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Neuropathic Disorders (6-Feb-2003)

K. G. Braund

Veterinary Neurological Consulting Services, Dadeville, Alabama, USA.

Neuropathic Disorders

The peripheral nervous system (PNS) comprises the cranial nerves, spinal nerve roots, dorsal root ganglia, the peripheral nerve trunks (motor and sensory nerves), the terminal branchings of motor nerves as they innervate skeletal muscle, and the peripheral autonomic system [1]. Disorders of the parent cell bodies located in the spinal cord (and/or brainstem) are discussed under motor neuron diseases. In people, dorsal root ganglion degenerations are described as sensory neuropathies, while in animals such disorders are sometimes called ganglionopathies or sensory neuronopathies. In the chapter on Localization, I have arbitrarily classified small animal neuropathies into hereditary/degenerative and developmental disorders, and acquired toxic, traumatic, metabolic, inflammatory/infectious, neoplastic/paraneoplastic, and vascular disorders (see neuropathic syndrome). Peripheral nerve disorders are common and usually well-recognized in dogs and cats, although in some instances problems may arise in distinguishing neuropathies from diffuse muscle disease, certain CNS disorders, or skeletal problems. In general, most acquired neuropathies are seen in both dogs and cats, although hereditary disorders are more commonly reported in dogs. Both sophisticated electrodiagnostic testing and qualitative/quantitative pathological studies have further defined peripheral nerve disease in small animals. Despite these advances, the etiology of many neuropathies in dogs and cats continues to be uncertain, in contrast with the situation in people, in whom approximately 10 to 15% of neuropathies remain cryptogenic [2].

The following neuropathic disorders will be described in this chapter and have been listed alphabetically:

Abbreviations -
ADH (adrenal-dependent hyperadrenocorticism); ATPase (myofibrillar adenosine triphosphatase); BAER (brainstem auditory evoked response); CK (creatine kinase); CMAP (compound muscle action potential); CSF (cerebrospinal fluid); CNS (central nervous system); CT (computed tomography); EDX (electrodiagnostic); EMG (electromyography); HAC (hyperadrenocorticism); HSMN (hereditary sensory and motor neuropathy); MRI (magnetic resonance imaging); NADH-TR (reduced nicotinamide adenine dinucleotide tetrazolium reductase); NCV (nerve conduction velocity); PAS (periodic acid-Schiff); PDH (pituitary-dependent hyperadrenocorticism); PNS (peripheral nervous system); SSN (subacute sensory neuropathy)

Alaskan Malamute Polyneuropathy
A progressive polyneuropathy has been reported in young mature Alaskan Malamutes [3]. Male and female dogs were affected and the mean age of onset of clinical signs was 14.6 $\pm$ 3.1 months (range 10 to 18 months). Clinical signs included progressive paraparesis slowly progressing to thoracic limb weakness, incoordination with stumbling or toe-dragging, synchronous pelvic limb gait when running, exercise intolerance and collapse, inability to walk up stairs, inability to jump, difficulty standing, paraspinal (especially lumbar) or appendicular hyperesthesia, hyporeflexia, muscle atrophy (especially in distal limb muscles), proprioceptive deficits, and, in some cases, tetraplegia. A hoarse bark and /or inspiratory stridor were noted in 2 dogs. Electromyographic (EDX) testing revealed diffuse fibrillation potentials and positive sharp waves in limb muscles, especially in muscles below the elbow and stifle. Motor nerve conduction velocities were either normal or low-normal (50 to 60 m/sec) or slow (28 to 47 m/sec). Sensory NCV was normal in one dog tested. No decremental response to repetitive nerve stimulation was seen in one dog tested. Results of routine hematologic and blood biochemical analyses and thyrotropin response testing, blood lead concentration, serum cholinesterase activity, and immunologic function were normal. Ophthalmoscopy, spinal radiography, urinalysis, edrophonium testing were negative. Pathological findings in skeletal muscles included neurogenic muscle atrophy characterized by fiber size variation with atrophic/hypertrophic fibers, more frequent type 2 angular fiber atrophy, and fiber type grouping, without evidence of inflammation or antimuscle antibodies. In peripheral nerves, microscopic changes included focal or diffuse loss of myelinated nerve fibres, myelinoaxonal necrosis, increased endoneurial fibrosis, occasional infiltrating macrophages, and variable demyelination or remyelination. Axonal degeneration and nerve fiber loss were more prominent in distal parts of the nerves. Axonal degeneration was also noted in the sensory saphenous nerve. Ultrastructural changes included loss of myelinated fibers, axonal degeneration, presence of numerous Büngner bands, denervated Schwann cell subunits, collagen pockets, and occasional regenerating clusters. No onion-bulb formation was seen. Myelin debris, membranous bodies, and prominent organelles, especially mitochondria were observed in axons and Schwann cell cytoplasm. Macrophages were occasionally seen within Schwann cell cytoplasm of myelinated fibers containing degenerating axons. Some axons had a watery appearance with apparent loss of normal cytoskeletal components. There was no evidence of axonal neurofilamentous accumulation or tubovesicular aggregates. The nature and distribution of abnormal electrophysiological and pathological findings were suggestive of a distal sensorimotor polyneuropathy. Prognosis is guarded to poor since the disorder appears to be progressive in most dogs. Response to corticosteroids and azathioprine have been unsatisfactory. However, less clinically affected dogs may have a favorable prognosis and lead a reasonably normal life style (several dogs that we have followed are alive at 8 years of age). The cause of this condition remains obscure, although recessive inheritance is suspected. In a recent report from Germany, EDX and histopathological abnormalities were detected in clinically normal relatives of affected dogs [4]. Interestingly, abnormal vocalization was also noted in some affected dogs. Note that the signalment, age of onset, and clinical course of this disease are similar to those reported in Norwegian Alaskan Malamutes, a hereditary (autosomal recessive) polyneuropathy that was believed to have been eradicated in Norway in 1982 [5,6]. The Norwegian dogs had evidence of coughing, regurgitation, and megaesophagus, proximal and distal abnormalities on electrodiagnostic testing, atrophy of laryngeal muscles, primarily demyelinative changes in nerves at all levels (Dr. L. Moe, personal communication, 1997), and a guarded to favorable prognosis, often with clinical recurrences. It seems likely that these two conditions are manifestations of the same disorder, although we had initially suggested the term "idiopathic polyneuropathy of Alaskan Malamutes" to distinguish the present condition from the hereditary neuropathy of the Norwegian dogs [3]. Future studies should help clarify if these neuropathies are different expressions of the same disorder.

Birman Cat Distal Polyneuropathy
A degenerative polyneuropathy has recently been reported in several litters of Birman cats bred from the same parents. A recessive mode of inheritance is suspected [7]. Pathologically, the central nervous system (CNS) lesions were most prominent in the lateral pyramidal tracts of the lumbar spinal cord, the fasciculi gracili of the dorsal column in the cervical spinal cord, and the cerebellar vermian white matter. Lesions were characterized by diffuse loss of myelinated fibers and fibrillary astrocytosis. Inflammatory changes were not seen. Neurons of the cerebral cortex, cerebellum, and brainstem were normal. In the PNS, numerous degenerating nerve fibers were observed in the sciatic nerves but not in the spinal nerve

roots. No changes were found in the cauda equina, dorsal root ganglia, or ventral horn cells. Ultrastructurally, degenerating ovoids consisting of myelin debris and disrupted axons were frequently observed. Selective involvement of distal portions of the CNS and PNS suggested that this disorder is a distal central-peripheral axonopathy (dying-back disease). Clinical signs were first noted in cats 8 to 10 weeks of age. Affected cats fell frequently and had a tendency to stand and walk on their hocks which were held in an adducted fashion. The gait was characterized by slight hypermetria in all limbs and there was progressive pelvic limb ataxia. Analysis of blood and CSF was normal. Nerve conduction velocity studies were normal; however, EMG revealed presence of fibrillation potentials and positive sharp waves in pelvic limbs. Prognosis is poor. Presently, there is no treatment. Future breeding trials should confirm that this condition is caused by a genetic defect and help characterize the exact mode of inheritance.

Brachial Plexus Avulsion

The brachial plexus consists of the large nerve plexus which gives rise to the nerves which supply the thoracic limb. It is formed by the ventral branches of the 6th, 7th and 8th cervical and the 1st and 2nd thoracic spinal nerves [8-11]. Traumatic injury to the brachial plexus is often encountered clinically in animals, especially dogs, in which there is traction of the thoracic limb or severe abduction of the scapula. Typically, it is the nerve roots, not the plexus itself, that bear the brunt of traumatic avulsive injury because of the lower resistance of nerve roots to stretch (due to lack of a perineurium). The ventral roots are more susceptible to traumatic stretch than the dorsal roots. Avulsion is usually intradural and the lesion in dogs is diffuse rather than circumscribed with involvement of fibers at many different levels [12,13].

Degenerative changes in dorsal and ventral nerve roots and ventral branches of spinal nerves are characterized by axonal necrosis, myelin fragmentation, and loss of myelinated fibers. Many fibers are damaged where they penetrate the leptomeninges, resulting in neuroma formation. Retrograde changes are observed in the ventral horn cells, characterized by chromatolysis, cell swelling and neuronal depletion. Retraction balls may be seen. Dorsal column degeneration occurs only with lesions central to the dorsal root ganglion.

Clinical signs reflect the distribution of damage to nerve roots, branches, and plexal cords rather than direct peripheral nerve involvement. Signs may vary from weakness of single muscle groups, without sensory loss, to paralysis of all thoracic limb muscle groups with accompanying sensory loss (e.g., with a lesion from C6 to T1 - 2). A lesion that involves spinal cord segments C8 - T1 may produce ipsilateral loss of the panniculus reflex; while involvement of the T1 - 3 roots, which contains preganglionic sympathetic fibers, frequently results in partial Horner's syndrome (characterized by anisocoria). Patterns of cutaneous anesthesia associated with brachial plexus avulsions have been described in the dog [14]. Conscious pain presentation is usually impaired to a variable degree in all dogs with brachial plexus avulsion. In general, desensitized areas of skin may be detected on lateral, medial, dorsal, and palmar surfaces of the affected thoracic limb. Brachial plexus avulsion may be confused with radial paralysis since the clinical signs of avulsion are predominantly those of radial nerve paralysis at the level of the shoulder [15]. Table 1 outlines some differentiating features between these conditions.

Table 1. Radial Nerve Paralysis Versus Brachial Plexus Avulsion.

	Radial Nerve (C6 - T2)	**Brachial Plexus** (C6 - T2)
Level of injury	Radial nerve	Brachial plexus
Muscle atrophy	Triceps, carpal extensors	Any forelimb muscle
Sensory loss (skin)	Craniolateral forearm, dorsal paw	Any forelimb skin zone
Panniculus reflex	Present	± absent ipsilaterally
Horner's syndrome	No	± yes (often partial if present)

Modified from Braund KG. Clinical syndromes in veterinary neurology. St. Louis: Mosby, 1994 [16].

Diagnosis is most commonly based on historical and clinical data [17]. Electrodiagnostic (EDX) testing is useful for detecting muscle denervation, especially minor degrees which cannot be uncovered by routine neurological examination. This information may be helpful in those cases where muscle-tendon transposition is being considered for surgical management. Myelography may occasionally demonstrate a contrast-outlined diverticulum at the level of the cervicothoracic junction. More recent studies suggest a diagnostic and prognostic role for CT-myelography [18]. It has been

reported that exploration of the brachial plexus is not productive since the extent of the lesion cannot be determined at that level [19]. In general, the prognosis is guarded to poor. EDX testing will detect early changes in reinnervation and recovery. Some fibers, following acute injury, may show a temporary conduction block, from which they will recover within a few days. Since the roots of the radial nerve are commonly injured in brachial plexus avulsion, an electrodiagnostic evaluation of the radial nerve may provide early prognostic information: prognosis being poor in animals with initial, decreased radial nerve conduction velocity [19,509]. If this situation remains unchanged after 4 weeks, with concurrent severe EMG changes in the triceps muscle, there is virtually no chance of spontaneous recovery. In a recent study of prognostic factors in dogs with brachial plexus avulsion, the best predictor of complete recovery was pain perception, with 5 of 7 dogs with normal sensation recovering completely [509]. Muscle tendon transpositions have been successful in some dogs with partial avulsion. Carpal fusion may be useful in animals with adequate triceps muscle function that have a tendency to knuckle over on their paws [20]. Amputation of the affected limb may be necessary if the limb is severely excoriated from dragging or self-mutilation. Experimental studies in dogs suggest that ventral root reimplantation can successfully promote reinnervation [21,22]. Successful bypass coaptation procedures for cervical nerve root avulsion have been reported in people [23].

Brachial Plexus Neuropathy-Neuritis

This is a rare, bilaterally symmetrical, neurological condition reported in dogs and cats that involves the nerves of the brachial plexus [24,25]. It has been suggested that this canine disorder may be the result of an allergic or hypersensitivity reaction similar to serum neuritis in man following prophylactic inoculations such as tetanus antiserum. The proposed pathogenesis is that the allergic condition produces spinal nerve swelling and subsequent compression at the level of the intervertebral foramina. In people, acute brachial plexus neuritis is an uncommon disorder characterized by severe shoulder and upper arm pain followed by marked upper arm weakness [26]. At least some forms are considered to represent an immuno-allergic mechanism [27,28]. Brachial plexus neuritis has also been recently reported in a man associated with herpes zoster [29].

Clinical signs described in a 9 month old Great Dane were characterized by acute onset of thoracic limb paresis with depressed or absent reflexes and hypotonia, facial paresis and neurogenic atrophy in all thoracic limb muscles. Pain perception appeared diminished over antebrachial regions. EMG studies revealed denervation potentials and absence of evoked muscle action potentials in the thoracic limbs. CSF evaluation was normal. Axonal degeneration was observed in a biopsy of a sensory branch of the radial nerve. This dog manifested two allergic episodes with facial edema and generalized urticaria over a 48 hour period prior to development of neurological signs. Immunological testing indicated that these signs were related to an all horse-meat diet. Three weeks prior to onset of signs the dog had been vaccinated with modified-live rabies virus. No improvement was noted in this dog 49 days after onset of clinical signs even with glucocorticoid therapy. Pathological findings include severe, asymmetrical axonal and myelin degeneration (characteristic of Wallerian degeneration) of peripheral nerves of the brachial plexus. The changes were most severe in the proximal ventral roots where there was axonal loss, variable axonal regenerating clusters, increased endoneurial fibrosis, many lipid-containing macrophages, and many endoneurial mast cells. Retrograde chromatolytic lesions were seen in the ventral horns cells of the cervical intumescence as well as in dorsal root ganglion cells. In a 1.5 year old Doberman Pinscher with brachial plexus neuropathy characterized by axonal degeneration, slight improvement was reported 4 months after signs first developed. No treatment was given. A milder form of brachial plexus neuropathy has been reported in several dogs presented with shifting thoracic limb lameness and diffuse EMG changes typical of denervation [20]. Myelography and CSF analysis were normal. Some of these dogs were steroid-responsive, while others clinically improved when fed poultry-based diets that contained no beef or horse products.

Brachial plexus neuropathy has been reported in a cat with clinical signs similar to those in the dog [30]. Reflexes in thoracic limbs were depressed and nerve conduction velocity was markedly reduced in the median nerve; however, EMG studies in thoracic limbs were normal. The cat recovered spontaneously over a three-week period. The neuropathy was thought to be causally related to vaccination with modified live rabies virus.

