cerebrospinal fluid of dogs with encephalomyelitis attributable to canine distemper virus infection: 13 cases (1980-1987). J Am Vet Med Assoc 1989; 195:977-980.
117. Cornwell HJ, Thompson H, McCandlish IA, et al. Encephalitis in dogs associated with a batch of canine distemper (Rockborn) vaccine. Vet Rec 1988; 122:54-59.
118. Bestetti G, Fatzer R, Frankhauser R. Encephalitis following vaccination against distemper and infectious hepatitis in the dog. An optical and ultrastructural study. Acta Neuropathol (Berl) 1978; 43:69-75.
119. Hartley WJ. A post-vaccinal inclusion body encephalitis in dogs. Vet Pathol 1974; 11:301-312.
120. Krakowka S, Olsen RG, Axthelm MK, et al. Canine parvovirus infection potentiates canine distemper encephalitis attributable to modified live-virus vaccine. J Am Vet Med Assoc 1982; 180:137-139.
121. Cantile C, Baroni M, Arispici M. A case of narcolepsy-cataplexy associated with distemper encephalitis. Zentralbl Veterinarmed A 1999; 46:301-308.
122. McCandlish IA, Cornwell HJ, Thompson H, et al. Distemper encephalitis in pups after vaccination of the dam. Vet Rec 1992; 130:27-30.
123. Smith-Maxie LL, Parent JP, Rand J, et al. Cerebrospinal fluid analysis and clinical outcome of eight dogs with eosinophilic meningoencephalomyelitis. J Vet Intern Med 1989; 3:167-174.
124. Bennett PF, Allan FJ, Guilford WG, et al. Idiopathic eosinophilic meningoencephalitis in rottweiler dogs: three cases (1992-1997). Aust Vet J 1997; 75:786-789.
125. Schultze AE, Cribb AE, Tvedten HW. Eosinophilic meningoencephalitis in a cat. J Am Anim Hosp Assoc 1986; 22:623-627.
126. Yamamoto JK, Sparger E, Ho EW, et al. Pathogenesis of experimentally induced feline immunodeficiency virus infection in cats. Am J Vet Res 1988; 49:1246-1258.
127. Dow SW, Poss ML, Hoover EA. Feline immunodeficiency virus: a neurotropic lentivirus. J Acquir Immune Defic Syndr 1990; 3:658-668.
128. Podell M, March PA, Buck WR, et al. The feline model of neuroAIDS: understanding the progression towards AIDS dementia. J Psychopharmacol 2000; 14:205-213.
129. Yamamoto JK, Hansen H, Ho EW, et al. Epidemiologic and clinical aspects of feline immunodeficiency virus infection in cats from the continental United States and Canada and possible mode of transmission. J Am Vet Med Assoc 1989; 194:213-220.
130. Hopper CD, Sparkes AH, Gruffydd-Jones TJ, et al. Clinical and laboratory findings in cats infected with feline immunodeficiency virus. Vet Rec 1989; 125:341-346.
131. Abramo F, Bo S, Canese MG, et al. Regional distribution of lesions in the central nervous system of cats infected with feline immunodeficiency virus. AIDS Res Hum Retroviruses 1995; 11:1247-1253.
132. Dow SW, Dreitz MJ, Hoover EA. Exploring the link between feline immunodeficiency virus infection and neurologic disease in cats. Vet Med 1992; 87:1181-1184.
133. Sparkes AH, Hopper CD, Millard WG, et al. Feline immunodeficiency virus infection. Clinicopathologic findings in 90 naturally occurring cases. J Vet Intern Med 1993; 7:85-90.
134. Gunn-Moore DA, Pearson GR, Harbour DA, et al. Encephalitis associated with giant cells in a cat with naturally occurring feline immunodeficiency virus infection demonstrated by in situ hybridization. Vet Pathol 1996; 33:699-703.
135. Pedersen NC, Yamamoto JK, Ishida T, et al. Feline immunodeficiency virus infection. Vet Immunol Immunopathol 1989; 21:111-129.
136. Hurtrel M, Ganiere JP, Guelfi JF, et al. Comparison of early and late feline immunodeficiency virus encephalopathies. AIDS 1992; 6:399-406.
137. Phillips TR, Prospero-Garcia O, Puaoi DL, et al. Neurological abnormalities associated with feline immunodeficiency virus infection. J Gen Virol 1994; 75:979-987.
138. English RV, Nelson P, Johnson CM, et al. Development of clinical disease in cats experimentally infected with feline immunodeficiency virus. J Infect Dis 1994; 170:543-552.
139. Poli A, Abramo F, Di Iorio C, et al. Neuropathology in cats experimentally infected with feline immunodeficiency virus: a morphological, immunocytochemical and morphometric study. J Neurovirol 1997; 3:361-368.
140. Meeker RB, Azuma Y, Bragg DC, et al. Microglial proliferation in cortical neural cultures exposed to feline immunodeficiency virus. J Neuroimmunol 1999; 101:15-26.
141. Mitchell TW, Buckmaster PS, Hoover EA, et al. Neuron loss and axon reorganization in the dentate gyrus of cats

infected with the feline immunodeficiency virus. J Comp Neurol 1999; 411:563-577.
142. Yu N, Billaud JN, Phillips TR. Effects of feline immunodeficiency virus on astrocyte glutamate uptake: implications for lentivirus-induced central nervous system diseases. Proc Natl Acad Sci U S A 1998; 95:2624-2629.
143. Power C, Buist R, Johnston JB, et al. Neurovirulence in feline immunodeficiency virus-infected neonatal cats is viral strain specific and dependent on systemic immune suppression. J Virol 1998; 72:9109-9115.
144. Podell M, Oglesbee M, Mathes L, et al. AIDS-associated encephalopathy with experimental feline immunodeficiency virus infection. J Acquir Immune Defic Syndr 1993; 6:758-771.
145. Barr M, Phillips TR. FIV and FIV-related disease In: Ettinger S and Feldman EC, eds. Textbook of veterinary internal medicine. 5th ed. Philadelphia: WB Saunders Co, 2000; 433-444.
146. Sellon RK. Feline immunodeficiency virus infection In: Greene CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 84-96.
147. Weiss RC, Scott FW. Pathogenesis of feline infetious peritonitis: pathologic changes and immunofluorescence. Am J Vet Res 1981; 42:2036-2048.
148. Petersen NC, Boyle JF. Immunologic phenomena in the effusive form of feline infectious peritonitis. Am J Vet Res 1980; 41:868-876.
149. Foley JE, Lapointe JM, Koblik P, et al. Diagnostic features of clinical neurologic feline infectious peritonitis. J Vet Intern Med 1998; 12:415-423.
150. Gaskell R, Dawson S. FIP-related disease In: Ettinger S and Feldman EC, eds. Textbook of Veterinary Internal Medicine. 5th ed. Philadelphia: WB Saunders, 2000; 438-444.
151. Vennema H, Poland A, Foley J, et al. Feline infectious peritonitis viruses arise by mutation from endemic feline enteric coronaviruses. Virology 1998; 243:150-157.
152. Weiss RC, Scott FW. Antibody-mediated enhancement of disease in feline infectious peritonitis: comparisons with dengue hemorrhagic fever. Comp Immunol Microbiol Infect Dis 1981; 4:175-189.
153. Olsen CW. A review of feline infectious peritonitis virus: molecular biology, immunopathogenesis, clinical aspects, and vaccination. Vet Microbiol 1993; 36:1-37.
154. Jacobse-Geels HEL, Daha MR, Horzinek MC. Antibody, immune complexes, and complement activity fluctuations in kittens with experimentally induced feline infectious peritonitis. Am J Vet Res 1982; 43:666-670.
155. Barlough J, Stoddart C. Feline coronaviral infections In: Greene C, ed. Infectious diseases of the dog and cat. Philadelphia: WB Saunders Co, 1990; 300-312.
156. Wolfe L, Griesemer R. Feline infectious peritonitis: review of gross and histopathologic lesions. J Am Vet Med Assoc 1971; 158:987-993.
157. Wolfe L, Griesemer R. Feline infectious peritonitis. Pathol Vet 1966; 3:255-270.
158. Slauson DO, Finn JP. Meningoencephalitis and panophthalmitis in feline infectious peritonitis. J Am Vet Med Assoc 1972; 160:729-734.
159. Pedersen NC, Boyle JF, Floyd K. Infection studies in kittens, using feline infectious peritonitis virus propagated in cell culture. Am J Vet Res 1981; 42:363-367.
160. Pedersen NC, Black JW. Attempted immunization of cats against feline infectious peritonitis, using avirulent live virus or sublethal amounts of virulent virus. Am J Vet Res 1983; 44:229-234.
161. Pedersen NC. An overview of feline enteric coronavirus and feline infectious peritonitis virus infections. Feline Pract 1995; 23:7-?
162. Pedersen NC. A review of feline infectious peritonitis and feline enteric coronavirus infections. Part 2. Feline Pract 1983; 13:5-20.
163. Grahn B. The feline coronavirus infections: feline infectious peritonitis and feline coronavirus enteritis. Vet Med 1991; 86:376-393.
164. Barlough JE, Summers BA. Encephalitis due to feline infectious peritonitis virus in a twelve-week-old kitten. Feline Pract 1984; 14:43-46.
165. Rohrbach BW, Legendre AM, Baldwin CA, et al. Epidemiology of feline infectious peritonitis among cats examined at veterinary medical teaching hospitals. J Am Vet Med Assoc 2001; 218:1111-1115.