Congenital Hypomyelination Neuropathy

In contrast with CNS hypomyelination, hypomyelination of the peripheral nerves is rare, but has been reported in two Golden Retriever littermates [31,32]. Both dogs were presented for pelvic limb ataxia at 7 week of age. Both had a crouched stance, mild pelvic limb atrophy, and weakness. Circumduction was evident in pelvic limbs when walking, and a bunny hop gait was present when running. Segmental spinal reflexes were depressed or absent in all limbs. Motor nerve conduction velocities were markedly reduced in sciatic-tibial and ulnar nerves. Needle EMG studies were normal except for rare denervation potentials in a few muscle groups. Teased nerve fibers were difficult to see because of lightness of myelin staining. Light and electron microscopic findings included reduced number of myelinated axons, presence of myelinated sheaths inappropriately thin for the calibre of the fiber, poor myelin compaction, increased numbers of Schwann cell nuclei, increased concentration of neurofilaments in myelinated axons, many Schwann cells with voluminous cytoplasm, and

increased perineurial collagen. Onion bulb formation was not seen and there was no evidence of demyelination. In contrast to controls, a poor correlation was seen between numbers of myelin lamellae (ML) and axonal circumference (AC). The frequency distribution of ML ranged from 5 to 55 lamellae in affected animals (mean, 28 lamellae) compared to 20 to 140 lamellae in controls (mean, 66 lamellae). The ML/AC ratio was reduced in nerves of affected dogs. Morphometric results indicated that fibres of all calibres were hypomyelinated. Axons appeared normal. Possible Schwann cell defect or abnormal axon-Schwann cell signaling were suggested to account for the hypomyelination [31]. The defect appears to be reversible since both dogs clinically improved. Repeat nerve biopsies around 2 years of age showed that myelination had increased, although it was still less than normal. Motor nerve conduction velocity studies also showed improvement, but were only about half normal values. Both affected dogs were able to live a normal life span.

The condition appears similar to the rare congenital hypomyelination neuropathy (CHN) in children [33]. CNN is a member of a heterogeneous group of hereditary demyelinating/dysmyelinating peripheral neuropathies that includes hereditary neuropathy with liability to pressure palsies (HNPP), Charcot - Marie - Tooth disease (CMT), and Dejerine-Sottas syndrome (DSS), all of which may represent a spectrum of related "myelinopathies" due to an underlying defect in myelination [34]. Some forms of CHN are associated with missense point mutations of PMP22 (peripheral myelin protein 22) leading to possible disruption of Schwann cell growth and differentiation [35,36]. CHN has also been identified in people with a mutation in the gene for protein zero (P0) [37].

Note that hypomyelination may also occur in various storage disorders. Using ultrastructural morphometric studies of G-ratios, we have recently identified universal hypomyelination in cats with alpha-mannosidosis [38] and in dogs with globoid leukodystrophy [39].

Dancing Doberman Disease

Dancing Doberman disease (DDD) is a term given to a chronic, slowly progressive, neuromuscular disease that, to date, has only been described in Doberman Pinschers [40,41]. Recent studies suggest the condition is inherited as an autosomal recessive trait (Dr. Janet Steiss, Tuskegee University, unpublished data, 2002). DDD was originally regarded as being either a behavioral disorder or a sensory neuropathy [40], and later as a possible distal polyneuropathy [42]. Dogs of either gender, from 6 months to 7 years of age, initially manifest flexion of one pelvic limb when standing. Similar signs may be noted in the opposite pelvic limb several months later, and affected dogs begin to alternately flex and extend each pelvic limb in a dancing motion and prefer to sit rather than stand. The condition progresses insidiously over several years. There is apparent pelvic limb weakness, proprioceptive deficits, and gradual atrophy of pelvic limb musculature, especially the gastrocnemius muscles. Pelvic reflexes are normal or hyperactive. Affected dogs do not appear to be in pain based on subjective examination, including manipulation or palpation of the affected limb(s) or spine. Mild numbers of positive sharp waves and fibrillation potentials have been detected on EMG testing in some animals, primarily involving the gastrocnemius muscle(s). Bizarre high frequency discharges may develop after several years. Sensory and motor nerve conduction velocities are normal. Results of hematology, blood chemistries, serum creatine kinase levels, thyroid function testing, CSF analysis, and joint fluid examinations are within normal limits. Histopathologic changes in most muscles are minimal. However, changes are seen in the gastrocnemius muscle(s) including multifocal atrophy and hypertrophy, numerous fibers with internal nuclei, focal necrosis, endomysial/perimysial fibrosis, and sometimes, histochemical fiber type grouping. These changes resemble findings seen in adult canine myotonic myopathy. Reported nerve changes in older dogs are variable, but including demyelination and remyelination, and occasional axonal necrosis [41]. In samples from one 9 year old Doberman examined in my laboratory, the nature and incidence of neurogenic changes in several peripheral nerves and nerve roots were similar between left and right pelvic limbs and between proximal and distal samples, thus ruling against a distal neuropathy in this case. The incidence of changes was considered to be higher than those associated with normal aging. In another nerve biopsy examined in our laboratory from a 1 year old Doberman with clinical signs of Dancing Doberman disease, severe degenerative changes were seen that were dominated by axonal necrosis. In a recent study of DDD conducted at Scott-Ritchey Research Center, Auburn University College of Veterinary Medicine (Dr. Janet Steiss, Tuskegee University, unpublished data), degenerative changes were found in mixed, sensory, and sympathetic nerves suggesting either a sensorimotor autonomic neuropathy or possibly a sensory autonomic neuropathy. In this study, ultrastructural changes included myelinoaxonal necrosis and scattered presence of denervated Schwann cells involving myelinated and unmyelinated fibers. The proprioceptive deficits and mild or absent EMG changes in most muscles (with the exception of the gastrocnemius muscle) might suggest that DDD is a sensory neuropathy, with similarities to the rare hereditary sensory and autonomic neuropathies in humans (HSAN) [43]. In these conditions, there is selective involvement of the peripheral sensory and autonomic neurons, with axonal degeneration. The symptoms are related to which population of neurons is affected. In some types of HSAN, patients are afflicted with the abnormal sensation of burning soles or other forms of dysesthesia. Similar discomfort associated with pressure on the feet could account for the constant lifting of the feet in dogs with DDD. The changes in the gastrocnemius muscles from DDD dogs remain enigmatic and do not appear to be neurogenic, although there are instances in which myopathic-appearing lesions (e.g., rounded atrophic/hypertrophic with

central nuclei, fiber splitting, increased endomysial fibrosis, whorled, and fiber degeneration/regeneration) occur in primary neuropathies, e.g., Charcot - Marie - Tooth disease type 2, a form of hereditary sensory and motor neuropathy in people [44]. Perhaps the muscle changes reflect some form of reflex sympathetic dystrophy, a syndrome characterized by a triad of autonomic, motor, and sensory symptoms associated with abnormally increased sympathetic tone [45]. The presence of abnormal thermographic patterns seen in some affected dogs might be compatible with an imbalance between activity of sympathetic vascoconstrictor nerves supplying arteries and those supplying veins, potentially leading to muscle necrosis/atrophy [46]. Further studies should help clarify this confusing disorder.
At present, there is no treatment. Therapeutic trials using diazepam and primidone have not been effective. The long-term prognosis for a pain-free, acceptable pet is good [41]. To date, there have been no reports of spontaneous clinical improvement or resolution of signs in any affected dogs.

Deafness
Deafness or hearing loss may be conductive, sensorineural, or central. In animals, as in humans, the most common type of deafness is sensorineural hearing loss associated with a lesion in the cochlear or eighth cranial nerve (see below).
Conductive deafness stems from problems within the external or middle ear cavities so that sound is not conducted into the inner ear. The most common cause of conductive deafness is chronic otitis externa-media, sometimes in association with cholesteatomas [47]. Other causes include external ear canal occlusion or ablation, atresia of the external acoustic meatus, rigidity or rupture of the tympanic membrane, damage to the ossicular chain (stapes, malleus and incus), or fluid within the middle ear [48,49]. Congenital palatine defects in dogs and cats may predispose to middle ear disease and hearing loss [50]. Conduction deafness has been noted in Scottish fold osteodystrophy [51]. Central hearing loss resulting from damage to CNS auditory pathways is rare in people and in animals. Central deafness has been noted in Labrador retrievers with spongy degeneration of the CNS [52]. In one study of deaf Dalmatian puppies, morphological abnormalities were found in the temporal lobes, medial geniculate bodies, acoustic tracts of the tectal surface, caudal colliculi, pons, medulla oblongata and trapezoid bodies, indicative of retarded development of the CNS (with a 40% reduction in the area of the acoustic cortex) [53].
Sensorineural deafness resulting from cochlear abnormalities may be congenital or hereditary, acquired due to ototoxic drugs or inflammatory diseases, or associated with normal aging.
Congenital sensorineural deafness is usually present from birth, or within a few weeks post-natally, and it is permanent. Some animals are affected unilaterally. The etiology of congenital deafness is unclear. Maternal exposure to ototoxic drugs, such as streptomycin, or viral infection has been suggested as a cause in some instances of congenital deafness [54]; however, the incidence of deafness from these causes is considered to be low [55]. Autosomal recessive disorders have been reported in Bull Terriers [56], Doberman Pinschers [57], and in colony Pointers selectively bred for excessive nervous behavior [58], and have been cited for Rottweilers and Pointers [55]. Congenital deafness is frequently associated with pigmentation disorders such as a white coat color and blue eyes [55,59-62]. Coat color abnormalities have been linked with the "merle" color gene. In heterozygotes, this dominant gene will increase the amount of white in the animal's coat, cause dappling in the pigmented portions of the coat, and also alter the pigment in the tapetum and iris. In the homozygous state the gene commonly produces a nearly all white animal that is deaf and blind. Congenital/hereditary deafness is frequently seen in blue-eyed white cats (transmitted as an autosomal dominant trait), Dalmatians, Australian Heelers, English Setters, Catahoulas, and Australian Shepherds. The Dalmatian reportedly has the highest prevalence of deafness of all canine breeds, with an overall incidence from 15 to 30% [54,63-65]. The condition in Dalmatians is consistent with an autosomal recessive, multifactorial gene with incomplete penetrance [66]. The deafness may be unilateral (most common) or bilateral. In a recent study involving > 3000 Dalmatians, an increased prevalence of deafness was found in females, especially in those with two blue eyes [67]. In this study, there was no difference in the prevalence of hearing loss between offspring of deaf mothers and the offspring of deaf sires.
Congenital deafness has been noted in numerous canine breeds (Old English Sheepdogs, Norwegian Dunkerhound, dappled Dachshund, Harlequin Great Dane, Shetland Sheepdog, Samoyed, Great Pyrenees, Sealyham Terrier, Greyhound, Beagle, Maltese Terrier, Bulldog, Boxer, Akita, American Staffordshire Terrier, Fox Terrier, Miniature Poodle, Papillon, Ibizan Hound, Kuvasz, Saint Bernard, Rhodesian Ridgeback, Scottish Terrier, West Highland White Terriers, Cocker Spaniels, Border Collies, Scotch Collies, Boston Terriers, Walker American Foxhounds, and Shropshire Terriers [55,68], but the mode of inheritance remains to be defined.
In animals with congenital deafness, pathological findings consist of total or partial agenesis of the organ of Corti, the spiral ganglion, and the cochlear nuclei [69-72]. Additionally, in congenitally deaf Collie and Dalmatian puppies, partial collapse of the saccule, atrophy of the saccular nerve and obliteration of the cochlear duct have been described [73]. Some forms of hereditary deafness are thought to be associated with cochleosaccular degeneration in which the stria vascularis is atrophic due to absence of normal pigment cells [55,72]. This leads to secondary degeneration of the organ of Corti, and collapse of the saccule. In a study of congenital deafness and vestibular disease in young Doberman Pinscher puppies, histopathologic

studies revealed that all affected puppies had a non-inflammatory neuroepithelial degeneration of the cochlea with a progressive loss of the auditory sensory hair cells, resulting in almost complete loss of the organ of Corti by 11 weeks of age [57].

Acquired sensorineural deafness can result from various ototoxic agents [74,75]:

1. Aminoglycoside antibiotics are the most common ototoxic drugs. These drugs concentrate in perilymph and endolymph, thus exposing the cochlear hair cells to high concentrations of the drugs (note that cochlear hair cell activity is dependent on endolymph fluid production by the stria vascularis). While all aminoglycoside antibiotics can damage auditory and vestibular receptors, streptomycin and gentomycin have their greatest effects on the vestibular system, whereas, neomycin, kanamycin, tobramycin, and amikacin sulfate produce more damage to the auditory peripheral receptors. The toxic effects of these drugs is believed to be heightened if the tympanic membrane is perforated. Experimental studies suggest enhanced ototoxicity with nutritional deficiency [76].
2. Other ototoxic antibiotics - topical polymixin B and chloramphenicol.
3. Antiseptic solutions - ethanol, iodine, iodophors, chlorhexidine, benzalkonium chloride, benzethonium chloride, and cetrimide. Chlorhexidine combined with cetrimide is especially toxic in dogs and cats. Interestingly, the use of 0.2% chlorhexidine acetate is reportedly safe when instilled into the external ear canals of normal dogs for a period of 3 weeks (and no signs of ototoxicity occurred in dogs with surgically perforated tympanic membranes) [77].
4. Diuretics - ethacrynic acid, bumetanide, and furosemide. These agents induce changes in the stria vascularis of the cochlear.
5. Antineoplastic agents - cisplastin, which acts on the hair cells in similar fashion to the aminoglycoside antibiotics.
6. Miscellaneous agents used in otic preparation - propylene glycol, ceruminolytic agents and detergents, especially if the tympanic membrane is ruptured.
7. Overdosage with closantel, a salicylanilide derivative, produced a reversible hearing loss in a dog [78].