166. Kornegay JN. Feline infectious peritonitis: the central nervous system form. J Am Anim Hosp Assoc 1978; 14:580-584.
167. Pedersen NC. Feline infectious peritonitis: something old, something new. Feline Pract 1976; 6:42-46, 48-51.
168. Tamke PG, Peterson MG, Dietze AE, et al. Acquired hydrocephalus and hydromelia in a cat with feline infectious peritonitis: a case report and brief review. Can Vet J 1988; 29:997-1000.
169. Krum S, Johnson K, Wilson J. Hydrocephalus associated with the noneffusive form of feline infectious peritonitis. J Am Vet Med Assoc 1975; 167:746-748.
170. Baroni M, Heinold Y. A review of the clinical diagnosis of feline infectious peritonitis viral meningoencephalomyelitis. Prog Vet Neurol 1995; 6:88-94.

171. Rand JS, Parent J, Percy D, et al. Clinical, cerebrospinal fluid, and histological data from twenty-seven cats with primary inflammatory disease of the central nervous system. Can Vet J 1994; 35:103-110.
172. Kline KL, Joseph RJ, Averill DR. Feline infectious peritonitis with neurologic involvement: clinical and pathological findings in 24 cats. J Am Anim Hosp Assoc 1994; 30:111-118.
173. Legendre AM, Whitenack DL. Feline infectious peritonitis with spinal cord involvement in two cats. J Am Vet Med Assoc 1975; 167:31-32.
174. Fatzer R. Meningitis and granulomatous chorio-ependymitis in cats. [German]. Schweizer Archiv fur Tierheilkunde. 1975; (11)117:633-640.
175. Pedersen NC. Serologic studies of naturally occurring feline infectious peritonitis. Am J Vet Res 1976; 37:1449-1453.
176. Foley JE, Poland A, Carlson J, et al. Risk factors for feline infectious peritonitis among cats in multiple- cat environments with endemic feline enteric coronavirus. J Am Vet Med Assoc 1997; 210:1313-1318.
177. Gamble DA, Lobbiani A, Gramegna M, et al. Development of a nested PCR assay for detection of feline infectious peritonitis virus in clinical specimens. J Clin Microbiol 1997; 35:673-675.
178. Paltrinieri S, Parodi MC, Cammarata G, et al. Type IV hypersensitivity in the pathogenesis of FIPV-induced lesions.J Vet Med Series B 1998; 45:151-159.
179. Andrew SE. Feline infectious peritonitis. Vet Clin North Am Small Anim Pract 2000; 30:987-1000.
180. Baldwin CW, Scott FW. Attempted immunization of cats with feline infectious peritonitis virus propagated at reduced temperatures. Am J Vet Res 1997; 58:251-256.
181. Fehr D, Holznagel E, Bolla S, et al. Placebo-controlled evaluation of a modified life virus vaccine against feline infectious peritonitis: safety and efficacy under field conditions. Vaccine 1997; 15:1101-1109.
182. Kronevi T, Nordstrom M, Moreno W, et al. Feline ataxia due to nonsuppurative meningoencephalomyelitis of unknown aetiology. Nord Vet Med 1974; 26:720-725.
183. Hoff EJ, Vandevelde M. Non-suppurative encephalomyelitis in cats suggestive of a viral origin. Vet Pathol 1981; 18:170-180.
184. Vandevelde M, Braund KG. Polioencephalomyelitis in cats. Vet Pathol 1979; 16:420-427.
185. Lundgren AL, Ludwig H. Clinically diseased cats with non-suppurative meningoencephalomyelitis have Borna disease virus-specific antibodies. Acta Vet Scand 1993; 34:101-103.
186. Lundgren AL, Czech G, Bode L, et al. Natural Borna disease in domestic animals others than horses and sheep. Zentralbl Veterinarmed [B] 1993; 40:298-303.
187. Lundgren AL. Feline non-suppurative meningoencephalomyelitis. A clinical and pathological study. J Comp Pathol 1992; 107:411-425.
188. Fatzer R. Leukodystrophic diseases in the brain of young cats. Schweiz Arch Tierheilkd 1975; 117:641-648.
189. Csiza CK, De Lahunta A, Scott FW, et al. Spontaneous feline ataxia. Cornell Vet 1972; 62:300-322.
190. Lundgren AL, Zimmermann W, Bode L, et al. Staggering disease in cats: isolation and characterization of the feline Borna disease virus. J Gen Virol 1995; 76:2215-2222.
191. Lundgren AL, Lindberg R, Ludwig H, et al. Immunoreactivity of the central nervous system in cats with a Borna disease-like meningoencephalomyelitis (staggering disease). Acta Neuropathol 1995; 90:184-193.
192. Lundgren AL, Johannisson A, Zimmermann W, et al. Neurological disease and encephalitis in cats experimentally infected with Borna disease virus. Acta Neuropathol (Berl) 1997; 93:391-401.
193. Nakamura Y, Watanabe M, Kamitani W, et al. High prevalence of Borna disease virus in domestic cats with neurological disorders in Japan. Vet Microbiol 1999; 70:153-169.
194. Berg A-L. Borna disease in cats In: Bonagura JD, ed. Kirk's current veterinary therpy XIII. Small animal practice. Philadelphia: WB Saunders, 2000; 976-978.
195. Wyatt JM, Pearson GR, Smerdon TN, et al. Naturally occurring scrapie-like spongiform encephalopathy in five domestic cats. Vet Rec 1991; 129:233-236.
196. Wells GA, McGill IS. Recently described scrapie-like encephalopathies of animals: case definitions. Res Vet Sci 1992; 53:1-10.BR> 197. Wilesmith JW, Ryan JB, Atkinson MJ. Bovine spongiform encephalopathy: epidemiological studies on the origin. Vet Rec 1991; 128:199-203.
198. Fraser H, Pearson GR, McConnell I, et al. Transmission of feline spongiform encephalopathy to mice. Vet Rec 1994; 134:449.
199. Narang H. Origin and implications of bovine spongiform encephalopathy. Proc Soc Exp Biol Med 1996; 211:306-322.
200. Stevenson MA, Wilesmith JW, Ryan JB, et al. Temporal aspects of the epidemic of bovine spongiform encephalopathy in Great Britain: individual animal-associated risk factors for the disease. Vet Rec 2000; 147:349-354.
201. Brown P. Transmissible spongiform encephalopathy In: Goetz C, Pappert E, Schmitt B, eds. Textbook of clinical neurology. Philadelphia: WB Saunders Co, 1999; 869-875.
202. Goldwater PN. Bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease: implications for Australia.

Med J Aust 2001; 175:154-158.
203. Prusiner SB, Gabizon R, McKinley MP. On the biology of prions. Acta Neuropathol 1987; 72:299-314.
204. Hope J, Morton LJ, Farquhar CF, et al. The major polypeptide of scrapie-associated fibrils (SAF) has the same size, charge distribution and N-terminal protein sequence as predicted for the normal brain protein (PrP). EMBO J 1986; 5:2591-2597.
205. Wells GA, Scott AC, Wilesmith JW, et al. Correlation between the results of a histopathological examination and the detection of abnormal brain fibrils in the diagnosis of bovine spongiform encephalopathy. Res Vet Sci 1994; 56:346-351.
206. McBride PA, Bruce ME, Fraser H. Immunostaining of scrapie cerebral amyloid plaques with antisera raised to scrapie-associated fibrils (SAF). Neuropathol Appl Neurobiol 1988; 14:325-336.
207. Narang HK. Lingering doubts about spongiform encephalopathy and Creutzfeldt-Jakob disease. Exp Biol Med (Maywood) 2001; 226:640-652.
208. Wyatt JM, Pearson GR, Gruffydd-Jones TJ. Feline spongiform encephalopathy. Feline Pract 1993; 21:7-9.
209. Pearson GR, Gruffydd-Jones TJ, Wyatt JM, et al. Feline spongiform encephalopathy. Vet Rec 1991; 128:532.
210. Leggett MM, Dukes J, Pirie HM. A spongiform encephalopathy in a cat. Vet Rec 1990; 127:586-588.
211. Bratberg B, Ueland K, Wells GAH. Feline spongiform encephalopathy in a cat in Norway. Vet Rec 1995; 136:444.
212. Pearson GR, Wyatt JM, Gruffydd-Jones TJ, et al. Feline spongiform encephalopathy: fibril and PrP studies. Vet Rec 1992; 131:307-310.
213. Ryder SJ, Wells GA, Bradshaw JM, et al. Inconsistent detection of PrP in extraneural tissues of cats with feline spongiform encephalopathy. Vet Rec 2001; 148:437-441.
214. Vandevelde E. Neurologic diseases of suspected infectious origin In: Greene CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 530-539.
215. Vandevelde M, Fatzer R, Fankhauser R. Immunohistological studies on primary reticulosis of the canine brain. Vet Pathol 1981; 18:577-588.
216. Russo ME. Primary reticulosis of the central nervous system in dogs. J Am Vet Med Assoc 1979; 174:492-500.
217. Glastonbury JR, Frauenfelder AR. Granulomatous meningoencephalomyelitis in a dog. Aust Vet J 1981; 57:186-189.
218. Cuddon PA, Smith-Maxie L. Reticulosis of the central nervous system in the dog. Compend Contin Educ Pract Vet 1984; 6:23-29, 32.