Neuroepithelial degeneration, in which the organ of Corti is primarily affected, reportedly occurs mainly with acquired deafness [55]. Acquired sensorineural deafness occurred in a 3 year old Collie dog with disseminated protothecosis, in which *Prototheca* organisms disrupted the tectorial membrane and destroyed the organ of Corti [79]. Other causes of acquired sensorineural hearing loss in people include toxin exposure (e.g., high dose aspirin), Ménière's disease (paroxysmal symptoms of tinnitus, fluctuating hearing, monaural fullness, and episodic vertigo), and noise [80].
Normal Aging - Hearing impairment is also commonly noted in dogs with normal aging. The loss of ability to perceive or discriminate sounds associated with aging in people is termed "presbyacusis". In one study, hearing loss in older dogs was associated with atrophy and loss of spiral ganglion neurons of the cochlea [81]. This loss of neurons and nerve fibers in the osseous spiral lamina was thought to be secondary to loss of hair cells and supporting cells in the organ of Corti. Similar changes have been previously reported in a 20 year old dog and in a 19 year old cat with progressive hearing loss [82].
While hearing is very difficult to assess accurately using response to sounds such as clapping, electrodiagnostic testing using the brainstem auditory evoked response (BAER) method (also known as auditory brainstem response) can provide early diagnosis of deafness, allowing breeders and owners to avoid propagating further affected litters [64,83-85]. The BAER is the only reliable method of identifying animals with unilateral hearing loss [86]. Bone conduction thresholds, using a bone vibrator against the head (e.g., mastoid process, mandible or zygomatic arch), can also be used to confirm conductive hearing impairment in the dog in the same way as in humans [87,88]. The ear canals open between 12 and 14 days in dogs and at 5 days after birth in cats. Mature hearing patterns are established by 30 to 40 days of age in dogs (e.g., 67Hz to 45kHz) and by 20 to 30 days in cats (e.g., 45Hz to > 64kHz) [55]. Deaf animals can be difficult to arouse from sleep, may be more aggressive than normal littermates, and may be very vocal. There is no treatment.
Deafness also has been reported in young dogs and cats accompanied by signs of peripheral vestibular disease. It has been seen in colony Beagles, Akita and Doberman Pinscher puppies, and Siamese kittens [89]. Clinical signs, which usually begin at 3 - 12 weeks of age, include head tilt, circling, and ataxia. Nystagmus is not a feature of this disorder, but there is a deficit in normal eye movements. With the exception of the Doberman Pinscher puppies in which severe degenerative lesions were found (see above), histopathologic lesions have not been reported. The vestibular signs are generally not progressive, and improvement is usually seen over a period of weeks or months. This is probably due to visual and somatosensory compensation rather than resolution of the problem. Deafness in these animals is usually permanent. In affected Doberman Pinschers (in which the disease is inherited as an autosomal recessive trait), hearing was absent in all puppies three weeks of age or older.
Prognosis in animals with hearing loss will vary according to the cause. Treatments are mainly focused on preventing further damage, e.g., avoidance of ototoxic medications in animals with mild sensorineurial damage. Correction of causes of conductive deafness may be ameliorative. Hearing aids seem to work best in human patients with conductive deafness [80].

At this time, comprehensive trials evaluating hearing aids are lacking in dogs and cats with hearing loss. There is a recent report on surgical placement of a bone-anchored hearing aid in a dog with conductive deafness [90].

Diabetic Neuropathy

Spontaneous diabetes mellitus is a well-recognized metabolic disorder in dogs and cats associated with impaired utilization of carbohydrates and enhanced lipid and protein use. Central nervous system effects of this metabolic condition relate to two hyperglycemic syndromes: diabetic ketoacidosis and nonketotic hyperosmolar hyperglycemia (see diabetes mellitus). Diabetes mellitus may also be associated with peripheral nerve disease, with sporadic cases of spontaneous diabetic neuropathy reported in adult dogs and cats [91-98]. Recently, a retrospective study encompassed 19 cats with spontaneously-occuring diabetes neuropathy [519].

Clinical signs of diabetic neuropathy are extremely variable ranging from an insidious subclinical condition to one with an acute or chronic onset of weakness, progressive paraparesis, proprioceptive deficits, muscle atrophy and depressed spinal reflexes. Cats often assume a plantigrade posture in pelvic limbs. Lumbosacral hyperesthesia has been noted in affected dogs and cats [93,94,96]. Diabetic cataracts may be present. Hypotension has been documented in a dog with diabetic neuropathy [94].

Electrodiagnostic (EDX) testing has revealed fibrillation potentials, positive sharp waves and fasciculation potentials in muscles, decreased motor and sensory nerve conduction velocities, and decreased amplitudes of evoked compound muscle action potentials (CMAPs). Temporal dispersion/diminished amplitude of CMAPs evoked by stimulation at the hip, as compared with potentials evoked by stimulation at the hock [94,99], suggest conduction block. Rarely, bizarre-high frequency discharges (myotonic-like) have been recorded in dogs with clinical/subclinical diabetic neuropathy [94,99]. In the cat retrospective study, EMG abnormalities were mainly restricted to the most severely affected cases [519].

Pathological findings reported in dogs and cats range from active axonal degeneration to demyelination-remyelination and axonal regeneration, along with neurogenic skeletal muscle fiber atrophy [91,93,96,100]. In a 8 year old female Doberman Pinscher with diabetic neuropathy, axonal degeneration was the dominant finding (involving approximately 35 to 40% of teased nerve fibers) in biopsies of lateral and medial plantar nerves [93]. In one teased nerve fiber study involving diabetic dogs without signs of clinical neuropathy, the dominant lesions were demyelination, remyelination, and less prominent axonal degeneration and teased nerve fibers with evidence of axonal regeneration [91]. Semi-thin sections revealed scattered thinly myelinated fibers and regenerating clusters of myelinated fibers. Early onion-bulb formation was seen ultrastructurally. Morphometric analysis revealed that the changes occurred in larger-caliber fibers from distal plantar nerves but not in more proximal tibial nerves. The results of this study, and the EDX testing of these dogs [99], suggest that some forms of diabetic neuropathy in dogs (and cats?) reflect a distal polyneuropathy that involves motor and sensory nerves.

Diagnosis is based on laboratory evidence of diabetes mellitus (hyperglycemia, glycosuria, insulin assays) and clinical, neurological, electrophysiological, and nerve biopsy data. EDX testing is a useful non-invasive technique for detecting animals with subclinical diabetic neuropathy [99]. Prognosis is guarded; however, partial or full recovery can occur with good diabetic control from insulin therapy [93,94,96]. A high fibre diet has been shown to significantly improve glycemic control and quality of life in dogs with diabetes mellitus [528]. Preliminary studies suggest that sulindac (a substituted indene acetic acid) may ameliorate some histological abnormalities in experimental diabetic dogs [527].

We have observed a polyneuropathy (dominated by axonal degeneration) in a diabetic 4 month old Chow Chow puppy with pancreatic islet cell hypoplasia in which there was absence of delta cells, and diminished numbers of alpha and beta cells [101]. We have also seen degenerative changes in nerves from young Keeshonds with inherited diabetes mellitus (K.G. Braund and J.W. Kramer JW, unpublished data). Prognosis is guarded. At present, there is no effective treatment for the diabetic neuropathy; however adequate and long-term dietary and insulin control of the hyperglycemia can result in marked clinical improvement [93,102].

In people, a variety of PNS disorders may be seen with diabetes, including focal disorders (focal myopathies and mononeuropathies, often associated with injections and entrapment/compression/infarction, respectively), segmental disorders such as diabetic polyradiculoneuropathy, and generalized neuropathies such as diabetic distal symmetrical sensorimotor polyneuropathy (DDSPN) and diabetic autonomic neuropathy [103]. Diabetic autonomic neuropathy often occurs as a continuum of the symmetrical polyneuropathy [104]. DDSPN is the most common form and its glove-stocking distribution of paresthesia and numbness, the distal to proximal gradient of EDX abnormalities, and predominantly axonal involvement (especially of large myelinated fibers) are consistent with a dying-back neuropathy [105], while autonomic involvement leads to a various dysautonomic signs, including hypotension, pupillary miosis, and constipation. One characteristic pathological feature of diabetic nerves is hyalinization of endoneurial microvessels, typically associated with reduplication and thickening of microvascular basement membranes, and perineurial cells may have a thickened basal lamina [106,107]. Recent studies have also demonstrated significant abnormalities of the perineurium in the spontaneously diabetic dog (total perineurial sheath thickness, mean perineurial lamellar width, total interlamellar space, and perineurial cell basement membrane thickness [108]). Endoneurial capillary basement membrane area was significantly increased in

experimentally-induced (alloxan/streptozotocin) diabetic dogs [527], similar to that found in diabetic people. In this report, there was no loss of capillaries.
The pathogenesis of diabetic neuropathy remains unknown, although interaction of multiple factors is considered likely [109-111], including interactions between vascular factors (decreased nerve perfusion/endoneurial hypoxia, changes in endoneurial microvasculature) and metabolic factors (hyperglycemia, enhanced glycation end product formation, intraneural polyol pathway activation, protein C activation, and omega-6 essential fatty acid dysmetabolism) [112,113]. One study in diabetic cats demonstrated evidence of polyol pathway activity (marked increases in nerve fructose without appreciable sorbitol accumulation) [519]. Deficiency of several neurotrophic factors, namely nerve growth factor, neurotrophin-3, and insulin-like growth factors have also been implicated in diabetic neuropathy [114,115]. Preliminary clinical trials have demonstrated improvement in signs and symptoms of sensory neuropathy in human patients with lower extremity vascular occlusive disease after intramuscular injection of naked DNA encoding vascular endothelial growth factor [116], although it is uncertain if these positive effects result from an angiogenic activity (formation of new blood vessels) or a direct neurotrophic effect [117]. Inflammatory cell infiltrates in nerves of diabetic people (particularly in those with diabetic autonomic neuropathy) also suggests that inflammatory or immune mechanisms may be involved [110]. While axonal degeneration appear to be the dominant pathology in patients with DDSPN, it remains to be determined if the myelin changes are secondary to an axonopathy or develop from a primary schwannopathy [105]. Note that insulin deficiency is probably not related to the diabetic neuropathy since nerves (just as the CNS) are not dependent on insulin for glucose uptake/energy utilization [118].

Distal Denervating Disease
This degenerative neuropathy is reportedly the most common canine polyneuropathy in the United Kingdom [119,120], but has not been reported elsewhere. In this disorder there is no breed, sex, or age predisposition. The etiology and pathogenesis are presently unknown. Affected animals have had no history of exposure to toxins. The rate of onset of clinical signs is variable from 1 week to greater than 1 month. The main presenting sign reported is tetraparesis. In some dogs, the head and neck cannot be supported and there is loss of voice. Mastication, swallowing, respiration and bladder function are unimpaired. Pain sensation is preserved. Muscle atrophy may be prominent, especially involving proximal extensor muscles. There is hypotonia and depressed or absent patellar reflexes. Facial nerve dysfunction has been observed. Moderate to marked spontaneous potentials (fibrillations and positive sharp waves) are present in limb, paraspinal, masticatory muscles, and tongue. Motor nerve conduction velocities are in the low-normal range. The amplitude of evoked potentials is reduced. Sensory nerve potentials are normal. Pathologically, there is degeneration of the distal intramuscular axons with collateral sprouting. Skeletal muscle changes are typical of neurogenic atrophy. Proximal and middle portions of peripheral nerves are normal, and there is no evidence of sensory nerve damage. The prognosis for full recovery is good, with appropriate nursing care. Most dogs recover spontaneously within 4 to 6 weeks of onset of clinical signs. Recurrence has not been reported. The condition is clinically similar to Coonhound paralysis and idiopathic polyradiculoneuritis, although the later diseases tend to run a more acute course.

Distal Symmetrical Polyneuropathy
A distal symmetric sensorimotor polyneuropathy has been reported in young adult Great Danes (1.5 to 5 years) [121,122]. The cause and pathogenesis are not known; however, an inherited dying-back process of peripheral axonopathy has been suggested. Clinical signs include chronic pelvic limb paresis that progresses to involve thoracic limbs, and bilateral atrophy of head (masticatory) and distal limb muscles. A reduced response to painful stimuli has been observed. Electrodiagnostic studies reveal fibrillation potentials, positive sharp waves in distal limb muscles (below stifle and elbow), and absence of evoked muscle action potentials. Diagnosis is based on clinical, electrodiagnostic, and nerve biopsy data. Prognosis is poor. Affected dogs have shown no response to corticosteroids or thyroid hormone supplementation. Results of pathological and morphometric studies of peripheral nerves reveal myelinated nerve fiber degeneration and loss, especially of larger-caliber fibers, which are accentuated in distal parts of appendicular and laryngeal nerves. Varying degrees of demyelination and remyelination may also be present. Sensory and autonomic nerves are affected to a lesser degree. No lesions are found in the CNS.
In a 3 year old, male Setter-cross, an almost identical polyneuropathy was noted after canine heartworm disease therapy (thiacetarsamide), which was complicated by disseminated intravascular coagulation [123]. Indeed, it now seems that this polyneuropathy is not specific for Great Danes, since we have seen similar clinical signs and pathology in several other large-breed dogs, including Chesapeake Bay Retriever, St. Bernard, Newfoundland, Collie, Labrador Retriever, and Rottweiler (see Rottweiler Sensorimotor Polyneuropathy). Treatment, including corticosteroids, has been disappointing in dogs with distal symmetrical polyneuropathies; however, results of a recent therapeutic trial using prosaptide TX14(A), a homologue of a neurotrophic peptide sequence within the lysosomal protein sapsonin C, indicated promising beneficial clinical and pathological effects in some dogs [512].

Dysautonomia

This disease has been frequently reported in cats [124-134] and dogs [129,135-142]. It was first reported in cats by Key and Gaskell [124] in the United Kingdom, where it is still mainly restricted, although it now appears to have a world-wide distribution [143]. It is much less common in the United Kingdom today than it was in the 1980's, although there have been recent outbreaks in closed cat colonies [144,145]. The etiopathogenesis of this disease is unknown. Immunological studies in affected cats have revealed no abnormalities [146]. In one study, there was no consistent factor identified when management, vaccinal status, and drug therapy were examined [147]. Attempts to transmit the disease have been unsuccessful. However, recent demonstration of antibodies against the nicotinic ganglion acetylcholine receptor in some dogs with dysautonomia (as also found in human patients [513]) suggests a possible autoimmune basis for this disease [514].

The condition has been reported in cats from 6 weeks to 11 years of age. In the majority of cases, clinical signs develop in less than 48 hours, but may take up to 7 days. Historically, cats begin vomiting/retching and become depressed and anorexic. The third eyelid protrudes, pupils are dilated and poorly responsive to light stimulation (but usually responsive to pilocarpine), and lacrimation is reduced. Cats may be febrile, emaciated, constipated (sometimes with fecal impaction) and dehydrated. Urinary and fecal incontinence may develop. Sneezing may occur and the nose is often dry. Dried exudate may block the external nares. Occasionally, very mild posterior ataxia or more generalized paresis, depressed proprioception, and absent anal reflex have been detected. Many cats have bradycardia of less than 120 beats/minute. Some animals manifest transient syncopal episodes. A clinical grading system has been proposed [148]. Megaesophagus is often present and is usually associated with regurgitation. The putative role of the parasympathetic system in the development of the megaesophagus appears somewhat complicated. This sign usually occurs with damage to the special visceral efferent system emanating from the solitary tract/nucleus [149]. The parasympathetic vagal nucleus gives rise to the general visceral efferent (GVE) axons that innervate the smooth muscle of the digestive system, and while experimental lesions of the parasympathetic nucleus reportedly cause esophageal paralysis in cats, it has been suggested that the GVE vagal neurons are not critical for direct initiation of smooth muscle activity in the digestive tract since intestinal peristalsis and colonic mass movement are maintained by intrinsic neural mechanisms [149].

Dysautonomia in dogs is common in parts of the United States [142], especially around SW Missouri, NE Oklahoma, and Eastern Kansas. More than 50 canine cases have been confirmed at the University of Missouri (Dr. Dennis O'Brien, University of Missouri; personal communication, 2000). Recently, the condition was diagnosed in a family of German Shorthaired Pointers (the dam and 4 of 5 puppies) [150]. In dogs, signs may be non-specific [151]: lethargy, depression, anorexia, retching, regurgitation, vomiting, salivation, constipation, or more commonly, diarrhea. Other signs include dry crusty nose, dry oral mucous membranes, subnormal Schirmer tear tests, dilated or anisocoric pupils (poorly responsive to light), prolapsed nictitating membranes, megaesophagus, decreased anal tone, and distended incontinent urinary bladder. Heart rate is often < 120 beats/minute (even after exercise), and neurological abnormalities such as twitching jaw muscles, cervical hyperesthesia, dilated anal sphincter, and decreased patellar reflexes have been observed sporadically. Affected dogs of different breeds have ranged in age from 4 weeks to 5 years.