219. Cordy DR. Canine granulomatous meningoencephalomyelitis. Vet Pathol 1979; 16:325-333.
220. Braund KG. Granulomatous meningoencephalomyelitis. J Am Vet Med Assoc 1985; 186:138-141.
221. Braund KG, Vandevelde M, Walker, TL, et al. Granulomatous meningoencephalomyelitis in six dogs. J Am Vet Med Assoc 1978; 172:1195-1200.
222. Alley MR, Jones BR, Johnstone AC. Granulomatous meningoencephalomyelitis of dogs in New Zealand. N Z Vet J 1983; 31:117-119.
223. Robin D, Delverdier M, Raymond I, et al. Granulomatous meningoencephalomyelitis in a dog: case report. [French]. Revue de Médecine Vétérinaire 1993; 144:879-884.
224. Fankhauser R, Fatzer R, Luginbuhl H. Reticulosis of the central nervous system (CNS) in dogs. Adv Vet Sci Comp Med 1972; 16:35-71.
225. Demierre S, Tipold A, Griot-Wenk ME, et al. Correlation between the clinical course of granulomatous meningoencephalomyelitis in dogs and the extent of mast cell infiltration. Vet Rec 2001; 148:467-472.
226. Kipar A, Baumgartner W, Vogl C, et al. Immunohistochemical characterization of inflammatory cells in brains of dogs with granulomatous meningoencephalitis. Vet Pathol 1998; 35:43-52.
227. Sutton RH, Atwell RB. Nervous disorders in dogs associated with levamisole therapy. J Small Anim Pract 1982; 23:391-397.
228. Vandevelde M, Boring JG, Hoff EJ, et al. The effect of levamisole on the canine central nervous system. J Neuropathol Exp Neurol 1978; 37:165-173.
229. Harris CW, Didier PJ, Parker AJ. Simultaneous central nervous system reticulosis in two related Afghan hounds. Compend Contin Educ Pract Vet 1988; 10:304,306,308-310.
230. Thomas JB, Eger C. Granulomatous meningoencephalomyelitis in 21 dogs. J Small Anim Pract 1989; 30:287-293.
231. Munana KR, Luttgen PJ. Prognostic factors for dogs with granulomatous meningoencephalomyelitis: 42 cases (1982-1996). J Am Vet Med Assoc 1998; 212:1902-1906.
232. Sorjonen DC. Clinical and histopathological features of granulomatous meningoencephalomyelitis in dogs. J Am Anim Hosp Assoc 1990; 26:141-147.
233. Garmer NL, Naeser P, Bergman, AJ. Reticulosis of the eyes and the central nervous system in a dog. J Small Anim Pract 1981; 22:39-45.
234. Fischer C, Liu S-K. Neuro-ophthalmologic manifestations of primary reticulosis of the central nervous system in a dog. J Am Vet Med Assoc 1971; 158:1240-1248.

235. Smith JS, de Lahunta A, Riis RC. Reticulosis of the visual system in a dog. J Small Anim Pract 1977; 18:643-652.
236. Sarfaty D, Carrillo JM, Greenlee PG. Differential diagnosis of granulomatous meningoencephalomyelitis, distemper, and suppurative meningoencephalitis in the dog. J Am Vet Med Assoc 1986; 188:387-392.
237. Bailey CS, Higgins RJ. Characteristics of cerebrospinal fluid associated with canine granulomatous meningoencephalomyelitis: a retrospective study. J Am Vet Med Assoc 1986; 188:418-421.
238. Bichsel P, Vandevelde M, Vandevelde E, et al. Immunoelectrophoretic determination of albumin and IgG in serum and cerebrospinal fluid in dogs with neurological diseases. Res Vet Sci 1984; 37:101-107.
239. Murtaugh RJ, Fenner WR, Johnson GC. Focal granulomatous meningoencephalomyelitis in a pup. J Am Vet Med Assoc 1985; 187:835-836.
240. Gearhart M, de Lahunta A, Summers B. Cerebellar mass in a dog due to granulomatous meningoencephalomyelitis. J Am Anim Hosp Assoc 1986; 22:683-686.
241. Speciale J, Van Winkle T, Steinberg S, et al. Computer tomography in the diagnosis of focal granulomatous meningoencephalitis: retrospective evaluation of three cases. J Am Anim Hosp Assoc 1992; 28:327-332.
242. Appel M, Bistner SI, Menegus M, et al. Pathogenicity of low-virulence strains of two canine adenovirus types. Am J Vet Res 1973; 34:543-550.
243. Greene C. Infectious canine hepatitis and canine acidophil cell hepatitis. In: Greene C, ed. Infectious Diseases of the Dog and Cat. Philadelphia: WB Saunders Co, 1990; 242-251.
244. Madigan J. Lyme disease update. In: Proceedings of the10th Annu Meet Vet Med Forum, ACVIM 1992; 692-695.
245. Greene CE, Appel M, Straubinger R. Lyme borreliosis In: Greene, CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 282-293.
246. Breitschwerdt E. Tick-transmitted diseases. In: Proceedings of the 9th Annu Meet Vet Med Forum, ACVIM 1991; 137-142.
247. Feder B, Joseph R, Moroff S, et al. Borrelia burgdorferi antibodies in canine cerebrospinal fluid. In: Proceedings of the 9th Annu Meet Vet Med Forum, ACVIM 1991; 137.
248. Azuma Y, Kawamura K, Isogai H, et al. Neurologic abnormalities in two dogs suspected [of] Lyme disease. Microbiology & Immunology 1993; 37:325-329.
249. Mandel NS, Senker EG, Bosler EM, et al. Intrathecal production of Borrelia burgdorferi-specific antibodies in a dog with central nervous system Lyme borreliosis. Compend Contin Educ Pract Vet 1993; 15:581-586.
250. Tipold A. Diagnosis of inflammatory and infectious diseases of the central nervous system in dogs: a retrospective study. J Vet Intern Med 1995; 9:304-314.
251. Tipold A. Steroid-responsive meningitis-arteritis in dogs In: Bonagura JD, ed. Kirk's Current Veterinary Therapy XIII: small animal practice. Philadelphia: WB Saunders Co, 2000; 978-981.
252. Felsburg PJ, HogenEsch H, Somberg RL, et al. Immunologic abnormalities in canine juvenile polyarteritis syndrome: a naturally occurring animal model of Kawasaki disease. Clin Immunol Immunopathol 1992; 65:110-118.
253. Kelly DF, Grunsell CSG, Kenyon CJ. Polyarteritis in the dog: a case report. Vet Rec 1973; 92:363-366.
254. Brooks PN. Necrotizing vasculitis in a group of Beagles. Lab Anim 1984; 18:285-290.
255. Albassam MA, Houston BJ, Greaves P, et al. Polyarteritis in a Beagle. J Am Vet Med Assoc 1989; 194:1595-1597.
256. Hayes TJ, Roberts GK, Halliwell WH. An idiopathic febrile necrotizing arteritis syndrome in the dog: beagle pain syndrome. Toxicol Pathol 1989; 17:129-137.
257. Scott-Moncrieff JCR, Snyder PW, Glickman LT, et al. Systemic necrotizing vasculitis in nine young Beagles. J Am Vet Med Assoc 1992; 201:1553-1558.
258. Harcourt RA. Polyarteritis in a colony of beagles. Vet Rec 1978; 102:519-522.
259. Kemi M, Usui T, Narama I, et al. Histopathology of spontaneous panarteritis in Beagle dogs. Jap J Vet Sci 1990; 52:55-61.
260. Spencer A, Greaves P. Periarteritis in a Beagle colony. J Comp Pathol 1987; 97:121-128.
261. Meric SM, Child G, Higgins RJ. Necrotizing vasculitis of the spinal pachyleptomeningeal arteries in three Bernese Mountain dog littermates. J Am Anim Hosp Assoc 1986; 22:459-465.
262. Meric S, Perman V, Hardy R. Corticosteroid-responsive meningitis in ten dogs. J Am Anim Hosp Assoc 1985; 21:677-684.
263. Presthus J. Aseptic suppurative meningitis in Bernese Mountain dogs. Eur J Companion Anim Pract 1991; 1:24-28.
264. Irving G, Chrisman C. Long-term outcome of five cases of corticosteroid-responsive meningomyelitis. J Am Anim Hosp Assoc 1990; 26:324-328.
265. Tipold A, Jaggy A. Steroid responsive meningitis-arteritis in dogs: long-term study of 32 cases. J Small Anim Pract 1994; 35:311-316.
266. Tipold A, Vandevelde M, Zurbriggen A. Neuroimmunological studies in steroid-responsive meningitis-arteritis in dogs. Res Vet Sci 1995; 58:103-108.

267. Bammert M, van Ham L, Jaggy A, et al. "Is TGF-α1 responsible for excessive intrathecal and systemic IgA production in steroid responsive meningitis-arteritis in dogs?" In: Proceedings of the 14th Annu Symp, ESVN 2000; 53.
268. Tipold A. Steroid-responsive meningitis-arteritis in dogs: computed tomographic findings. In: Proceedings of the 14th Annu Symp, ESVN 2000; 52.
269. Snyder PW, Kazacos EA, Scott-Moncrieff JC, et al. Pathologic features of naturally occurring juvenile polyarteritis in beagle dogs. Vet Pathol 1995; 32:337-345.
270. Hoff EJ, Vandevelde M. Necrotizing vasculitis in the central nervous systems of two dogs: case report. Vet Pathol 1981; 18:219-223.
271. Tipold A, Moore P, Zurbriggen A, et al. Lymphocyte subset distribution in steroid responsive meningitis- arteriitis in comparison to different canine encephalitides. Zentralbl Veterinarmed A 1999; 46:75-85.
272. Tipold A, Somberg R, Felsburg P. Involvement of a superantigen in sterile purulent meningitis and arteritis of dogs. [German]. Tierarztl Prax 1996; 24:514-518.
273. Burgener I, Van Ham L, Jaggy A, et al. Chemotactic activity and IL-8 levels in the cerebrospinal fluid in canine steroid responsive meningitis-arteriitis. J Neuroimmunol 1998; 89:182-190.
274. Cizinauskas S, Jaggy A, Tipold A. Long-term treatment of dogs with steroid-responsive meningitis- arteritis: clinical, laboratory and therapeutic results. J Small Anim Pract 2000; 41:295-301.
275. Dougherty SA, Center SA, Shaw EE, et al. Juvenile-onset polyarthritis syndrome in Akitas. J Am Vet Med Assoc 1991; 198:849-856.
276. Hess PR, Sellon RK. Steroid-responsive, cervical, pyogranulomatous pachymeningitis in a dog. J Am Anim Hosp Assoc 1997; 33:461-468.
277. Meric SM. Canine meningitis. A changing emphasis. J Vet Intern Med 1988; 2:26-35.
278. Platt S, Radaelli S. Bacterial meningoencephalitis in dogs: a retrospective study of 23 cases (1990-1999). In: Proceedings of the 14th Annu Symp, ESVN 2000; 30-31.
279. Sims MA. Flavobacterium meningosepticum: a probable cause of meningitis in a cat. Vet Rec 1974; 95:567-569.
280. Bullmore C, Sevedge J. Canine meningoencephalitis. J Am Anim Hosp Assoc 1978; 14:387-394.
281. Hudson M. Bacterial meningitis. J Am Anim Hosp Assoc 1976; 12:88-91.
282. Kornegay JN, Lorenz MD, Zenoble RD. Bacterial meningoencephalitis in two dogs. J Am Vet Med Assoc 1978; 173:1334-1336.
283. Spangler EA, Dewey CW. Meningoencephalitis secondary to bacterial otitis media/interna in a dog. J Am Anim Hosp Assoc 2000; 36:239-243.
284. Roos K. Nonviral infections In: Goetz C and Pappert E, eds. Textbook of clinical neurology. Philadelphia: WB Saunders Co, 2000; 842-867.
285. Zwahlen A, Nydegger UE, Vaudaux P, et al. Complement-mediated opsonic activity in normal and infected human cerebrospinal fluid: early response during bacterial meningitis. J Infect Dis 1982; 145:635-646.
286. Spellerberg B, Tuomanen EI. The pathophysiology of pneumococcal meningitis. Ann Med 1994; 26:411-418.
287. Greene CE. Meningitis In: Kirk RW, ed. Current veterinary therapy VIII. Philadelphia: WB Saunders Co, 1983; 735-738.
288. Feldman BF, Ruehl WW. Examination of body fluids. Mod Vet Pract 1984; 65:295-298.
289. Irwin PJ, Parry BW. Streptococcal meningoencephalitis in a dog. J Am Anim Hosp Assoc 1999; 35:417-422.
290. Lowrie C, Kumar K, Moore J, et al. A preliminary study of magnetic resonance imaging (MRI) in experimental canine meningitis. Compan Anim Pract 1989; 19:3-6.
291. Meric SM. Corticosteroid therapy for bacterial meningitis in dogs. Cornell Vet 1990; 80:3-6.
292. Jacobs G, Medleau L. Cryptococcosis In: Greene CE, ed. Infectious diseases of the dog and cat. Philadelphia: WB Saunders Co, 1998; 383-390.
293. Palmer AC, Herrtage ME, Kaplan W. Cryptococcal infection of the central nervous system of a dog in the United Kingdom. J Small Anim Pract 1981; 22:579-586.
294. Sutton RH. Cryptococcosis in dogs: a report on 6 cases. Aust Vet J 1981; 57:558-564.
295. Jergens AE, Wheeler CA, Collier LL. Cryptococcosis involving the eye and central nervous system of a dog. J Am Vet Med Assoc 1986; 189:302-304.
296. Panciera DL, Bevier D. Management of cryptococcosis and toxic epidermal necrolysis in a dog. J Am Vet Med Assoc 1987; 191:1125-1127.
297. Berthelin CF, Bailey CS, Kass PH, et al. Cryptococcosis of the nervous system in dogs. Part 1: epidemiologic, clinical, and neuropathologic features. Prog Vet Neurol 1994; 5:88-97.
298. Malik R, Dill-Macky E, Martin P, et al. Cryptococcosis in dogs: a retrospective study of 20 consecutive cases. J Med Vet Mycology 1995; 33:291-297.
299. Tiches D, Vite CH, Dayrell-Hart B, et al. A case of canine central nervous system cryptococcosis: management with

fluconazole. J Am Anim Hosp Assoc 1998; 34:145-151.
300. Pal M. Feline meningitis due to Cryptococcus neoformans var. neoformans and review of feline cryptococcosis. Mycoses 1991; 34:313-316.
301. Medleau L, Greene CE, Rakich PM. Evaluation of ketoconazole and itraconazole for treatment of disseminated cryptococcosis in cats. Am J Vet Res 1990; 51:1454-1458.
302. Ramos-Vara JA, Ferrer L, Visa J. Pathological findings in a cat with cryptococcosis and feline immunodeficiency virus infection. Histol Histopathol 1994; 9:305-308.
303. Gerds-Grogan S, Dayrell-Hart B. Feline cryptococcosis: a retrospective evaluation. J Am Anim Hosp Assoc 1997; 33:118-122.
304. Krohne SG. Canine systemic fungal infections. Vet Clin North Am Small Anim Pract 2000; 30:1063-1090.
305. Kurtz HJ, Sharpnack S. Blastomyces dermatitidis meningoencephalitis in a dog. Pathol Vet 1969; 6:375-377.
306. Nasisse MP, van Ee RT, Wright B. Ocular changes in a cat with disseminated blastomycosis. J Am Vet Med Assoc 1985; 187:629-631.
307. Breider MA, Walker TL, Legendre AM, et al. Blastomycosis in cats: five cases (1979-1986). J Am Vet Med Assoc 1988; 193:570-572.
308. Schaer M, Johnson KE, Nicholson AC. Central nervous system disease due to histoplasmosis in a dog: a case report. J Am Anim Hosp Assoc 1983; 19:311-316.
309. Pryor WH Jr., Huizenga CG, Splitter GA, et al. Coccidioides immitis encephalitis in two dogs. J Am Vet Med Assoc 1972; 161:1108-1112.
310. Burtch M. Granulomatous meningitis caused by Coccidioides immitis in a dog. J Am Vet Med Assoc 1998; 212:827-829.
311. Migaki G, Casey HW, Bayles WB. Cerebral phaeohyphomycosis in a dog. J Am Vet Med Assoc 1987; 191:997-998.
312. Schroeder H, Jardine JE, Davis V. Systemic phaeohyphomycosis caused by Xylohypha bantiana in a dog. J S Afr Vet Assoc 1994; 65:175-178.
313. Anor S, Sturges BK, Lafranco L, et al. Systemic phaeohyphomycosis (Cladophialophora bantiana) in a dog - clinical diagnosis with stereotactic computed tomographic-guided brain biopsy. J Vet Intern Med 2001; 15:257-261.
314. Foil C. Miscellaneous fungal infections In: Greene CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 420-430.
315. Lincoln SD, Adcock JL. Disseminated geotrichosis in a dog. Pathol Vet 1968; 5:282-289.
316. Mullaney TP, Levin S, Indrieri RJ. Disseminated aspergillosis in a dog. J Am Vet Med Assoc 1983; 182:516-518.
317. Patterson J, Rosendal S, Humphrey J, et al. A case of disseminated paecilomycosis. J Am Anim Hosp Assoc 1983; 19:569-574.
318. March PA, Knowles K, Dillavou CL, et al. Diagnosis, treatment, and temporary remission of disseminated paecilomycosis in a vizsla. J Am Anim Hosp Assoc 1996; 32:509-514.
319. Berthelin CF, Legendre AM, Bailey CS, et al. Cryptococcosis of the nervous system in dogs, part 2: diagnosis, treatment, monitoring, and prognosis. Prog Vet Neurol 1994; 5:136-146.
320. VanSteenhouse JL, DeNovo RC Jr. Atypical Histoplasma capsulatum infection in a dog. J Am Vet Med Assoc 1986; 188:527-528.
321. Legendre AM. Blastomycosis In: Greene, CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 371-377.
322. Malik R, Wigney DI, Muir DB, et al. Cryptococcosis in cats: clinical and mycological assessment of 29 cases and evaluation of treatment using orally administered fluconazole. J Med Vet Mycol 1992; 30:133-144.
323. Mason KV. Canine neural angiostrongylosis: the clinical and therapeutic features of 55 natural cases. Aust Vet J 1987; 64:201-203.
324. Mason KV. Haematological and cerebrospinal fluid findings in canine neural angiostrongylosis. Aust Vet J 1989; 66:152-154.
325. McKenzie BE, Lyles DI, Clinkscales JA. Intracerebral migration of Cuterebra larva in a kitten. J Am Vet Med Assoc 1978; 172:173-175.