Diagnosis may be facilitated by ocular pharmacological testing to confirm post-ganglionic sympathetic and parasympathetic dysfunction [127,131,142,148]. For example, rapid pupillary constriction following instillation of 0.1 to 0.05 % pilocarpine into the eyes of affected animals is suggestive of denervation hypersensitivity [127]. Decreased urinary catecholamine measurements (e.g., catecholamines and catecholamine metabolites, metanephrine and vanillylmandelic acid) are indicative of sympathetic failure and may be another useful diagnostic tool [127,152]. The bradycardia typically is unaffected by administration of anticholinergic drugs, such as atropine.

While many of the clinical signs (e.g., dry mucous membranes, mydriasis, regurgitation/constipation) suggest involvement of the parasympathetic nervous system (although bradycardia reflects sympathetic involvement) [153], the pathology primarily involves neuronal perikarya especially of autonomic ganglia, both sympathetic and parasympathetic [125,126,153,154]. Note that some signs, such as proprioceptive deficits and anal sphincter dysfunction, are non-autonomic. Lesions are characterized by chromatolytic changes in autonomic neurons (with loss of Nissl substance and eccentric/pyknotic nuclei), neuronal degeneration and loss, neuronophagia, and occasionally mild mononuclear perivascular cuffing (in one report, the majority of mononuclear cells were T lymphocytes [140]). In another report, 2 of the least affected cats had evidence of eosinophilic polymorphonuclear cells in several autonomic ganglia [144]. Ultrastructurally, there are dilated cisternae of rough endoplasmic reticulum, loss of Golgi complex, and large stacks of smooth parallel membranes which suggest possible disruption of neuronal glycoprotein biosynthesis [155,156]. In a dog with dysautonomia, numerous multilamellated bodies and myelin figures were seen in neuronal cytoplasm [137]. Degeneration has been found in many autonomic nerves with variable changes in myelinated and unmyelinated axons, including increased numbers of microtubules, which can be misaligned, vesicles, and branched vesiculotubular arrays of smooth endoplasmic reticulum. Changes are also frequently present in dorsal nucleus of the vagus and motor nuclei of cranial nerves III, V, VI, VII, and XII, ventral horn cells, and intermediolateral gray matter of spinal cord [140]. Note that degenerative changes (axonal

degeneration, demyelination) may also be found in peripheral somatic nerves (e.g., common peroneal nerve) of dogs and cats. In cats, enteric neurons are also affected based on reported depletion of immunoreactivity for vasoactive intestinal polypeptide, metenkephalin, and substance P in peptidergic neurons throughout the gastrointestinal tract [148]. Sensory ganglia (e.g., dorsal root ganglia and ganglia of cranial nerves) are affected to a much lesser degree. The pathology has features in common with grass sickness of horses.

No specific treatment is available but supportive therapy is indicated and can be successful [132,157]. One review recommends correction of hypovolemia, hypothermia, hypoglycemia, and other electrolyte abnormalities; metoclopramide for vomiting and enhanced gastrointestinal motility; bladder evacuation (e.g., manually and/or with bethanechol); enemas for constipation; and total parenteral nutrition or tube gastrostomy for long-term alimentation [148,158]. Ophthalmic administration of parasympathomimetic drugs (e.g., 0.25 to 1.0 % pilocarpine) may stimulate lacrimal and oral secretions [157]; however, repetitious vomiting/regurgitation may become a complication [127]. Prognosis in dogs and cats is guarded to poor [158], especially in animals that suffer from persistent regurgitation/vomiting with heightened risk of inhalation pneumonia [148,151]. In one study, 28 of 40 cats did not survive the illness [154]. Cats that begin to produce secretions and eat and drink have the best prognosis. Clinical recovery make take up to 12 months. In affected dogs, mortality may exceed 90% [142,158].

In people, autonomic nervous system disorders may be associated with (a) diffuse autonomic failure (pandysautonomia), subcategorized into preganglionic, ganglionic/postganglionic, and peripheral neuropathies/neuronopathies with autonomic failure, and (b) those related to pure cholinergic or adrenergic disorders [159].

Facial Paralysis

Idiopathic facial nerve paralysis of acute onset has been reported in mature dogs and cats (e.g., > 5 years). There is an apparent predisposition for Cocker Spaniels, Pembroke Welsh Corgis, Boxers, English Setters, and Domestic Longhair cats [160,161]. The cause of this condition is unknown. The facial paralysis is unrelated to otitis media. In one study of 95 dogs and cats with facial paralysis, the condition was considered to be idiopathic in 75% of dogs and 25% of cats [161].

Clinical signs are characterized by ear drooping, lip commissural paralysis, sialosis, deviation of the nose away from the affected side, and collection of food on the paralyzed side of the mouth. Menace response testing and palpebral reflexes are absent. Facial paralysis may be bilateral in some animals. There is no evidence of Horner's syndrome in animals with idiopathic facial paralysis. Electrodiagnostic testing may reveal spontaneous denervation potentials (e.g., fibrillations potentials and positive sharp waves) in superficial facial muscles. Stimulation of the facial nerve external to the stylomastoid foramen may fail to evoke muscle action potentials. Skull radiographic/imaging studies are usually non-contributory. Pathological studies of facial nerve biopsies may reveal active degeneration of large- and small-caliber myelinated fibers [160,162]. Inflammation has not been reported. Ultrastructurally, numerous macrophages may be present along with ovoids, Schwann cell proliferation, collateral sprouting, and various stages of remyelination. Prognosis is guarded. Improvement may take place in a few weeks or months, or may never occur. Chronic lip paralysis may result in permanent contracture, and the inability to close the eyelids often leads to corneal lesions due to lack of lacrimal lubrication. In one study, dogs with facial paralysis were ten times more likely to develop keratoconjunctivitis sicca, possibly as a result of damage to the parasympathetic preganglionic neurons within the facial nerve that pass to the lacrimal gland [161] (note that these parasympathetic fibers leave the facial nerve at the level of the inner ear, so decreased tear secretion will indicate a facial nerve lesion between the medulla and the middle ear [149]). Artificial tears may assist with corneal dryness. In a recent report of idiopathic facial paralysis of 35 days duration in a 7 year old female Yorkshire Terrier, acupuncture treatments (every other day for the first week, then once a week for the next 3 weeks) resulted in complete facial symmetry, normal ear movement and sensation, and voluntary closure of the eyelids [163].

In people, up to 75% of all cases of facial paralysis are also of unknown etiology and are called Bell’s palsy [164]. High risk patients include those with diabetes mellitus or multiple sclerosis, and pregnant women [165]. Present knowledge suggests that Bell’s palsy is most likely caused by herpes simplex infection and administration of acyclovir and corticosteroids facilitates recovery in most patients [166].

Acquired unilateral or bilateral facial paresis or paralysis in animals has also been seen in association with myriad disorders including polyradiculoneuritis (e.g., Coonhound paralysis), hypothyroidism, insulinomas, laryngeal paralysis-polyneuropathy complex, myasthenia gravis, botulism, middle ear infection/neoplasia, paraneoplastia, borreliosis, trauma external to the stylomastoid foramen (e.g., compression of the superficial branches of the facial nerve in anesthetized animals that have been lying in lateral recumbency for prolonged periods of time), extracranial tumors, or in conjunction with petrosal bone fracture [149,167-175]. Peripheral and /or central facial paralysis may be seen with brainstem inflammation or neoplasia (including pituitary tumors), and cerebral ischemia associated with parasitic migration [149,176-179]. It may occur secondary to surgical ablation of the external ear canal or bulla osteotomy for chronic otitis externa-media [180-185]. Intermittent facial spasms have been seen in dogs with idiopathic facial paralysis [161] and chronic otitis media [186], and may occur in animals with central brainstem lesions [187], presumably associated with increased

irritability of the facial nerve or facial nucleus. Facial twitching was seen in a cat with a pancreatic endocrine tumor (insulinoma), removal of which resulted in clinical remission [188]. Idiopathic paradoxic lacrimation ("crocodile tears") reported in a cat may have resulted from prior facial nerve paralysis affecting autonomic innervation [189]. In people, this condition (also known as Bogorad's syndrome) may follow facial palsy and is thought to result from aberrant migration of regenerating preganglionic parasympathetic fibers to the pterygopalatine ganglion rather than to the submandibular ganglion. Consequently during meals, stimulus for salivation results in stimulation of the lacrimal gland and increased tearing [165].

Familial German Shepherd Neuropathy

A familial neuropathy has been reported in three older (10 years of age) German Shepherd dogs (one male, two females) that were littermates [190]. Progressive clinical signs, beginning around 9 years of age, included unsteady hind limb gait, tetraparesis, marked hind limb muscle atrophy, and depressed reflexes. Serological studies showed marked elevation in total lipids, CK levels, lactic dehydrogenase, and moderate decrease in aspartate aminotransferase concentration. Grossly, the sciatic nerves appeared swollen and fibrotic in two of the dogs. Microscopic changes in nerves included marked endoneurial fibrosis, loss of myelinated fibers, regenerating clusters, and numerous thinly myelinated axons. Active axonal degeneration was also seen, along with evidence of segmental demyelination/remyelination. No lesions were found in trigeminal and vagosympathetic nerves. Neurogenic muscle atrophy was observed in skeletal muscles (especially hind limb and paraspinal muscles) characterized by muscle atrophy/hypertrophy, endomysial fibrosis, fatty infiltration, mild regeneration, and histochemical fiber type grouping. Collateral ramifications/sprouting and multiple terminal arborizations were noted in terminal axons entering muscle. Based on these findings, the disorder was considered to represent an axonopathy with a dying-back pattern. Absence of onion-bulbs and the axonal lesions in these older dogs also suggested similarities to HSMN type II neuropathy in people, a usually dominant (sporadic and recessive cases are less commonly seen), distal axonopathy characterized by diffuse loss of larger-caliber myelinated fibers, little or no active degeneration, and prominent cluster formation [105].

The familial nature of this late-onset German Shepherd disorder is enhanced by the reported involvement of two other littermates (with less severe clinical signs), and the history that similar signs occurred in the mother and grandmother.

Giant Axonal Neuropathy

Giant axonal neuropathy (GAN) is a rare inherited (autosomal recessive) neurological disease of German Shepherd dogs [191,192]. The pathogenesis of GAN is unknown, however it may represent a genetic defect in slow axonal transport affecting a wide variety of intermediate filaments [120], or altered neurofilament configuration [193,194]. An inborn error of metabolism of enzyme-linked sulfhydryl containing proteins, leading to impaired production of energy needed for normal organization of intermediate filaments has been proposed in human patients with GAN [195]. The neurofilaments in dogs with GAN have a normal polypeptide composition [196] and are morphologically similar to those seen in human GAN.

In dogs, neurological signs are noted around 14 to 16 months of age, are more obvious in pelvic limbs, and are progressive. Signs are characterized by paresis, proprioceptive loss, diminished patellar reflexes, and pelvic limb hypotonia with atrophy of muscles below the stifles. Conscious perception of pain is gradually reduced in pelvic limbs. Bark may be lost or diminished and there may be fecal incontinence. Megaesophagus develops around 18 months resulting in regurgitation and occasional inhalation pneumonia. By 18 to 24 months of age, tetraparesis is pronounced. Note that affected dogs often have a very tight curl of their hair coats [193] (kinky/curly hair is a characteristic finding in children with GAN).

Electrophysiologically, amplitudes of evoked compound muscle action potentials are decreased several months prior to clinical evidence of neuropathy [192,193]. This decrease is progressive. Denervation potentials are demonstrated by EMG in distal muscles of pelvic and thoracic limbs by 18 months of age.

Pathologically, the disease is characterized by loss of myelinated nerve fibers and presence of giant axons in myelinated and unmyelinated fibers [197-199]. Myenteric and distal vagal axons are also affected. The swollen axons contain masses of disordered 10 nm neurofilaments in both nodal and paranodal locations. Axonal collections of paracrystalline structures may also be seen in canine and human GAN nerves [194]. Similar morphological changes are found in the CNS with axonal swellings found in the distal portions of the spinal long tracts (e.g., caudal lumbar segments and rostral cervical segments) and their terminations in the cerebellar vermis, in the distal optic pathways, nuclei of the habenulo - interpeduncular tract, various thalamic relay nuclei, and the cerebral cortex [191,198,199]. Other organelles that may accumulate include mitochondria, membranous bodies, glycogen bodies, amorphous electron dense material, and occasionally, smooth endoplasmic reticulum [199]. Adjacent astrocytic processes may be enlarged with excessive whorling of the glial filaments. Attenuation of the myelin sheath over the swellings is seen in the PNS and CNS. The predominance of lesions in both PNS and CNS at the distal ends of large motor and sensory nerve fibers suggests that the disease represents a central-peripheral, distal axonopathy [191,192,198]. Similar lesions are seen in experimental studies of various neurotoxins, including acrylamide, IDPN, n-hexane, and methyl-n-butyl ketone [200]; however, the axonal neurofilamentous accumulations in

human and canine GAN differ from those seen with 2,5-hexanedione neuropathy [194].
Diagnosis is based on signalment, clinical, electrodiagnostic, and pathological (nerve biopsy) data. Prognosis is poor. There is no treatment.

Hyperadrenocortical (Cushing's) Neuropathy
In our laboratory, we have found evidence of a peripheral neuropathy in several dogs with hyperadrenocorticism. Changes have included demyelination, remyelination, occasional axonal degeneration, and neurogenic atrophy in muscle, sometimes accompanied by signs of reinnervation (fiber type grouping). These changes have been observed in dogs with and without histopathological evidence of hyperadrenocortical (Cushing's) myopathy. Electrodiagnostic changes may include fibrillation potentials and positive sharp waves, along with significantly slowed nerve conduction velocities [515].

Hyperlipidemia
Hyperlipidemia is defined as an excess of blood lipids, and as most lipids in blood are incorporated into lipoproteins and transported by these particles, the condition is also called hyperlipoproteinemia [201]. Lipoproteins may be separated into four major classes: chylomicrons, very low-density lipoproteins, low-density lipoproteins, and high-density lipoproteins [201-203]. Chylomicrons and very low-density lipoproteins are involved primarily in triglyceride transport, while low-density lipoproteins and high-density lipoproteins are involved with cholesterol transport [204]. Chylomicrons are composed predominantly of triglyceride and are cleared from the plasma by lipoprotein lipase and its cofactor, apoprotein C-II (apo C-II). Removal of triglyceride from the core of the chylomicron leaves a cholesterol-rich remnant particle that is removed from the circulation by the liver [201,202,205]. Lipid disorders infrequently involve the nervous system in dogs and cats, with the notable exception of hyperchylomicronemia, a familial condition in cats that is characterized by fasting hyperchylomicronemia. This lipid disorder appears to have a world-wide distribution, with reports from New Zealand, United States, and Europe [206-209]. Various breeds of cats have been documented including Domestic Shorthair, Himalayan, European, Persian, Siamese, and Domestic Longhair [205,208]. The underlying biochemical lesion is associated with a reduction in lipoprotein lipase activity. Subsequent biochemical studies indicate that the lipoprotein lipase (LPL) is produced in an inactive form similar to the class III type defect characterized in human LPL deficiency, and that heterozygous cats have intermediate LPL activity [210,211]. A mutation in the lipoprotein lipase gene is the molecular basis of chylomicronemia [212]. The condition is inherited as an autosomal recessive trait [205,208]. Pathologically, hyperchylomicronemia is characterized by presence of xanthomata (lipid granulomas) within many organs, including skin, liver, spleen, lymph nodes, kidney, adrenal glands, heart, and peripheral nerves [209]. These masses are distinguished by the presence of many large macrophages with vacuolated cytoplasm ("foam cells") within a coagulum of blood, degenerating blood components, fibrin, serum, and lipids. Ceroid, lipofuscin, hemosiderin, and crystal of triglycerides and cholesterol may also be seen. The xanthomata may be smooth, are often lobulated, and may be up to 5 cm in diameter. They are thought to arise either from frank hemorrhage or from the leakage of lipid-rich plasma perivascularly. Trauma is thought to predispose to xanthomata formation in peripheral nerves [205]. Nerve involvement is most noticeable at sites such as the spinal foramina and over bony prominences, where they are susceptible to stretching and compression associated with normal vertebral movement. Nerve bundles closely associated with the xanthomata show compression of fascicles (the masses typically are located outside the perineurium) which leads to secondary axonal degeneration and nerve fiber loss.

Clinical signs reflect involvement of various peripheral neuropathies:

a. Horner's syndrome (ptosis, miosis, enophthalmos and prolapse of the third eyelid)
b. Facial nerve paralysis (absence of corneal and palpebral reflexes)
c. Tibial nerve paralysis (overflexion of the tarsus)
d. Femoral nerve paralysis (atrophy of quadriceps muscles and absence of patellar reflex)
e. Trigeminal nerve paralysis (temporal muscle atrophy, inability to prehend and chew food)
f. Radial nerve paralysis (inability to extend digits)
g. Recurrent laryngeal nerve paralysis (dyspnea and cyanosis due to impaired abduction of vocal cords).

Neuropathic signs are usually not seen until cats are at least eight months of age; however, paraplegia reportedly due to thrombotic occlusion of the aorta has been seen in an affected four week old Siamese kitten [208]. Recurrent pancreatitis and/or hepatosplenomegaly are rarely seen in affected cats [205].
Blood samples from affected cats have the appearance of "cream of tomato soup". Funduscopic examination may reveal the presence of lipemia retinalis. Serum lipoprotein studies show a significant increase in chylomicrons and a smaller increase in very low density lipoproteins. Cholesterol and triglyceride serum values are increased and there is a significant reduction

in lipoprotein lipase activity. Other serum chemistry findings are within normal limits, including serum thyroxine levels. Prognosis is usually favorable, since all of the clinical manifestations of hyperchylomicronemia are reversible provided that the plasma triglyceride levels are reduced [205]. Peripheral neuropathies in affected cats resolve after 2 to 3 months on a low fat (e.g., as little as 10 g/day), high fiber diet. Gene replacement therapies are in progress [213]. A transient hyperlipidemia and anemia has been reported in kittens with significantly lower LPL activity (apo C-II function was normal) but without the above-mentioned LPL gene mutation [204]. None of these cats subsequently (as adults) developed xanthomata affecting nerve roots.

Idiopathic hyperlipoproteinemia is commonly seen in Miniature Schnauzers and Beagles with defective lipid metabolism characterized by hypertriglyceridemia and moderate cholesterol elevation [203]. The pathogenesis of this condition remains uncertain but may be associated with decreased activity of LPL. Abnormalities in lipoproteins include increased serum levels of low-density/very low-density lipoproteins with or without hyperchylomicronemia [201]. Affected animals have signs of abdominal distress, seizures, and occasionally, pancreatitis [214,215].
Secondary hyperlipidemia may occur in dogs and cats with various metabolic disorders including hypothyroidism, acute pancreatitis, diabetes mellitus, hyperadrenocorticism, and renal disease, and cholestatic hepatic disorders [201,216].

Hyperoxaluria
Hyperoxaluria, primary or secondary, is occasionally seen in dogs and cats. Primary hyperoxaluria is considered to be an autosomal recessive disorder associated with renal failure from oxalate nephropathy and neurological signs in young Domestic Shorthair cats of either gender, resulting in death before one year of age [217-219]. This condition was initially observed in a closed cat colony in 1984. Affected cats develop acute renal failure between 5 and 9 months of age due to deposition of oxalate crystals within the kidney tubules. Signs include anorexia, dehydration, marked weakness, and depression. Kidneys are often enlarged and seem to be painful when palpated. Affected cats develop a crouching, cow-hocked stance, and are reluctant to stand or walk. Neurological examination reveals deficiencies in postural reaction testing, depressed patellar and withdrawal reflexes, absent cutaneous trunci reflex, and a reduced response to pain. Abnormal spontaneous potentials (positive sharp waves, fibrillation potentials, and high frequency discharges) are detected on EMG testing. Clinical signs in cats often deteriorate to the point that euthanasia is necessary. There is progressive increase in blood urea nitrogen and creatinine values, as well as increased serum levels of glucose, phosphate, and potassium. Urine contains increased oxalate and L-glycerate levels. Biochemical studies in affected cats have revealed deficient liver enzymatic activities of D-glycerate dehydrogenase and glyoxylate reductase, which are the deficient enzyme activities in human primary hyperoxaluria type 2 (PH2) [220]. Heterozygote cats appear to have intermediate liver levels of these enzymes.
Histopathological examination of kidneys reveal presence of numerous birefringent crystals within the tubules, interstitial fibrosis, and occasionally, periglomerular fibrosis. In the spinal cord, large swellings with a homogeneous appearance are observed in proximal axons of ventral horn cells. Ultrastructural examination shows that the swellings are due to accumulation of neurofilaments. Swollen axons are also seen in ventral roots, intramuscular nerves, and in dorsal root ganglia. Oxalate crystals are not observed within axons. Muscle changes are considered to represent neurogenic atrophy. Diagnosis may be made in affected cats before they develop clinical signs by identifying L-glycerate in urine. This metabolite is not present in urine of normal cats. Prognosis is grave. There is no treatment.
This inherited feline condition is now considered to be analogous to PH2 (L-glyceric aciduria) in people, an inherited condition characterized by recurring calcium oxalate kidney stones. The pathogenetic mechanisms associated with the lesions in the nervous system of the cats are not clear. Note that liver levels of the enzyme serine:pyruvate/alanine:glyoxylate aminotransferase, functional deficiency of which causes primary hyperoxaluria type 1 (PH1) in people and in Tibetan Spaniels [221,222], are normal in these cats. Peripheral nerve trunk involvement, as well as sensory and sympathetic ganglia, has been reported in people (but not in dogs) with PH1 with deposition of oxalate crystal within axons and in the walls of perineurial arterioles, leading to axonal degeneration, and demyelination [223,224]. Multiple calcium oxalate crystals are also seen in muscle surrounded by inflammatory infiltrates. In some patients with primary hyperoxaluria and renal failure, chronic hemodialysis may favor the development of neuropathy [225]. PH1 in people is an autosomal recessive disease. D-glycerate dehydrogenase/glyoxylate reductase levels are normal in people and affected dogs [222].
Secondary hyperoxaluria may also occur in cats and dogs following ingestion of the antifreeze ethylene glycol, which is metabolized to glycolic acid, glyoxalate, and oxalate. Oxalate nephrosis and renal sclerosis has been reported in a cat following renal transplantation [226]. There was no evidence of primary type 2 hyperoxaluria in this cat.

Hypertrophic Neuropathy

Hypertrophic neuropathy is an autosomal recessive neurological disease that has been reported in Tibetan Mastiff dogs [227-230]. This disease is also known as canine inherited hypertrophic neuropathy. Clinical signs appear in animals from 7 to 10 weeks of age and consist of rapidly developing generalized weakness, hyporeflexia/areflexia, muscle hypotonia, and dysphonia. No other cranial nerve signs are reported. Severely affected puppies may become totally recumbent within 3 weeks of onset with subsequent development of sternal compression and limb contractures. Some puppies may regain the ability to stand and walk, but remain weak. Mild muscle wasting occurs and ambulatory puppies have a shuffling, plantigrade gait. Pain perception is normal.

Electrodiagnostic studies reveal progressive, moderate to severe reduction in nerve conduction velocities. Transient EMG abnormalities (positive sharp waves, fibrillation potentials, and high frequency potentials) may be seen early in the course of the disease but tend to disappear 2 or more months after onset of signs. Temporal dispersion of evoked muscle action potentials is reported in chronically affected dogs. There is variable elevation in CSF protein.

Pathologically, this disease results in a reduced density of myelinated fibers in peripheral nerves and nerve roots, widespread demyelination, and primitive onion-bulb formation with relatively little axonal degeneration. There is no inflammation. A constant feature is accumulation of actin-like filaments (6 to 7 nm in diameter) in Schwann cell cytoplasm, either in an adaxonal location or in cytoplasmic compartments within the myelin sheath. Experimental nerve transplantation studies point to a Schwann cell defect, possibly involving the cytoskeleton [231]. Ultrastructurally, some degenerating and remyelinating axons are surrounded by concentric layers of Schwann cell cytoplasm. Macrophages often invade the degenerating myelin sheaths. Morphological evidence of axonal injury is unusual, although ovoids and Büngner's bands are occasionally seen.

Diagnosis is based on signalment, clinical, electrodiagnostic, and nerve biopsy data. Prognosis is guarded. There is no treatment. This canine hypertrophic demyelinating neuropathy has similarities to hereditary sensory and motor neuropathy (HSMN) type I, also known as Charcot-Marie-Tooth disease (CMT) type I, and HSMN type III (also known as Dejerine-Sottas disease, a variant of CMT) [43].

A condition that has some similarities to inherited hypertrophic neuropathy in the Tibetan Mastiff dog has been reported in two unrelated cats around 1 year of age with signs of intention tremor, mild sensory abnormalities, depressed reflexes, and urinary-fecal incontinence [232]. Grossly, peripheral nerves (motor/sensory and autonomic) appeared thickened. Microscopic studies of peripheral and autonomic nerves revealed demyelination and onion-bulb formation, endoneurial fibrosis, and presence of inner perineurial mucoid masses. Axonal degeneration was not a feature. The condition was considered to resemble HSMN type I in people. Summers and colleagues also reported a hypertrophic neuropathy in a 1 year old male Domestic cat with generalized tremors, plantigrade gait, proprioceptive deficits, forelimb spasticity/hypermetria, progressive ataxia, and depressed nociception over paws, face and nasal vestibule [200]. Signs began around 7 months of age. Myelin sheaths of larger axons appeared thinly myelinated or demyelinated and there was onion-bulb formation. Ultrastructural changes revealed presence of filaments and accumulation of granular material within Schwann cell cytoplasm similar to that seen in Tibetan Mastiffs. Again, axonal changes were minimal. However, in their cat, degenerative changes (demyelination, spheroid formation, Wallerian degeneration, and astrocytic scarring) were observed in dorsal, lateral, and ventral funiculi of the spinal cord. Axonal degeneration extended to the medulla oblongata, caudal cerebellar peduncles, and accessory cuneate nucleus.

Pathological findings with some similarities to those seen in Tibetan Mastiffs have been observed in Beagle-Basset puppies (around 14 weeks of age), with widespread demyelinating radiculoneuropathy [200]. These puppies had megaesophagus, aspiration pneumonia, generalized weakness, diffuse muscle atrophy (especially proximally), absent patellar reflexes, and EDX findings of widespread denervation potentials (including facial and masticatory muscles) and decreased motor NCV.

Hypoglycemic Neuropathy

Severe hypoglycemia (e.g., 18 to 45 mg/dl; normal = 80 - 120 mg/dL) in dogs and cats (less frequently) is most commonly associated with insulinomas with CNS signs of neuroglycopenia (generalized seizures, weakness, ataxia, collapse, lethargy, transient blindness, and abnormal behavior, e.g., hysteria) and sympathoadrenal stimulation (muscle tremors, nervousness, restlessness, and hunger) seemingly relating to the dependence of the CNS on glucose [103] (see hypoglycemia). An infrequently encountered complication of insulinoma-associated hypoglycemia in dogs is polyneuropathy [233-239]. Onset and clinical course may be acute to sub-acute (several days) or insidious/chronic (weeks to months). Clinical signs range from paraparesis to tetraplegia, facial paresis/paralysis, hyporeflexia/areflexia (e.g., myotatic and cutaneous trunci reflexes), hypotonia, and muscle atrophy (e.g., appendicular/masticatory/facial), sometimes in conjunction with seizures. In one report involving 3 severely-affected dogs, seizures or other signs of CNS dysfunction were not observed [238]. In another dog, seizures were seen approximately 16 months after initial signs of tetraparesis [239]. There is also a report of an affected dog with a history of recurring episodes of hind limb weakness, each episode lasting about 30 minutes, and with the dog appearing normal between episodes (seizures were not seen in this dog) [234]. Sensory nerve involvement is suggested by

presence of a lick granuloma in some dogs [233,234]. A subclinical polyneuropathy has also been reported in dogs [235]. Electrodiagnostic (EDX) testing has shown presence of abnormal spontaneous potentials (positive sharp waves, fibrillation potentials), and slowed motor nerve conduction velocities [235]. In several dogs, EDX data point to a distal distribution of the neuropathy (distal axonopathy), including presence of fibrillation potentials/positive sharp waves below the elbow and stifle [234,235]. CSF studies have been normal [239]. Histopathological findings in motor and sensory nerves from affected dogs include moderate to severe axonal necrosis, nerve fiber loss (affecting medium- and large-caliber myelinated fibers), and variable demyelination-remyelination [235,239,240]. Muscle changes reflect neurogenic atrophy, e.g., fiber size variation associated with scattered angular atrophic fibers and hypertrophic fibers (both type 1 and type 2A fibers, especially the latter). Diagnosis of insulinoma is based on the demonstration of high serum insulin level in the presence of fasting hypoglycemia (see hypoglycemia). The peripheral neuropathy diagnosis is suggested by clinical signs, and confirmed by EDX testing and nerve biopsy.

Treatment strategies have yet to be determined in dogs. Since most of the pancreatic tumors tend to be malignant (unlike the situation in people), prognosis is guarded to poor in dogs with insulinomas regardless of the presence of a polyneuropathy or not. In one report, oral treatment with prednisolone or prednisone at 1 mg/kg daily for 10 days and then every other day was successful in almost completely reversing all neurological signs for several months before the dog was euthanized because of occurrence of uncontrollable seizures [239]. Interestingly, there was no correlation between the blood glucose levels and clinical recovery (glucose levels remained low while insulin levels remained high when the dog was almost completely normal). Similarly, normalization of serum glucose levels using intravenous dextrose failed to improve clinical signs in one report involving 3 dogs with insulinoma-related neuropathies [238]. There is a report of clinical recovery in an ambulatory, hypoglycemic 7 year old female German Shepherd (with seizures, reduced exercise tolerance and dysphonia) following surgical removal of the insulinoma [241]. Streptozocin reportedly resulted in rapid reversal of the peripheral neuropathy in 2 dogs with pancreatic islet cell tumors [520]. The streptozocin was administered at a dosage of 500 mg/m^2, IV, every 3 weeks and combined with a protocol for induction of diuresis.