326. Hatziolos BC. Cuterebra larva causing paralysis in a dog. Cornell Vet 1967; 57:129-145.
327. Hatziolos BC. Cuterebra larva in the brain of a cat. J Am Vet Med Assoc 1966; 148:787-793.
328. Williams KJ, Summers BA, de Lahunta Ad. Cerebrospinal cuterebriasis in cats and its association with feline ischemic encephalopathy. Vet Pathol 1998; 35:330-343.
329. Okolo MI. Cerebral cysticercosis in rural dogs. Microbios 1986; 47:189-191.
330. Jauregui PH, Marquez-Monter H. Cysticercosis of the brain in dogs in Mexico City. Am J Vet Res 1977; 38:1641-1642.
331. Botha WS. Cerebral cysticercosis in a dog. J S Afr Vet Assoc 1980; 51:127.
332. Buback JL, Schulz KS, Walker MA, et al. Magnetic resonance imaging of the brain for diagnosis of neurocysticercosis

in a dog. J Am Vet Med Assoc 1996; 208:1846-1848.
333. Ruttinger P, Hadidi H. MRI in cerebral toxocaral disease. J Neurol Neurosurg Psychiatry 1991; 54:361-362.
334. Rudmann DG, Kazacos KR, Storandt ST, et al. Baylisascaris procyonis larva migrans in a puppy: a case report and update for the veterinarian. J Am Anim Hosp Assoc 1996; 32:73-76.
335. Thomas JS. Encephalomyelitis in a dog caused by Baylisascaris infection. Vet Pathol 1988; 25:94-95.
336. Huss BT, Miller MA, Corwin RM, et al. Fatal cerebral coenurosis in a cat. J Am Vet Med Assoc 1994; 205:69-71.
337. Hayes MA, Creighton, SR. A coenurus in the brain of a cat. Can Vet J 1978; 19:341-343.
338. Smith MC, Bailey CS, Baker N, et al. Cerebral coenurosis in a cat. J Am Vet Med Assoc 1988; 192:82-84.
339. Slocombe RF, Arundel JH, Labuc R, et al. Cerebral coenuriasis in a domestic cat. Aust Vet J 1989; 66:92-93.
340. Pumarola M, van Niel MH. Obstructive hydrocephalus produced by parasitic granulomas in a dog. Zentralbl Veterinarmed A 1992; 39:392-395.
341. Patton C, Garner F. Cerebral infarction caused by heartworms (Dirofilaria immitis) in a dog. J Am Vet Med Assoc 1970; 156:600-605.
342. Donahoe JM, Holzinger EA. Dirofilaria immitis in the brains of a dog and a cat. J Am Vet Med Assoc 1974; 164:518-519.
343. Fukushima K, Hutsell D, Patton S, et al. Aberrant dirofilariasis in a cat. J Am Vet Med Assoc 1984; 184:199-201.
344. Cooley AJ, Clemmons RM, Gross TL. Heartworm disease manifested by encephalomyelitis and myositis in a dog. J Am Vet Med Assoc 1987; 190:431-432.
345. McManus EC, Pulliam JD. Histopathologic features of canine heartworm microfilarial infection after treatment with ivermectin. Am J Vet Res 1984; 45:91-97.
346. Perry AW, Hertling R, Kennedy MJ. Angiostrongylosis with disseminated larval infection associated with signs of ocular and nervous disease in an imported dog. Can Vet J 1991; 32:430-431.
347. Martin MWS, Ashton G, Simpson VR, et al. Angiostrongylosis in Cornwall: clinical presentations of eight cases. J Small Anim Pract 1993; 34:20-25.
348. Reifinger M, Greszl J. Pulmonary angiostrongylosis with systemic distribution and central nervous system symptoms in a dog. [German]. Journal of Veterinary Medicine Series B 1994; 41:391-398.
349. Buick T, Campbell R, Hutchinson G. Spinal nematodiasis of the dog associated with Ancyostoma caninum. Aust Vet J 1977; 53:602-603.
350. Mason KV, Prescott CW, Kelly W, et al. Granulomatous encephalomyelitis of puppies due to Angiostrongylus cantonensis. Aust Vet J 1976; 52:295.
351. Barron CN, Saunders LZ. Visceral larva migrans in the dog. Pathol Vet 1966; 3:315-330.
352. Richards M, Sloper J. Hypothalamic involvement by "visceral" larva migrans in a dog suffering from diabetes insipidus. Vet Rec 1964; 76:449-451.
353. Georgi JR, De Lahunta A, Percy DH. Cerebral coenurosis in a cat. Report of a case. Cornell Vet 1969; 59:127-134.
354. Mandelker L, Brutus R. Feline and canine dirofilarial encephalitis. J Am Vet Med Assoc 1971; 159:776.
355. Hamir AN. Heartworm (Dirofilaria immitis) in the brain of a dog. Vet Rec 1987; 120:207-208.
356. Luttgen P, Crawley R. Posterior paralysis caused by epidural dirofilariasis in a dog. J Am Anim Hosp Assoc 1981; 17:57-59.
357. Shires PK, Turnwald GH, Qualls CW, et al. Epidural dirofilariasis causing paraparesis in a dog. J Am Vet Med Assoc 1982; 180:1340-1343.
358. Blass CE, Holmes RA, Neer TM. Recurring tetraparesis attributable to a heartworm in the epidural space of a dog. J Am Vet Med Assoc 1989; 194:787-788.
359. Glass EN, Cornetta AM, de Lahunta A, et al. Clinical and clinicopathologic features in 11 cats with Cuterebra larvae myiasis of the central nervous system. J Vet Intern Med 1998; 12:365-368.
360. Collins GH, Rothwell TLW, Malik R, et al. Angiostrongylosis in dogs in Sydney. Aust Vet J 1992; 69:170-171.
361. Mason R, Hartley W, Randall M. Spongiform degeneration of the white matter in a Samoyed pup. Aus Vet Pract 1979; 9:11-13.
362. Perrin IV, Bestetti GE, Zanesco SA, et al. [Diabetes insipidus centralis caused by visceral larva migrans of the neurohypophysis in the dog]. Schweiz Arch Tierheilkd 1986; 128:483-486.
363. Ramsey IK, Littlewood JD, Dunn JK, et al. Role of chronic disseminated intravascular coagulation in a case of canine angiostrongylosis. Vet Rec 1996; 138:360-363.
364. Soland J, Bolt G. Hypovolaemic shock after anthelmintic treatment of canine angiostrongylosis. J Small Anim Pract 1996; 37:594-596.
365. Gaunt SD, McGrath RK, Cox HU. Disseminated protothecosis in a dog. J Am Vet Med Assoc 1984; 185:906-907.
366. Tyler DE, Lorenz MD, Blue JL, et al. Disseminated protothecosis with central nervous system involvement in a dog. J Am Vet Med Assoc 1980; 176:987-993.

367. Migaki G, Font RL, Sauer RM, et al. Canine protothecosis: review of the literature and report of an additional case. J Am Vet Med Assoc 1982; 181:794-797.
368. Greene CE. Protothecosis In: Greene CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 430-435.
369. Perez J, Ginel PJ, Lucena R, et al. Canine cutaneous protothecosis: an immunohistochemical analysis of the inflammatory cellular infiltrate. J Comp Pathol 1997; 117:83-89.
370. Thomas JB, Preston N. Generalised protothecosis in a collie dog. Aust Vet J 1990; 67:25-27.
371. Hollingsworth SR. Canine protothecosis. Vet Clin North Am Small Anim Pract 2000; 30:1091-1101.
372. Blogg JR, Sykes JE. Sudden blindness associated with protothecosis in a dog. Aust Vet J 1995; 72:147-149.
373. Imes GD, Lloyd JC, Brightman MP. Disseminated prothothecosis in a dog. Onderstepoort J Vet Res 1977; 44:1-6.
374. Cook JR Jr., Tyler DE, Coulter DB, et al. Disseminated protothecosis causing acute blindness and deafness in a dog. J Am Vet Med Assoc 1984; 184:1266-1272.
375. Font RL, Hook SR. Metastatic protothecal retinitis in a dog. Electron microscopic observations. Vet Pathol 1984; 21:61-66.
376. Moore FM, Schmidt GM, Desai D, et al. Unsuccessful treatment of disseminated protothecosis in a dog. J Am Vet Med Assoc 1985; 186:705-708.
377. Ginel PJ, Perez J, Molleda JM, et al. Cutaneous protothecosis in a dog. Vet Rec 1997; 140:651-653.
378. Dubey JP, Lappin MR. Toxoplasmosis and neosporosis In: Greene C, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 493-509.
379. Baril L, Ancelle T, Goulet V, et al. Risk factors for Toxoplasma infection in pregnancy: a case-control study in France. Scand J Infect Dis 1999; 31:305-309.
380. Dunn D, Wallon M, Peyron F, et al. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. Lancet 1999; 353:1829-1833.
381. Moller T, Neilsen S. Toxoplasmosis in distemper-susceptible carnivora. Pathol Vet 1964; 1:189-203.
382. Dubey JP, Carpenter JL, Speer CA, et al. Newly recognized fatal protozoan disease of dogs. J Am Vet Med Assoc 1988; 192:1269-1285.