In people, hypoglycemia-induced peripheral neuropathy due to insulinoma is uncommon, with only 34 patients being reported through 2000 [242]. The pathogenesis of the neuropathy remains unknown [110]. In people, the condition may be seen after several episodes of prolonged hypoglycemia, usually with obvious cerebral signs, and the neuropathy is typically symmetrical, predominantly distal, and usually sensorimotor [242]. A less severe polyneuropathy (predominantly sensory) occurred in schizophrenic patients treated with insulin shock therapy [243]. Experimental studies suggest that severe and mild hypoglycemia causes a distal axonopathy, with motor axons appearing more vulnerable than sensory axons [242,244-247]. Further, experimental studies indicate that nerve damage may result from the hypoglycemia due to disruption of fast anterograde axonal transport [248]. Both duration and severity of hypoglycemia (e.g., blood glucose < 1.5 mmol/L or 27 mg/dL and > 12 hours) appear to be risk factors for axonal degeneration [249] which, in one experimental study, occurred mainly in central fascicular regions of distal peripheral nerves, suggesting deficiency of energy substrate due to poor perfusion in watershed zones [250]. Impaired motor nerve conduction velocities and axonal atrophy have also been reported [251]. There is also the possibility that the hypoglycemia-induced peripheral neuropathy due to insulinoma represents a paraneoplastic neuropathy [236,239,247,252]. Paraneoplastic syndromes in humans are thought to be immunologically mediated since some patients have circulating antibodies that recognize antigens shared by neural elements and tumor cells [253]. The remarkable clinical response to corticosteroids in the canine case reported by van Ham and associates [239] certainly suggests possible immune-mediated pathogenetic mechanisms. Although a sensorimotor, symmetric, and predominantly distal neuropathy may be seen in human patients with paraneoplastic neuropathies (including insulinomas), no tumor-related immunologic alteration has yet been identified similar to the circulating antineuronal antibodies found in patients with paraneoplastic subacute sensory neuropathy (usually occurring in association with small cell lung cancer) [254]. In people, other possible causes of the neuropathy have included toxic factors produced by the tumor, metabolic causes (e.g., the tumor competing with the host for essential metabolites), vitamin/nutritional deficiency, vascular causes (e.g., vasculitis), and viral infections causes; however, definitive proof is lacking for each of these [252,255].

Hypothyroid Neuropathy

Hypothryroidism is common in dogs but rare in cats and most cases of acquired canine hypothyroidism are associated with immune-mediated lymphocytic thyroiditis/idiopathic thyroid atrophy [256,257]. A hypothyroid-associated neuropathy commonly occurs in mature to middle-aged dogs, usually of the large-breed variety. The few cases reported in the literature [258-261] do not reflect the prevalence of this metabolic neuropathy, based on muscle and nerve biopsy material that we have examined (both at the Scott-Ritchey neuromuscular laboratory at Auburn University and at my peripheral nerve laboratory) from numerous hypothyroid dogs. Sub-clinical cases have been recognized [534]. Clinical signs may include exercise intolerance, progressive weakness (e.g., paraparesis, tetraparesis), muscle atrophy (mainly appendicular) and depressed spinal reflexes. Other signs may include pelvic limb proprioceptive deficits, unilateral/bilateral facial nerve paresis/paralysis, ventrolateral strabismus, and decreased corneal/facial sensitivity. Intermittent forelimb lameness is less

commonly reported [533]. In one comprehensive study of the neurological manifestations of hypothyroidism in 29 dogs, lower motor neuron signs were seen in 11 dogs, 9 dogs had peripheral vestibular deficits, 4 had megaesophagus, and 5 had laryngeal paralysis [260]. Peripheral neuropathy has been seen in several hypothyroid dogs with megaesophagus and myasthenia gravis [261]. Electrodiagnostic studies in appendicular muscles have revealed multifocal patterns of fibrillation potentials, positive sharp waves, decreased motor and sensory nerve conduction velocities, and complex repetitive discharges. Similar changes may be found in facial muscles. In some instances, there is a lack of correlation between the degree of EMG abnormalities and the severity of the clinical weakness [258]. Dogs with vestibular deficits may have abnormal brainstem auditory-evoked responses [260]. CSF analysis usually reveals normal cellularity with normal or mild/moderate protein increase (25 - 110 mg/dL) [259,260]. Serum cholesterol levels are usually increased. Muscle changes reflect varying degrees of neurogenic atrophy (angular atrophy of muscle fibers, especially type 2 fibers; compensatory hypertrophy) while teased nerve fiber studies and semithin sections are typically characterized by mixed pathology involving demyelination/remyelination and axonal necrosis. The underlying pathology appears to be a sensorimotor polyneuropathy and, based on my experiences, at least some of these cases have a distal distribution (i.e., distal sensorimotor polyneuropathy).

Diagnosis is based on serological evidence of hypothyroidism (low serum T4 concentration and inadequate response to thyroid-stimulating hormone administration) [260]. Prognosis is often favorable. In one study involving 29 dogs, most dogs recovered within 2 to 3 months of thyroid hormone supplementation (20 µg/kg of L-thyroxine PO bid). Dogs with megaesophagus improved over 4 months, while dogs with laryngeal paralysis showed partial improvement after 5 months. One caveat is that we have encountered a number of dogs in which there is less dramatic or no clinical response to long-term thyroid hormone supplementation.

Note that affected dogs may also have generalized signs of hypothyroidism, including thinning of the haircoat, alopecia, dry skin with epidermal scales and flaking, etc.

The pathophysiology surrounding hypothyroid neuropathy remains unexplained [262]. In people with hypothyroidism, a mild peripheral neuropathy is relatively common and may include facial mononeuropathy, sensorineural hearing loss, distal sensory neuropathy, and sensorimotor polyneuropathy [103,263]. One study reported changes in nerves consistent with a dying back process and possible underlying slow axonal transport [264]. There may be preferential loss of larger caliber myelinated fibers [265]. Carpal tunnel syndrome (median nerve mononeuropathy at the wrist) is the most common mononeuropathy encountered [103]. As we have seen in dogs, the relative proportions of axonal degeneration (secondary to disturbance of neuronal metabolism?) and demyelination (primary Schwann cell involvement?) varies from case to case [264,266,267]. Onion bulb formations are infrequently found. Ultrastructural changes in affected human nerves include prominent cluster formations and excessive glycogen deposition in Schwann cells, myelinated and unmyelinated axons, endothelial cells, and perineurial cells [265,268].

Laryngeal Paralysis

Innervation of three of the four intrinsic laryngeal muscles (dorsal and lateral cricoarytenoid muscles and thyroarytenoid muscle) comes from the special visceral efferent axons of the recurrent laryngeal nerves. The fourth muscle (cricothyroid muscle) is supplied by the motor branch of the cranial laryngeal nerve [269]. The recurrent laryngeal nerve on each side is derived from the vagus nerve which in turn originates from the nucleus ambiguus in the brainstem [149]; so theoretically, a lesion in any of these anatomic locations might lead to laryngeal dysfunction. The efferent axons to the larynx are categorized as special visceral efferent fibers [149]. Laryngeal paralysis (LP) classically results from unilateral or more commonly, bilateral denervation of the laryngeal abductor muscles (dorsal cricoarytenoid muscles), which leads to impaired abduction of the vocal fold(s), glottic obstruction, and dyspnea [269-271].

Hereditary, idiopathic, and acquired forms of this potentially fatal disorder have been reported in dogs and cats. A hereditary form (autosomal dominant) has been documented in Bouvier des Flandres dogs either as unilateral or bilateral disease [270,272,273]. A inherited or presumed hereditary form has been reported in young Siberian Huskies, Husky cross-breeds, Bull Terriers, Dalmatians, Rottweilers, white-coated German Shepherds, and Pyrenean Mountain dogs [172,271,274-277,531]. Affected Huskies share a phenotype of blue eyes, and white freckled face. LP has also been recently reported in young Rottweiler puppies in association with neuroaxonal dystrophy [278] and spongy degeneration of the CNS [279]. The idiopathic form has been reported mostly in middle-aged and older large and giant breed dogs, such as St. Bernard, Chesapeake Bay Retriever, Irish Setter, Afghan Hound, Labrador Retriever and Rottweiler, but medium and small/toy breeds also may be affected [269,280-282]. Male dogs, particularly if castrated, were more frequently affected than females in one reported survey [280]. In another study, the severity of the laryngeal paralysis was correlated with increasing age in larger breed dogs [283]. Acquired LP is sporadically reported in dogs. Bilateral LP resulted from entrapment of both recurrent laryngeal nerves by fibrous tissue surrounding a peritracheal abscess (thought to be caused by a foreign body penetrating the wall of the esophagus) in an 8 month old Cocker Spaniel [284]. LP has also been seen in dogs as a surgical complication in the treatment of carotid body tumors [285] and thyroid carcinomas [286]. Trypanosomiasis was considered

to be the cause of LP in a 12 year old Labrador Retriever [287]. Laryngeal paralysis may be one of several signs seen in animals with rabies. LP in some older dogs has also been linked with hypothyroidism (see hypothyroid neuropathy) [260,280,281,288,532]. LP has also been reported in two older dogs as a possible complication of paraneoplastic neuropathy (both dogs were also hypothyroid) [289]. Dysphonia/LP may also be observed in animals with coonhound paralysis/idiopathic polyradiculoneuritis, chronic inflammatory demyelinating polyneuropathy, in German Shepherd dogs with giant axonal neuropathy, and in some dogs with sensory ganglioradiculitis.

In cats, congenital and idiopathic forms of LP have been reported sporadically and earlier reports favored castrated males [290-292]; however in a more recent study, no gender or breed predilection was noted, although 7/8 male cats were neutered and all females were spayed [293]. Acquired LP in cats has been reported as a result of trauma to the neck [294], lymphomatous infiltration of the vagus nerve [295], cystic thyroid adenoma [296], adenocarcinoma of the tympanic bulla and damage to the recurrent laryngeal nerve [297], and seen as a complication of lead poisoning [298], percutaneous ethanol injection for the treatment of hyperthyroidism [299], surgical repair of intrathoracic tracheal avulsion [300], surgical thyroidectomy [301], and other neck/mediastinal surgeries (e.g., removing a thyroid adenoma, ligation of a patent ductus arteriosus, thymectomy) [302,303].

Onset of clinical signs in the congenital/hereditary forms of LP in dogs is from 4 to 6 months of age. The acquired and idiopathic forms usually develop in older animals from 1 to 13 years of age. Clinical signs reflect respiratory, primarily inspiratory, distress and are characterized by increasing loss of endurance, progressive laryngeal stridor (especially on exertion), voice changes (dysphonia), dyspnea, cyanosis during episodes of severe dyspnea, and collapse with complete airway obstruction. Clinical signs are usually of several months duration. In cats, excessive head shaking and abnormal purring may also be noted. Megaesophagus is usually not a clinical feature of LP in cats, although it has been confirmed radiographically in occasional cats [293]. Note that unilateral paralysis (also termed laryngeal hemiplegia) in dogs may be subclinical [269,270], although in working dogs, such as racing Greyhounds and Siberian Husky sled dogs, unilateral paralysis can result in obstructive dyspnea and interfere with racing function [269]. In cats, unilateral LP can be subclinical [294] or result in mild clinical signs. Unilateral congenital and idiopathic forms tends to affect the left side of the larynx in dogs and cats [270,293].

Diagnosis of LP is based on clinical signs, laryngoscopy showing impaired abductor dysfunction, and EMG evidence of denervation potentials in the intrinsic laryngeal muscles. Ultrasound (echolaryngography) may also be a useful diagnostic technique [304]. There is histological evidence of neurogenic atrophy in laryngeal muscles. In the Bouviers, lesions found in the recurrent laryngeal nerves (e.g., axon fragmentation, digestion chambers, endoneurial fibrosis) were found at all levels of the nerves and were considered to be secondary to lesions involving the nucleus ambiguus [270]. Gliosis and neuronal atrophy of the vagal nuclei were reported in an affected Husky Cross puppy [271]. Degenerative changes, including axon and myelin degeneration, axonal loss, and endoneurial fibrosis have been noted in recurrent laryngeal nerve samples from older dogs with idiopathic LP [269].

Laryngeal paralysis has also been noted in dogs with clinical, electrodiagnostic (EDX), and pathological evidence of a more generalized polyneuropathy [281], which has been termed laryngeal paralysis polyneuropathy complex (LPPC) [172]. This condition has now been seen in young Dalmatians, Rottweilers, and Pyrenean Mountain dogs [172,276,277]. In addition to the clinical signs described above, other neurological abnormalities associated with the laryngeal paralysis included spinal hyporeflexia, limb muscle atrophy or fasciculations, limb hyperextension, facial/lingual paralysis, and hypermetria. Megaesophagus was a common feature in affected Dalmatians and Pyrenean Mountain dogs (megaesophagus was found in one affected Rottweiler, while regurgitation was associated with hiatal hernia/gastroesophageal intussusception in another puppy). Four of the five Rottweiler puppies had bilateral lenticular cataracts. Bilateral paralysis of the vocal folds (arytenoid cartilages) was noted in all dogs (although not always symmetrical) under light sedation. EMG abnormalities included fibrillation potentials and positive sharp waves in a variety of muscles including laryngeal, esophageal, facial, masticatory, and distal appendicular muscles. Nerve conduction velocities (NCVs) may be normal or mildly decreased. Direct evoked compound muscle action potentials have shown low amplitude without evidence of dispersion (polyphasic waves), suggestive of axonal degeneration. Congenital deafness has been demonstrated in several dogs using BAER testing. Neurogenic atrophy was observed in intrinsic laryngeal and appendicular muscles. Changes in cranial and appendicular nerves (motor and sensory, as well as in autonomic nerves) were dominated by axonal necrosis and loss of medium sized and larger-caliber myelinated fibers, with the intensity of the changes being more severe in distal parts of nerves (e.g., recurrent laryngeal nerve). Ultrastructural changes included loss of myelinated fibers, variable ovoid presence, marked increase in endoneurial collagen, numerous Büngner bands (denervated Schwann cells), and evidence of unmyelinated fiber involvement (e.g., collagen pockets, flattened axons, empty Schwann cell subunits). To date, no lesions have been found in the nucleus ambiguus of the brain stem. Morphological, morphometric, and/or EXD studies suggest that LP in Dalmatians, Rottweilers, and Pyrenean Mountain dogs represents a distal axonopathy (or dying-back disease).

While O'Brien and colleagues stated that no clinical evidence of central or peripheral nerve deficits were found in their cases of idiopathic LP in older, larger breed dogs (although they reported Wallerian degeneration in sciatic nerve from one

affected dog) [269], paresis and foot drop due to denervation of the cranial tibial muscle have been occasionally observed in affected young Bouviers [270]. Furthermore, signs of pelvic limb weakness are sometimes seen in older dogs with idiopathic LP [280,281]. In these animals, pelvic limb reflexes may be diminished and there may be evidence of abnormal spontaneous potentials (fibrillation potentials and positive sharp waves) on EMG studies, along with slowed motor NCVs. Muscle/nerve biopsies may show neurogenic muscle atrophy, (e.g., scattered angular atrophic fibers, small fiber group atrophy), demyelination, and variable axonal degeneration [281]. A more generalized neurological disorder has also been observed in two cats with laryngeal paralysis that were eventually euthanized because of progressive neuromuscular signs [292]. In summary, it appears that hereditary and idiopathic forms of LP in dogs and cats often may be related to a more generalized polyneuropathy.

Serum cholinesterase activity, thyroid testing, serum antinuclear antibody and rheumatoid factor titers, Coombs testing, and serum anti-acetylcholine receptor antibody levels are normal in dogs with LPPC, and there is no evidence of lead toxicity. Prognosis in dogs with congenital/hereditary LP is guarded to poor, especially if megaesophagus is present due to the high risk of inhalation pneumonia. Feeding of a liquid gruel from an elevated platform may be beneficial in dogs with megaesophagus. Laryngeal tie-back surgical procedures may provide dramatic relief of the dyspnea, but multiple surgeries may be required during the first 12 months. Additional complications in dogs are joint contractures (especially the carpus), which may be surgically managed by arthrodesis. Conversely, idiopathic paralysis in older dogs may have a favorable prognosis since megaesophagus is typically not a feature of the disorder, clinical signs of more generalized peripheral nerve disease appear to milder, and the dominant pathology in nerves is more likely to be demyelination rather than axonal degeneration. Harvey and colleagues reported that thyroid hormone supplementation resulted in marked clinical improvement in their older hypothyroid dogs with LP [288]. Surgical management, such as arytenoidectomy and vocal fold removal, arytenoid lateralization, cricoarytenoid laryngoplasty, and castellated laryngofissure may be very effective [292,305-308]. In one experimental study, bilateral arytenoid cartilage lateralization produced more consistent clinical improvement, a wider rima glottidis, increased inspiratory air flow, and a significant increase in post-operative arterial oxygen tension when compared to castellated laryngofissure [309]. Thyroarytenoid lateralization also requires less surgical time to perform than cricoarytenoid laryngoplasty [307]. Despite favorable reports, it should be noted that surgical repair of idiopathic/acquired forms of laryngeal paralysis may be associated with high postoperative complications (particularly aspiration pneumonia) and mortality rates [532]. (These complications were more commonly associated with bilateral arytenoid lateralization and partial laryngectomy techniques). Surgical intervention is also beneficial in cats with idiopathic LP [293,302], although prognosis is guarded to poor in suspected congenital/idiopathic cases developing progressive neuromuscular disease [292]. Prognosis for cats with mild signs (e.g., in those with traumatically-induced unilateral LP) may be favorable with conservative treatment, such as moving cats indoors, avoiding excitement, and restricting exercise [293]. Prognosis for animals with acquired LP will usually depend on the underlying cause. In cats with subclinical traumatic laryngeal hemiplegia, resolution of the impaired arytenoid cartilage abduction occurred spontaneously over several months [294]. Prevention of the inherited form by breeding control is indicated.

Note that LP may also be a component of the hereditary Alaskan Malamute polyneuropathy that was thought to be eradicated in Norway in 1982 [6]. Dysphonia has been observed in some Alaskan Malamutes with a similar if not identical condition that has been reported recently in the United States and Germany [3,4].

Optic Neuritis

Optic neuritis is an inflammatory condition of the optic nerve(s) that results in loss of vision. It may be associated with primary ocular disease or can occur secondary to systemic inflammatory disease. In most animals, the underlying cause is not determined. The condition is not uncommon, affecting dogs [310,311] more frequently than cats [312,313]. There is no apparent breed or gender predisposition, however, most affected dogs are older than 3 years of age.

In dogs, diagnostic considerations include canine distemper, ocular form of granulomatous meningoencephalomyelitis, systemic mycosis (e.g., cryptococcosis, blastomycosis), toxoplasmosis, neoplasia, trauma, and acute toxicity (e.g., lead, chlorinated hydrocarbon, or clioquinol toxicity, and closantel intoxication) [78,314-327]. Optic neuritis may also be seen as a complication of uveodermatologic syndrome, a disorder characterized by bilateral panuveitis and skin and hair depigmentation that is similar to human Vogt-Koyanagi-Harada syndrome in people [328], although the associated meningitis in the human disease has not been reported in dogs.

An apparently healthy animal may present with a history of unilateral or bilateral blindness of sudden onset. Pupils usually are unilaterally or bilaterally dilated and unresponsive to light stimulation. The disorder may be associated with orbital pain or pain with ocular movement [329]. Ophthalmoscopic examination may or may not be helpful. Ophtalmoscopic abnormalities may include an edematous, elevated optic disk and engorged retinal vessels. Focal hemorrhage may be present. Active or inactive chorioretinitis may accompany the optic neuritis. Atrophy of the optic nerve frequently follows repeated episodes of acute optic neuritis. Optic neuritis is distinguished from papilledema in that vision is preserved in the latter condition. Optic neuritis is termed "intrabulbar" if fundic changes are seen ophthalmoscopically or "retrobulbar" if no

changes are seen (note that acute optic neuritis is often retrobulbar) [329]. Neurological exam is frequently normal.
The first line of treatment should be directed at the primary disease process that initiated the optic neuritis. However, since the cause is frequently undetermined, the animal may be treated symptomatically with retrobulbar corticosteroids (e.g., betamethasone, 2.5 mg) in conjunction with oral corticosteroid administration (e.g., prednisolone, at 2 mg/kg daily, divided bid, for 10 to 14 days, followed by half this dosage for two more weeks, and gradual reduction to maintenance therapy every other day for up to one year). Prognosis is guarded. Clinical response to treatment can be difficult to assess and the course is unpredictable. Some animals have a return of vision within 1 or 2 days, while others may show only gradual improvement over several months. Clinical exacerbations may occur if treatment is prematurely stopped. In some animals, the disease process may progress, resulting in permanent structural changes and irreversible blindness.
Optic nerves were involved in a subclinical, inflammatory demyelinating CNS disorder in cats characterized by infiltrating lymphocytes, plasma cells and macrophages, and intracytoplasmic inclusions consisting of tubular structures with similarities to paramyxovirus nucleocapsids [330,331].

Paraneoplastic Neuropathy
The frequency of peripheral neuropathy in human patients with cancer (see also paraneoplastic disorders) varies with the screening technique employed. The clinical incidence of some forms of paraneoplastic neuropathy has been estimated to be 5 to 16% [254]. This figure increases to more than 40% if quantitative sensory testing or electrophysiological / pathological evaluation are performed, reflecting the high incidence of subclinical neuropathy [252,332-334]. As stated by Mcleod [255], the actual frequency of peripheral neuropathy in malignancy is difficult to ascertain since it "…depends on the pathological type and site of tumor, the stage and duration of the illness, the diligence with which it is sought, the techniques of investigation employed, and the criteria for diagnosis". Several paraneoplastic neuropathies have been recognized in human cancer patients [252,254,255,332]: subacute sensory neuropathy, sensorimotor neuropathy (including mild terminal neuropathy, severe rapidly evolving or relapsing sensorimotor neuropathies, microvasculitic neuropathy, and sensorimotor neuropathies associated with malignant monoclonal gammopathies), Guillain-Barré syndrome that is sometimes seen in association with Hodgkin's disease, and brachial plexitis. Paraneoplastic autonomic dysfunction may occur, usually accompanying other paraneoplastic syndromes. Pathological findings vary with the particular paraneoplastic neuropathy [254,255]. In subacute sensory neuropathy (SSN), there is loss of neurons in spinal ganglia along with focal inflammatory infiltrates, and dorsal column degeneration. In paraneoplastic sensorimotor neuropathies, axonal or demyelinating changes, either inflammatory or non-inflammatory, may be observed. The pathogenesis of some forms of paraneoplastic neuropathies appears to be related to molecular mimicry in which antibodies produced against the tumor cross-react with neural antigens, e.g., SSN is associated with circulating (serum and CSF) antineuronal antibodies (anti-Hu) expressing specificity for neuronal nuclear antigens [335,336]. In most instances, the malignancy is small cell lung cancer. In contrast to SSN, the underlying pathogenesis of paraneoplastic sensorimotor neuropathies (much more common than SSN) remains unclear but appears unassociated with immunological mimicry (no tumor-specific antibodies have been recognized) or tumor toxin [255]. The malignancy often involves the lung, but carcinomas have been found in a variety of organs (e.g., pancreas, stomach, rectum, uterus, breast, colon, cervix, kidney, prostate, and testis) [255]. Some forms of paraneoplastic sensorimotor neuropathies may represent dying-back axonopathies [254]. In some instances, paraneoplastic neuropathies may be obscured by neurotoxic chemotherapeutic agents, metabolic disorders, and inactivity [252].
The clinical or subclinical incidence of PNS paraneoplasia in animals is presently unknown; however, peripheral nerve lesions may be facilitated by presence of certain types of cancer in animals, as in people. In one prospective qualitative and quantitative study on the effects of cancer on the PNS in dogs, the highest percentage of abnormalities in teased nerve fibers from dogs with malignancies were found in bronchogenic carcinoma (59%), mammary adenocarcinoma (59%), malignant melanoma (48%), insulinoma (47%), osteosarcoma (39%), thyroid adenocarcinoma (35.5%) and mast cell tumor (32%) [236]. The major histopathological findings in this study included paranodal-segmental demyelination, remyelination, axonal degeneration, and myelin globules. Overall, 16 of 21 dogs (76%) had a significantly greater number of lesions in peripheral nerves than age-matched controls. It is interesting to note that two of the tumor cases in our prospective study (those with the highest number of abnormalities) were bronchogenic carcinomas. Such tumors have long been recognized for their intimate association with paraneoplastic neuropathies in people [337,338]. It was also evident that different types of malignancies (mammary adenocarcinoma, malignant melanoma, insulinoma, osteosarcoma, etc.) resulted in a differing incidence of neuropathy, a finding also well-recognized in human cancer patients. In addition, the severity of the neuropathy sometimes varied markedly with tumors of the same type, probably reflecting differences in the stage and duration of the illness. Of all the malignant tumors in our study, lymphosarcoma appeared to have the least neuropathic effect. The neuropathies in dogs of this study were mainly subclinical.
Clinical hallmarks of the neuropathic syndrome are reduced or absent spinal/cranial reflexes, flaccid weakness, reduced muscle tone, paralysis of limb or head muscles, and after 1 to 2 weeks, neurogenic muscle atrophy. Dysphonia may also be detected. Clinical neuropathies have been seen sporadically in dogs with malignant tumors, including bronchogenic

carcinoma, insulinoma, lymphosarcoma, fibrosarcoma, leiomyosarcoma, hemangiosarcoma, and undifferentiated sarcoma [170,234,235,289,339-341]. In two of these reports, the neuropathies had a distal distribution based on electrodiagnostic (EDX) and pathological studies [235,289]. Abnormal EDX findings include fibrillation potentials, positive sharp waves, and slowed motor nerve conduction velocities. In my peripheral nerve laboratory, I have examined nerve samples from dogs with synovial cell sarcoma and adrenal adenocarcinoma that were accompanied by clinical neuropathies.
In contrast with people [342], malignant monoclonal gammopathies (dysproteinemic neuropathies) rarely seem to involve the peripheral nerves in dogs or cats [343,344]; however, a polyneuropathy (based on EMG findings) was reported in a 12 year old German Shepherd with multiple myeloma and monoclonal hypergammaglobulinemia [345]. In people, dysproteinemic neuropathy or NAP (neuropathy associated with paraproteinemia) are relatively common and the paraproteins (circulating immunoglobulins, or M-Proteins) may be IgM, IgG, or IgA, consisting of the whole immunoglobulin molecule or only the heavy or light chain [342]. Diseases associated with NAP include monoclonal gammopathies of unknown significance (MGUS), multiple myeloma, Waldenstrom's macroglobulinemia, osteosclerotic myeloma/POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes), primary amyloidosis, lymphoproliferative diseases (lymphoma, leukemia), heavy chain disease, and cryoglobulinemia [342,346]. The majority of NAP cases appear to be IgM with myelin sheath anti-MAG (myelin-associated glycoprotein) activity and characteristic widely-spaced myelin lamellae (associated with separation of the intraperiod line), along with evidence of a distal sensorimotor symmetrical neuropathy characterized by demyelinating changes (active myelin breakdown, denuded axons, thinly myelinated fibers, and onion-bulb formations) [342,347]. Axonal degeneration and loss of myelinated fibers may also be present, especially in chronic cases.
Too few cases have been documented to evaluate treatment strategies of paraneoplastic neuropathies in dogs and cats. In a recent report, antineuronal antibodies were not found in 120 dogs with extraneural tumors suggesting that screening for ANNA may not be useful for detecting dogs with paraneoplastic neuropathies [516]. Prognosis is guarded to poor in cases that have been reported, although recovery occurred in one dog following surgical removal [341] and in another with multiple myeloma treated with melphalan and prednisolone [345].

Peripheral Nerve Tumors
Readers are referred to chapter 2 and Neoplasia of the Nervous System for a review of neoplasms involving peripheral nerves (see peripheral nerve tumors).

Polyradiculoneuritis
By definition, polyradiculoneuritis is an inflammatory condition primarily involving multiple nerve roots. It may be one of the more commonly observed and least understood conditions in dogs and cats. It is becoming evident that there are a number of nerve root disorders (polyradiculoneuritides or polyradiculoneuropathies) that are characterized clinically by sudden onset of paresis, paralysis, or tetraplegia. Cranial nerve involvement may be prominent and there may be a relapsing clinical course. Differentiation of these conditions from pure primary peripheral nerve disorders (those without nerve root involvement) or junctionopathies can be difficult but may be facilitated by electrodiagnostic (EDX) testing [86,348]. With nerve root lesions, there may be abnormal latencies in F-waves (small compound muscle action potentials [CMAPs] resulting from antidromic excitation of motor neurons) or H-waves (small CMAPs that occur following nerve stimulation resulting from impulses in sensory nerve fibers that monosynaptically excite ventral horn cells). The latency of the H-wave is about the same as the F-wave but requires functional dorsal roots, in addition to ventral roots and proximal peripheral nerve). Additional EDX testing includes determination of compound action potential amplitudes, F-ratios, F-wave amplitudes, and electromyography [349]. There may be increased levels of CSF protein without pleocytosis (albuminocytologic dissociation), and nerve root biopsy may show evidence of inflammatory cell infiltration. It is likely that many cases of polyneuritis are actually polyradiculoneuritides. A tentative classification of polyradiculoneuritis in dogs and cats follows. Readers should note that Coonhound paralysis and Idiopathic polyradiculoneuritis described below have been termed "acute canine polyradiculoneuritis" by some authors [433].