383. Munday BL, Dubey JP, Mason, RW. Neospora caninum infection in dogs. Aust Vet J 1990; 67:76-77.
384. Patitucci AN, Alley MR, Jones BR, et al. Protozoal encephalomyelitis of dogs involving Neospora caninum and Toxoplasma gondii in New Zealand. N Z Vet J 1997; 45:231-235.
385. Basso W, Venturini L, Venturini MC, et al. First isolation of Neospora caninum from the feces of a naturally infected dog. J Parasitol 2001; 87:612-618.
386. Lindsay DS, Ritter DM, Brake D. Oocyst excretion in dogs fed mouse brains containing tissue cysts of a cloned line of Neospora caninum. J Parasitol 2001; 87:909-911.
387. Dubey JP, Lindsay DS. Transplacental Neospora caninum infection in dogs. Am J Vet Res 1989; 50:1578-1579.
388. Dubey JP, Koestner A, Piper RC. Repeated transplacental transmission of Neospora caninum in dogs. J Am Vet Med Assoc 1990; 197:857-860.
389. Dubey JP, Lindsay DS. A review of Neospora caninum and neosporosis. Vet Parasitol 1996; 67:1-59.
390. Ham LMLv, Thoonen H, Barber JS, et al. Neospora caninum infection in the dog: typical and atypical cases. Vlaams Diergeneeskundig Tijdschrift 1996; 65:326-335.
391. Barber JS, Holmdahl OJM, Owen MR, et al. Characterization of the first European isolate of Neospora caninum (Dubey, Carpenter, Speer, Topper and Uggla). Parasitology 1995; 111:563-568.
392. Peters M, Wagner F, Schares G. Canine neosporosis: clinical and pathological findings and first isolation of Neospora caninum in Germany. Parasitol Res 2000; 86:1-7.
393. Atkinson R, Harper PA, Ryce C, et al. Comparison of the biological characteristics of two isolates of Neospora caninum. Parasitology 1999; 118:363-370.
394. Barber JS, Payne-Johnson CE, Trees AJ. Distribution of Neospora caninum within the central nervous system and other tissues of six dogs with clinical neosporosis. J Small Anim Pract 1996; 37:568-574.
395. Hass J, Shell L, Saunders G. Neurological manifestations of toxoplasmosis: a literature review and case summary. J Am Anim Hosp Assoc 1989; 25:253-260.
396. Heidel JR, Dubey JP, Blythe LL, et al. Myelitis in a cat infected with Toxoplasma gondii and feline immunodeficiency virus. J Am Vet Med Assoc 1990; 196:316-318.
397. Davidson MG, Rottman JB, English RV, et al. Feline immunodeficiency virus predisposes cats to acute generalized toxoplasmosis. Am J Pathol 1993;143:1486-1497.
398. Lappin MR, Greene CE, Winston S, et al. Clinical feline toxoplasmosis. Serologic diagnosis and therapeutic management of 15 cases. J Vet Intern Med 1989; 3:139-143.
399. Lappin MR, Greene CE, Prestwood AK, et al. Enzyme-linked immunosorbent assay for the detection of circulating

antigens of Toxoplasma gondii in the serum of cats. Am J Vet Res 1989; 50:1586-1590.
400. Dubey JP, Higgins RJ, Barr BC, et al. Sarcocystis-associated meningoencephalomyelitis in a cat. J Vet Diagn Invest 1994; 6:118-120.
401. Bjerkas I, Presthus J. Immuno-histochemical and ultrastructural characteristics of a cyst- forming sporozoon associated with encephalomyelitis and myositis in dogs. APMIS 1988; 96:445-454.
402. Bjerkas I, Presthus J. The neuropathology in toxoplasmosis-like infection caused by a newly recognized cyst-forming sporozoon in dogs. APMIS 1989; 97:459-468.
403. Dubey JP, Lindsay DS. Fatal Neospora caninum infection in kittens. J Parasitol 1989; 75:148-151.
404. Nesbit JW, Lourens DC, Williams MC. Spastic paresis in two littermate pups caused by Toxoplasma gondii. J S Afr Vet Assoc 1981; 52:243-246.
405. Cummings JF, de Lahunta Ad, Suter MM, et al. Canine protozoan polyradiculoneuritis. Acta Neuropathol (Berl) 1988; 76:46-54.
406. Uggla A, Dubey JP, Lundmark G, et al. Encephalomyelitis and myositis in a Boxer puppy due to a Neospora-like infection. Vet Parasitol 1989; 32:255-260.
407. Wolf M, Cachin M, Vandevelde M, et al. Clinical diagnosis of protozoal myositis-encephalitis syndrome (Neospora caninum) in puppies. [German]. Tierarztl Prax 1991; 19:302-306.
408. Cochrane SM, Dubey JP. Neosporosis in a Golden Retriever dog from Ontario. Can Vet J 1993; 34:232-233.
409. Braund K, Blagburn B, Toivio-Kinnucan M, et al. Toxoplasma polymyositis/polyneuropathy: a new clinical variant in two mature dogs. J Am Anim Hosp Assoc 1988; 24:93-97.
410. Graham JP, Newell SM, Voges AK, et al. The dural tail sign in the diagnosis of meningiomas. Vet Radiol Ultrasound 1998; 39:297-302.
411. Mayhew I, Smith K, Dubey J, et al. Treatment of encephalomyelitis due to Neospora caninum in a litter of puppies. J Small Anim Pract 1991; 32:609-612.
412. Bjorkman C, Uggla A. Serological diagnosis of Neospora caninum infection. Int J Parasitol 1999; 29:1497-1507.
413. Klein BU, Muller E. Seroprevalence of antibodies to Neospora caninum in dogs with and without clinical suspicion for neosporosis in Germany. [German]. Praktische Tierarzt 2001; 82:437-440.
414. Lindsay DS, Dubey JP. Immunohistochemical diagnosis of Neospora caninum in tissue sections. Am J Vet Res 1989; 50:1981-1983.
415. Ellis JT, McMillan D, Ryce C, et al. Development of a single tube nested polymerase chain reaction assay for the detection of Neospora caninum DNA. Int J Parasitol 1999; 29:1589-1596.
416. Spencer JA, Witherow AK, Blagburn BL. A random amplified polymorphic DNA polymerase chain reaction technique that differentiates between Neospora species. J Parasitol 2000; 86:1366-1368.
417. Stiles J, Prade R, Greene C. Detection of Toxoplasma gondii in feline and canine biological samples by use of the polymerase chain reaction. Am J Vet Res 1996; 57:264-267.
418. Reichel MP, Thornton RN, Morgan PL, et al. Neosporosis in a pup. N Z Vet J 1998; 46:106-110.
419. Greene CE, Cook JR Jr., Mahaffey EA. Clindamycin for treatment of Toxoplasma polymyositis in a dog. J Am Vet Med Assoc 1985; 187:631-634.
420. Dubey JP, Slife LN. Fatal encephalitis in a dog associated with an unidentified coccidian parasite. J Vet Diagn Invest 1990; 2:233-236.
421. Dubey JP, Speer CA. Sarcocystis canis n. sp. (Apicomplexa: Sarcocystidae), the etiologic agent of generalized coccidiosis in dogs. J Parasitol 1991; 77:522-527.
422. Trasti SL, Dubey JP, Webb DM, et al. Fatal visceral and neural sarcocystosis in dogs. J Comp Pathol 1999; 121:179-184.
423. Dubey JP, Hamir AN. Immunohistochemical confirmation of Sarcocystis neurona infections in raccoons, mink, cat, skunk, and pony. J Parasitol 2000; 86:1150-1152.
424. Haeber P, Blagburn B, Braund K, et al. Muscular sarcocystiasis in a domestic cat. In: Proceedings of the Southeastern Soc Parasitologists 1990.
425. Mathis A. Microsporidia: emerging advances in understanding the basic biology of these unique organisms. Int J Parasitol 2000; 30:795-804.
426. Wasson K, Peper RL. Mammalian microsporidiosis. Vet Pathol 2000; 37:113-128.
427. van Dellen AF, Botha WS, Boomker J, et al. Light and electron microscopical studies on canine encephalitozoonosis: cerebral vasculitis. Onderstepoort J Vet Res 1978; 45:165-186.
428. Shadduck JA, Bendele R, Robinson GT. Isolation of the causative organism of canine encephalitozoonosis. Vet Pathol 1978; 15:449-460.
429. Plowright W. An encephalitis-nephritis syndrome in the dog probably due to congenital encephalitozoon infection. J Comp Pathol 1952; 62:83-92.

430. Stewart CG, van Dellen AF, Botha WS. Canine encephalitozoonosis in kennels and the isolation of Encephalitozoon in tissue culture. J S Afr Vet Assoc 1979; 50:165-168.
431. Botha WS, van Dellen AF, Stewar, CG. Canine encephalitozoonosis in South Africa. J S Afr Vet Assoc 1979; 50:135-144.
432. Snowden K, Logan K, Didier ES. Encephalitozoon cuniculi strain III is a cause of encephalitozoonosis in both humans and dogs. J Infect Dis 1999; 180:2086-2088.
433. Szabo J, Pang V, Shadduck J. Encephalitozoonosis In: Greene C, ed. Infectious Diseases of the Dog and Cat. Philadelphia: WB Saunders Co, 1990; 786-791.
434. Didier J, Didier ES, Snowden K, et al. Encephalitozoonosis In: Greene C, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 465-470.
435. McInnes EF, Stewart CG. The pathology of subclinical infection of Encephalitozoon cuniculi in canine dams producing pups with overt encephalitozoonosis. J S Afr Vet Assoc 1991; 62:51-54.
436. Botha WS, Stewart CG, van Dellen AF. Observations on the pathology of experimental encephalitozoonosis in dogs. J S Afr Vet Assoc 1986; 57:17-24.
437. Szabo JR, Shadduck JA. Experimental encephalitozoonosis in neonatal dogs. Vet Pathol 1987; 24:99-108.
438. Stewart CG, Botha WS, van Dellen AF. The prevalence of Encephalitozoon antibodies in dogs and an evaluation of the indirect fluorescent antibody test. J S Afr Vet Assoc 1979; 50:169-172.
439. Stewart CG, Collett MG, Snyman H. The immune response in a dog to Encephalitozoon cuniculi infection. Onderstepoort J Vet Res 1986; 53:35-37.
440. Botha WS, Dormehl IC, Goosen DJ. Evaluation of kidney function in dogs suffering from canine encephalitozoonosis by standard clinical pathological and radiopharmaceutical techniques. J S Afr Vet Assoc 1986; 57:79-86.
441. Bjerkas I, Landsverk T. Identification of Toxoplasma gondii and Encephalitozoon cuniculi by immunoperoxidase techniques and electron microscopy, in stored, formalin-fixed, paraffin-embedded tissue. Acta Vet Scand 1986; 27:11-22.
442. Van Heerden J, Bainbridge N, Burroughs RE, et al. Distemper-like disease and encephalitozoonosis in wild dogs (Lycaon pictus). J Wildl Dis 1989; 25:70-75.
443. Berger SL, Palmer RH, Hodges CC, et al. Neurologic manifestations of trypanosomiasis in a dog. J Am Vet Med Assoc 1991; 198:132-134.
444. Barr S. Trypanosomiasis In: Greene C, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 445-450.
445. Barr SC, Van Beek O, Carlisle-Nowak MS, et al. Trypanosoma cruzi infection in Walker hounds from Virginia. Am J Vet Res 1995; 56:1037-1044.
446. Barr S, Baker D, Markovits J. Trypanosomiasis and laryngeal paralysis in a dog. J Am Vet Med Assoc 1986; 188:1307-1309.
447. Barr SC, Schmidt SP, Brown CC, et al. Pathologic features of dogs inoculated with North American Trypanosoma cruzi isolates. Am J Vet Res 1991; 52:2033-2039.
448. Barr SC, Dennis VA, Klei TR, et al. Antibody and lymphoblastogenic responses of dogs experimentally infected with Trypanosoma cruzi isolates from North American mammals. Vet Immunol Immunopathol 1991; 29:267-283.
449. Pittella JE, Meneguette C, Barbosa AJ, et al. Histopathological and immunohistochemical study of the brain in the acute and chronic phases of experimental trypanosomiasis cruzi in dogs. Ann Trop Med Parasitol 1990; 84:615-621.
450. Greene C. Acanthamebiasis In: Greene C, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 491-493.
451. Pearce JR, Powell HS, Chandler FW, et al. Amebic meningoencephalitis caused by Acanthamoeba castellani in a dog. J Am Vet Med Assoc 1985; 187:951-952.
452. Buergelt CD, Harrison LR, Bauer RW. Diagnostic exercise: pneumonia and CNS disturbances in young greyhound dogs. Lab Anim Sci 1991; 41:76-77.
453. Bauer RW, Harrison LR, Watson CW, et al. Isolation of Acanthamoeba sp. from a greyhound with pneumonia and granulomatous amebic encephalitis. J Vet Diagn Invest 1993; 5:386-391.
454. Taboada J, Merchant SR. Babesiosis of companion animals and man. Vet Clin North Am Small Anim Pract 1991; 21:103-123.
455. Taboada J. Babesiosis In: Greene C, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 473-481.
456. Jacobson LS, Lobetti RG, Vaughan-Scott T. Blood pressure changes in dogs with babesiosis. J S Afr Vet Assoc 2000; 71:14-20.
457. Schoeman T, Lobetti RG, Jacobson LS, et al. Feline babesiosis: signalment, clinical pathology and concurrent infections. J S Afr Vet Assoc 2001; 72:4-11.
458. Okoh AEJ. A case of cerebral babesiosis in the dog. Bull Anim Health Prod Afr 1978; 26:118-119.

459. Littman M. Clinical babesiosis in 26 dogs from Pennsylvania and New Jersey. In: Proceedings of the 9th Annu Meet Vet Med Forum, ACVIM 1991; 893.
460. Jacobson LS. Cerebellar ataxia as a possible complication of babesiosis in two dogs. J S Afr Vet Assoc 1994; 65:130-131.
461. Malherbe W. The manifestations and diagnosis of Babesia infections. Ann N Y Acad Sci 1956; 64:128-146.
462. Purchase H. Cerebral babesiosis in dogs. Vet Rec 1947; 59:269-270.
463. Jacobson LS, Clark IA. The pathophysiology of canine babesiosis: new approaches to an old puzzle. J S Afr Vet Assoc 1994; 65:134-145.
464. Jacobson LS, Lobetti RG. Rhabdomyolysis as a complication of canine babesiosis. J Small Anim Pract 1996; 37:286-291.
465. Harvey JW, Taboada J, Lewis JC. Babesiosis in a litter of pups. J Am Vet Med Assoc 1988; 192:1751-1752.
466. de Lahunta A. Veterinary Neuroanatomy and Clinical Neurology. 2nd ed. Philadelphia: WB Saunders Co, 1983; 384-385.
467. Cordy DR, Holliday TA. A necrotizing meningoencephalitis of pug dogs. Vet Pathol 1989; 26:191-194.
468. Kobayashi Y, Ochiai K, Umemura T, et al. Necrotizing meningoencephalitis in pug dogs in Japan. J Comp Pathol 1994; 110:129-136.
469. Bak EJ, Kim DY, Ki JH, et al. Necrotizing meningoencephalitis in a pug dog in Korea. [Korean]. Korean J Vet Res 1996; 36:441-445.
470. Hinrichs U, Tobias R, Baumgartner W. A case of necrotizing meningoencephalitis in a pug dog (pug dog encephalitis--PDE). Tierarztl Prax 1996; 24:489-492.
471. Bernardini M, Fatzer R, de Lorenzi, D. Case report of pug dog encephalitis. Veterinaria (Cremona) 1997; 11:131-132,135-136.
472. Beltran WA, Ollivet FF. Homonymous hemianopia in a pug with necrotising meningoencephalitis. J Small Anim Pract 2000; 41:161-164.
473. Kuwabara M, Tanaka S, Fujiwara K. Magnetic resonance imaging and histopathology of encephalitis in a Pug. J Vet Med Sci 1998; 60:1353-1355.
474. Bradley GA. Myocardial necrosis in a Pug dog with necrotizing meningoencephalitis. Vet Pathol 1991; 28:91-93.
475. Hasegawa T, Uchida K, Sugimoto M, et al. Long-term management of necrotizing meningoencephalitis in a pug dog. Canine Practice 2000; 25:20-22.
476. Koie H, Kurotobi EN, Sakai T. Double-chambered right ventricle in a dog. J Vet Med Sci 2000; 62:651-653.
477. Uchida K, Hasegawa T, Ikeda M, et al. Detection of an autoantibody from Pug dogs with necrotizing encephalitis (Pug dog encephalitis). Vet Pathol 1999; 36:301-307.
478. Stalis IH, Chadwick B, Dayrell-Hart B, et al. Necrotizing meningoencephalitis of Maltese dogs. Vet Pathol 1995; 32:230-235.
479. Cantile C, Chianini F, Arispici M, et al. Necrotizing meningoencephalitis associated with cortical hippocampal hamartia in a Pekingese dog. Vet Pathol 2001; 38:119-122.
480. Tipold A, Fatzer R, Jaggy A, et al. Necrotizing encephalitis in Yorkshire terriers. J Small Anim Pract 1993; 34:623-628.
481. Jull BA, Merryman JI, Thomas WB, et al. Necrotizing encephalitis in a Yorkshire Terrier. J Am Vet Med Assoc 1997; 211:1005-1007.
482. Robinson LE, Fishbein DB. Rabies. Semin Vet Med Surg (Small Anim) 1991; 6:203-211.
483. King AA, Turner GS. Rabies: a review. J Comp Pathol 1993; 108:1-39.
484. Kihm U, Flamand A, Pastoret PP, et al. Round table on epidemiology and control of fox rabies. Vet Microbiol 1992; 33:297-301.
485. Pastoret PP, Brochier B. Epidemiology and control of fox rabies in Europe. Vaccine 1999; 17:1750-1754.
486. Taylor D. Rabies: epizootic aspects. Vet Rec 1976; 99:157-160.
487. Fekadu M. Pathogenesis of rabies virus infection in dogs. Rev Infect Dis 1988; 10 Suppl 4:S678-683.
488. Eng TR, Fishbein DB. Epidemiologic factors, clinical findings, and vaccination status of rabies in cats and dogs in the United States in 1988. National Study Group on Rabies. J Am Vet Med Assoc 1990; 197:201-209.
489. McQuiston JH, Yager PA, Smith JS, et al. Epidemiologic characteristics of rabies virus variants in dogs and cats in the United States, 1999. J Am Vet Med Assoc 2001; 218:1939-1942.
490. Jackson AC. Rabies. Can J Neurol Sci 2000; 27:278-282.
491. Gillespie J, Timoney J. Rabies and other rhabdoviruses. In: Hagan W and Bruner D, eds. Infectious Diseases of Domestic Animals. 7th ed. Ithaca: Cornell University Press, 1981; 758-780.
492. Greene C, Dreesen D. Rabies. In: Greene CE, ed. Infectious Diseases of the Dog and Cat. Philadelphia: WB Saunders Co, 1990; 365-383.
493. Murphy FA, Bauer SP. Early street rabies virus infection in striated muscle and later progression to the central nervous

system. Intervirology 1974; 3:256-268.
494. Murphy FA, Bauer SP, Harrison AK, et al. Comparative pathogenesis of rabies and rabies-like viruses. Viral infection and transit from inoculation site to the central nervous system. Lab Invest 1973; 28:361-376.
495. Tsiang H, Koulakoff A, Bizzini B, et al. Neurotropism of rabies virus. An in vitro study. J Neuropathol Exp Neurol 1983; 42:439-452.
496. Murphy FA. Rabies pathogenesis. Arch Virol 1977; 54:279-297.
497. Fekadu M, Shaddock JH, Baer GM. Excretion of rabies virus in the saliva of dogs. J Infect Dis 1982; 145:715-719.
498. Cran HR. Some clinical observations on rabies. Vet Rec 1986; 118:23-24.
499. Johnson RT. Selective vulnerability of neural cells to viral infections. Brain 1980; 103:447-472.
500. Szlachta H, Habel R. Inclusions resembling Negri bodies in the brains of nonrabid cats. Cornell Vet 1953; 43:207-212.
501. Nietfeld JC, Rakich PM, Tyler DE, et al. Rabies-like inclusions in dogs. J Vet Diagn Invest 1989; 1:333-338.
502. Bestetti G, Rossi GL. The occurrence of cytoplasmic lamellar bodies in normal and pathologic conditions. Acta Neuropathol 1980; 49:75-78.
503. Minor R. Rabies in the dog. Vet Rec 1977; 101:516-520.
504. Whitfield SG, Fekadu M, Shaddock JH, et al. A comparative study of the fluorescent antibody test for rabies diagnosis in fresh and formalin-fixed brain tissue specimens. J Virol Methods 2001; 95:145-151.
505. Dietzschold B, Rupprecht CE, Tollis M, et al. Antigenic diversity of the glycoprotein and nucleocapsid proteins of rabies and rabies-related viruses: implications for epidemiology and control of rabies. Rev Infect Dis 1988; 10 Suppl 4:S785-798.
506. Wiktor TJ, Koprowski H. Antigenic variants of rabies virus. J Exp Med 1980; 152:99-112.
507. Wacharapluesadee S, Hemachudha T. Nucleic-acid sequence based amplification in the rapid diagnosis of rabies. Lancet 2001; 358:892-893.
508. Gupta PK, Singh RK, Sharma RN, et al. Preliminary report on a single-tube, non-interrupted reverse transcription-polymerase chain reaction for the detection of rabies virus in brain tissue. Vet Res Commun 2001; 25:239-247.
509. Pedersen NC, Emmons RW, Selcer R, et al. Rabies vaccine virus infection in three dogs. J Am Vet Med Assoc 1978; 172:1092-1096.
510. Esh JB, Cunningham JG, Wiktor TJ. Vaccine-induced rabies in four cats. J Am Vet Med Assoc 1982; 180:1336-1339.
511. Whetstone CA, Bunn TO, Emmons RW, et al. Use of monoclonal antibodies to confirm vaccine-induced rabies in ten dogs, two cats, and one fox. J Am Vet Med Assoc 1984;185:285-288.
512. Murphy FA, Bell JF, Bauer SP, et al. Experimental chronic rabies in the cat. Lab Invest 1980; 43:231-241.
513. Troy G, Vulgamott J, Turnwald G. Canine ehrlichiosis: a retrospective study of 30 naturally occurring cases. J Am Anim Hosp Assoc 1980; 16:181-187.
514. Greene CE, Burgdorfer W, Cavagnolo R, et al. Rocky Mountain spotted fever in dogs and its differentiation from canine ehrlichiosis. J Am Vet Med Assoc 1985; 186:465-472.
515. Neer M. Canine monocytic and granulocytic ehrlichiosis In: Greene CE, ed. Infectious Diseases of the Dog and Cat. Philadelphia: WB Saunders Co, 1998; 139-154.
516. Maretzki C, Fisher D, Greene CE. Granulocytic ehrlichiosis and meningitis in a dog. J Am Vet Med Assoc 1994; 205:1554-1556.
517. Panciera RJ, Ewing SA, Confer AW. Ocular histopathology of Ehrlichial infections in the dog. Vet Pathol 2001; 38:43-46.
518. Comer K. Rocky Mountain Spotted Fever. Vet Clin North Am Small Anim Pract 1991; 21:27-44.
519. Meinkoth J, Hoover J, Cowell R, et al. Ehrlichiosis in a dog with seizures and nonregenerative anemia. J Am Vet Med Assoc 1989; 195:1754-1755.
520. Davidson MG, Breitschwerdt EB, Nasisse MP, et al. Ocular manifestations of Rocky Mountain spotted fever in dogs. J Am Vet Med Assoc 1989; 194:777-781.
521. Buoro IBJ, Kanui TI, Atwell RB, et al. Polymyositis associated with Ehrlichia canis infection in two dogs. J Small Anim Pract 1990; 31:624-627.
522. Davidson MG, Breitschwerdt EB, Walker DH, et al. Vascular permeability and coagulation during Rickettsia rickettsii infection in dogs. Am J Vet Res 1990; 51:165-170.
523. Gasser AM, Birkenheuer AJ, Breitschwerdt EB. Canine Rocky Mountain Spotted fever: a retrospective study of 30 cases. J Am Anim Hosp Assoc 2001; 37:41-48.
524. Greene CE, Breitschwerdt EB. Rocky Mountain spotted fever, Q fever, and typhus In: Greene CE, ed. Infectious diseases of the dog and cat. 2nd ed. Philadelphia: WB Saunders Co, 1998; 155-165.
525. Grindem CB, Breitschwerdt EB, Perkins PC, et al. Platelet-associated immunoglobulin (antiplatelet antibody) in canine Rocky Mountain spotted fever and ehrlichiosis. J Am Anim Hosp Assoc 1999; 35:56-61.
526. Breitschwerdt EB, Davidson MG, Aucoin DP, et al. Efficacy of chloramphenicol, enrofloxacin, and tetracycline for

treatment of experimental Rocky Mountain spotted fever in dogs. Antimicrob Agents Chemother 1991; 35:2375-2381.
527. Greig B, Asanovich KM, Armstrong PJ, et al. Geographic, clinical, serologic, and molecular evidence of granulocytic ehrlichiosis, a likely zoonotic disease, in Minnesota and Wisconsin dogs. J Clin Microbiol 1996; 34:44-48.
528. Gorham JR, Foreyt W. Salmon poisoning disease In: Greene CE, ed. Infectious diseases of the dog and cat. Philadelphia: WB Saunders, 1998; 135-139.
529. Saito T, Alfieri A, Alfieri A, et al. Detection of canine distemper virus by RT-PCR in serum, leukocytes, cerebro-spinal fluid (CSF), and urine in dogs with distemper encephalitis. J Vet Intern Med 2001; 15:315.
530. Ryder S. The pathology of feline spongiform encephalopathy. In: Proceedings of the 14th Annu Symposium, ECVN 2000; 20.
531. Berthelin-Baker C, Ryder S, Cappello R, et al. Feline spongiform encephalopathy and prion diseases in domestic and zoo cats: a review of reported clinical signs and video presentation. In: Proceedings of the 14th Annu Symposium, ECVN 2000; 18-19.
532. McDonnell JJ, Carmichael KP, Bienzle D. Is there a myelopathy associated with feline leukemia virus? J Vet Int Med 2001; 15:290.
533. Amyx HL, Gibbs CJ, Gajdusek, DC. Experimental Creutzfeldt-Jakob disease in cats. In: Court L, Cathala F, eds. Unconventional viruses and the central nervous system. Paris: Mason, 1983; 358-362.
534. Kerwin SC, McCarthy RJ, VanSteenhouse JL, et al. Cervical spinal cord compression caused by cryptococcosis in a dog: successful treatment with surgery and fluconazole. J Am Anim Hosp Assoc 1998; 34:523-526.
535. Barber JS, Trees AJ. Clinical aspects of 27 cases of neosporosis in dogs. Vet Rec 1996; 139:439-443.
536. de Lahunta A. Veterinary Neuroanatomy and Clinical Neurology. 2nd ed. Philadelphia: WB Saunders Co, 1983; 150-151.
537. Farrow BR. Generalized tremor syndrome. In: Kirk RW, ed. Current Veterinary Therapy IX. Philadelphia: WB Saunders Co, 1986; 800-801.
538. Parker AJ. How do I treat "Little white shakers"? Prog Vet Neurol 1991; 2:151.
539. Bagley RS, Kornegay JN, Wheeler SJ, et al. Generalized tremors in Maltese: clinical findings in seven cases. J Am Anim Hosp Assoc 1993; 29:141-145.
540. Wagner SO, Podell M, Fenner WR. Generalized tremors in dogs: 24 cases (1984-1995). J Am Vet Med Assoc 1997; 211:731-735.
541. Summers B, Cummings J, de Lahunta A. Veterinary Neuropathology. St Louis: Mosby, 1995; 250-280.