Coonhound Paralysis -
Coonhound paralysis (CHP) is a sporadically-occurring neurological disease of dogs, occurring especially in raccoon-hunting breeds [350-353]. The pathogenesis is unknown. A raccoon bite has been a consistent antecedent in CHP. The condition has been reproduced experimentally by injection of raccoon saliva into a dog that had recovered from two earlier spontaneous attacks [354]. Results of this work suggested that raccoon saliva contains the etiologic factor for CHP and that only specifically susceptible dogs are at risk of developing CHP when exposed to this factor.
Interest has focused on CHP due to its resemblance to Guillain-Barre syndrome (GBS) in people and its potential as an elucidating model. Like the human syndrome, CHP may have an immunological pathogenesis, although results of one study of CHP did not conform with the evidence presented in GBS for an obligatory role of macrophages in initiating myelin

damage [355]. However, the observed changes do resemble those reported in immunological-mediated experimental allergic neuritis [356].
Pathological findings are associated with a polyradiculoneuritis, with both segmental demyelination and concurrent degeneration of myelin and axons. Leukocytic infiltration, consisting mostly of cells of the monocyte-macrophage series, and scattered aggregates of lymphocytes and plasma cells also are observed. Changes occur in peripheral nerves and nerve roots, especially in the latter and more consistently in ventral roots than dorsal roots. In one comprehensive study, lumbosacral roots and spinal nerves were more involved than thoracic and cervical roots and spinal nerves [357]. Neutrophils may be present early in severely affected dogs. Chromatolytic changes in spinal motoneurons may occur secondary to severe axonal degeneration in peripheral nerves and nerve roots.
The disease affects dogs of any breed, both sexes, and usually of adult age. Clinical signs frequently appear 7 to 11 days after an encounter with a raccoon. Onset is marked by weakness and pelvic limb hyporeflexia, although thoracic limb involvement may sometimes be the initial and dominant clinical sign. Paralysis progresses rapidly, resulting in a flaccid symmetric tetraplegia; however, milder forms without paralysis can occur. The duration of paralysis varies from several weeks to 2 or 3 months. Motor impairment is more pronounced than sensory changes, although many dogs appear to be hyperesthetic to sensory stimuli. Bladder and rectal paralysis are not usually observed. In severely affected animals, there may be complete absence of spinal reflexes, facial weakness, loss of voice, inability to lift the head, and labored respiration. Motor nerve conduction velocities may be markedly reduced and EMG studies reveal widespread denervation 6 to 7 days after the onset [355]. F-waves can be altered (e.g., prolonged F-wave latencies and F-wave dispersion, decreased F-wave amplitudes), depending on the clinical signs and duration of disease [358]. In addition, increased F-ratios, and decreased CMAPs may be helpful EDX features [349]. Note that in some cases, the EDX changes appear to have a distal distribution. Similar findings occur in people with GBS and it has been explained by the preferential involvement of longer nerves associated with their greater chance of being affected by a multifocal demyelinating process [524]. Elevated protein with normal cell counts in CSF has been reported, especially in samples obtained from lumbar puncture [353]. This protein is predominantly albumin and its origin is thought to be more consistent with protein transudation rather than intrathecal immunoglobulin production [511]. Presence of circulating antibodies against raccoon saliva has been demonstrated using ELISA assays [358].
Prognosis is usually favorable, but dogs with severe axonal degeneration may die from respiratory paralysis or may have protracted, incomplete recoveries, and some animals may not show any clinical improvement. Protection from future attacks is short-lived or nonexistent. Affected dogs may have a greater chance of redeveloping paralysis on subsequent encounters with raccoons [353]. Treatment is symptomatic. Corticosteroids in our experience have not been effective in expediting recovery. Good nursing care is essential, including physiotherapeutic rehabilitation.
In people, GBS (or acute inflammatory demyelinating polyradiculoneuropathy) appears to be an autoimmune disease, involving both cell-mediated and humoral factors (e.g., IgG and IgM antibodies) resulting from aberrant immune responses against various components of peripheral nerve fibers (the myelin sheath is the specific target structure) and is characterized by presence of inflammatory lesions (lymphocytes and macrophages) and localized demyelination throughout the PNS [347]. Axonal lesions also occur but are usually less severe than the demyelinating lesions. However, two forms of axonal-GBS are recognized: acute motor-sensory axonal neuropathy and acute motor axonal neuropathy [359,360]. Some forms of GBS appear to be related to *Campylobacter jejuni* infection (especially the axonal forms), while other antecedent events (or "triggers") include viral and spirochete infection, surgery, and vaccination (including some strains of rabies) [347]. While the existence of a primary axonal neuropathy in a small percentage of human patients having a poor prognosis has been reported [361,362], we found that the intensity and type of lesion in 13 GBS patients with severe clinical disease (all bed-ridden in an intensive care unit and most requiring assisted ventilation) had no predictive value for eventual clinical recovery, but was correlated with length of clinical course (axonal lesions dominated in 23% of patients, while axonal lesions in presence of the more classical demyelinating form of GBS was seen in a further 23% of patients) [363]. In people, supportive care is the cornerstone of treatment as the majority of patients recover once the acute stage is passed, while specific treatment includes plasmapheresis and intravenous immunoglobulins [347]. Corticosteroids are usually ineffective.

Idiopathic Polyradiculoneuritis -
A condition that appears to be identical to Coonhound paralysis with respect to onset, clinical signs, clinical course, EDX findings, and pathology occurs in dogs that have had no possible exposure to raccoons [364,365]. This condition has a world-wide distribution, occurs in countries where raccoon do not exist [366] and may have an incidence much higher than the literature suggests [367-369]. Mature dogs are typically affected; however, a suspected polyradiculoneuritis has also been reported in a 14 week old Rottweiler puppy in the UK [370]. Note that mild forms of polyradiculoneuritis may occur in dogs in which flaccid paralysis does not develop fully in any muscle group and animals maintain ambulatory function [368]. As with Coonhound paralysis, some dogs with idiopathic polyradiculoneuritis may require ventilatory support [367]. In my experience, pathological findings in peripheral nerve biopsy samples (e.g., common peroneal nerve) reflect the clinical

course of idiopathic polyradiculoneuritis: minimal changes are seen within the first 7 to 10 days of clinical signs. In chronic cases, the incidence of changes increases, usually reflecting a mixture of axonal degeneration, demyelination, and remyelination. Idiopathic polyradiculoneuritis is clinically, but not pathologically, similar to distal denervating disease, reportedly the most common canine polyneuropathy in the UK. In a recent study examining the relationship between acute polyradiculoneuritis and prior infection or exposure to various infectious agents, affected dogs had significantly higher serum IgG titers against *Toxoplasma gondii* than controls, although a causal relationship was not established [510]. Despite the clinical prevalence of polyradiculoneuritis, demonstration of inflammatory cell infiltrates in peripheral nerve biopsies (e.g., common peroneal nerve or tibial nerve sampled at the level of the stifle) seems to be very uncommon, as least in my experience. Undoubtedly, inflammation would be more frequently observed in nerve root biopsy samples. Idiopathic polyradiculoneuritis occurs infrequently in cats. As with dogs, demonstration of inflammatory cells in peripheral nerve biopsy samples from cats with clinical evidence of acute polyradiculoneuritis is unusual. Of all the feline peripheral nerves processed in my laboratory, I have seen only one case of polyneuritis in a cat with clinical signs suggestive of a polyradiculoneuritis. A severe, acute polyneuritis associated with anemia and transient icterus and fever was reported in a four year old neutered female cat [371]. Pathological findings were largely restricted to peripheral nerves and axons and consisted of extensive destruction of myelin and axons and macrophage infiltration. The variable presence of perivascular cuffs of lymphocytes and plasma cells was commensurate with an inflammatory disease and suggested a possible viral and/or immune-mediated etiology. Clinical signs included tetraparesis progressing to tetraplegia, lack of placing and tendon reflexes, depressed flexor reflexes, and hyperesthesia. Cranial nerves, perineal reflex and tail function were normal, as was mental status. Severe muscle wasting was present in all limbs after two weeks. EDX data were not available. Brain, spinal cord and nerve roots were not examined.

Cauda Equina Polyradiculoneuritis -
A polyradiculoneuritis has been reported in two dogs - a 9 year old female Labrador Retriever and an 8 month old female Yorkshire Terrier - that were presented with a lumbosacral syndrome (pelvic limb paraparesis, muscle hypotonia and atrophy, loss of patellar reflexes, and proprioceptive loss) [372]. Pain sensation, bladder function, and anal reflex were intact. Motor nerve conduction velocity was decreased in the sciatic-tibial nerves. Latency of F-waves was markedly increased following stimulation at the level of the greater trochanter and at the hock. Pathologically, lesions in both dogs were located in the lumbosacral nerve roots that comprise the cauda equina. Dorsal and ventral nerve roots, as well as dorsal root ganglia were involved. There was marked interstitial and perivascular infiltration of mononuclear cells (lymphocytes, plasma cells, and macrophages), axonal degeneration, demyelination, and remyelinating clusters. Milder changes were seen in nerve roots throughout the spinal cord, as well as in roots of the trigeminal nerve. Muscle changes reflected neurogenic atrophy. Intraneural injection of serum from an affected dog failed to induce demyelination in normal rat nerve. Serum levels of the myelin-specific protein, P2, were not elevated in either dog. Protein level in CSF was increased in one dog.

Chronic Inflammatory Demyelinating Polyneuropathy -
Over the past several years, we have accumulated data on a spontaneous demyelinating peripheral neuropathy that we have called chronic inflammatory demyelinating polyneuropathy (CIDP) [373]. Based on surveys of biopsies received from the Scott-Ritchey neuromuscular laboratory at Auburn University and from my private peripheral nerve laboratory, CIDP is one of the more common neuropathies seen in dogs and cats. This disorder occurs in dogs and cats of either gender and does not appear breed-related. Mature animals of any age may be affected (from 1 to 14 years). Onset of signs is usually insidious and the course is typically chronic, often relapsing, and frequently slowly progressive. Clinical signs are usually first noticed in the pelvic limbs and, in most animals, progress to involve the thoracic limbs. Clinical signs include tetraparesis, sometimes progressing to tetraplegia, stumbling gait, and hyporeflexia. Less commonly observed signs are muscle trembling (dogs), intermittent shifting limb lameness characterized by a plantigrade stance (cat), and ventroflexion of the head and neck (cat). Facial nerve paralysis or laryngeal paralysis are seen occasionally in dogs, while megaesophagus/regurgitation is found in some cats. Serological testing is normal, although one cat had an IgG monoclonal gammopathy. CSF analysis is usually normal, although occasional animals may show a moderate protein increase. Motor nerve conduction velocities (NCVs) are decreased, along with temporal dispersion, decreased amplitudes and prolonged latencies of the compound muscle action potentials. Slow sensory NCVs have also been noted. EMG studies in this report were either normal or revealed mild, patchy pattern of fibrillation potentials and positive sharp waves. Pathologically, changes in teased single fibers from peripheral nerves are dominated by multifocal paranodal demyelination, and sometimes segmental demyelination. Other changes include remyelination and variable numbers of fibers with internodal globules. Axonal degeneration is infrequently observed. Scattered, thinly myelinated fibers are seen on semithin sections. Severe changes may include presence of onion-bulbs and rarefaction of myelinated fibers. Ultrastructural studies reveal macrophages within myelinated fibers stripping the myelin sheaths, naked and remyelinating axons, and focal/multifocal endoneurial mononuclear cells, including lymphocytes, rare plasma cells, macrophages with myelin debris, and vacuolated fibroblasts.

Indirect immunofluorescence revealed positive IgG staining in peripheral nerve myelin sheaths from two dogs. No fluorescence was seen using anti-dog or anti-cat C3 (positive immunofluorescence to anti-human IgM and C3d was observed in control dog and cat nerve sections incubated with serum from a human patient with an IgM monoclonal gammopathy [374]). In skeletal muscle, minimal lesions are seen , apart from mild fiber size variation in some cases. Diagnosis is based on clinical signs, relapsing clinical history, and nerve biopsy studies. Prognosis is often favorable with treatment. The majority of dogs and cats (approximately 90%) were initially steroid-responsive (e.g., prednisolone at 1 - 2 mg/kg PO bid for at least a week followed by alternate day, reduced dosage for several weeks or several months), with many animals showing a return to normalcy following treatment. In some cases, the response to steroids is incomplete. Signs may relapse when treatment ceases (requiring addition treatment cycles) or upon reduction of the dose of steroids. Uncommonly, some animals with relapsing signs that are steroid-responsive may become steroid-resistant and deteriorate clinically.
The course of the disease, clinical signs, electrophysiology, and pathology have similarities to chronic inflammatory demyelinating polyneuropathy in people in whom weakness has a proximal distribution [262]. Most human patients with CIDP respond to corticosteroids and other immunosuppressive agents (e.g., azathioprine and cyclophosphamide), plasma exchange, and intravenous immunoglobulin (therapies aimed at treating immune-mediated disorders) [347].
Sporadic case reports of chronic relapsing polyradiculoneuritis in a dog [375] and a cat [376], chronic relapsing polyneuropathy in a cat [377], and prednisolone-responsive neuropathy in a cat [378], also appear very similar to CIDP.

Infectious Polyradiculoneuritis -
A severe polyradiculoneuritis and/or polymyositis associated with either *Toxoplasma gondii* or *Neospora caninum* occurs commonly in dogs, especially those less than one year of age (see toxoplasmosis). In one dog with diskospondylitis due to *Aspergillus terreus*, multiple granulomas with fungal elements were found in the subarachnoid space associated with the nerve roots of the cauda equina [379].

Postvaccinal Polyradiculoneuritis
Post-vaccinal polyradiculoneuritis (e.g., multivalent vaccine, inactivated rabies vaccine) has been reported only sporadically in dogs [380-382] with signs and clinical course similar to those in dogs with Coonhound paralysis. The condition, also known as postvaccinal inflammatory neuropathy (IPN), occurs rarely in people and is believed to be an autoimmune reaction triggered by the vaccine against some myelin, axonal or neuronal component [526].

Trigeminal Neuritis -
Trigeminal neuritis, or idiopathic trigeminal neuropathy, occurs commonly in dogs and sporadically in cats and is typically characterized by acute onset of jaw paralysis, inability to close the mouth, drooling, and difficulty eating and drinking [383-385]. Older animals are usually affected, although the condition may occur at any age. There is no apparent breed, sex, or seasonal predisposition, although in one retrospective study of 29 cases, Golden Retrievers were overrepresented [518]. In this study, trigeminal sensory deficits were found in 9 of 26 dogs (35%). Horner's syndrome (due to damage of postganglionic sympathetic fibers incorporated in segments of the trigeminal nerve and its ophthalmic branch) has been observed in several cases [149,518,525], as well as occasional facial nerve involvement [518]. EMG studies usually reflect abnormalities in muscles of mastication and CSF studies may be abnormal (usually characterized by a mild mononuclear pleocytosis, often with normal or mildy elevated protein content) [518]. Pathologically, a bilateral non-suppurative neuritis has been found in motor branches of the trigeminal nerve and ganglion, associated with demyelination and occasional fiber degeneration, and accompanied by inflammatory infiltrates consisting predominantly of macrophages and B and T lymphocytes [149,525]. Masticatory muscle changes may reflect variable neurogenic atrophy, usually without evidence of inflammatory cell infiltrates. The disease appears to be self limiting and recovery usually occurs in 3 to 4 weeks, but some cases may take several months to resolve. Corticosteroid administration appears not to affect the clinical course of the disease [518]. Supportive fluid and nutrient intake may be necessary. Definitive antemortem diagnosis of trigeminal neuritis is complicated by the fact that biopsy of the trigeminal nerve is difficult.
The severity of muscle atrophy, the clinical course, and clinical recovery may depend upon the extent of axonal degeneration present. If it is the dominant lesion, then prognosis can be guarded. Note that some animals with rabies may present with signs of trigeminal neuritis.
Definitive classification of this disorder awaits more detailed pathologic studies on a greater number of cases, although the few cases examined histologically are suggestive of immune-mediated disease [525]. I think that it is also possible that trigeminal neuritis in some instances may represent a focal manifestation of a more diffuse polyradiculoneuritis. Note that bilateral trigeminal neuropathy in a dog has been reported in association with lymphosarcoma [386], and an invasive intracranial juvenile parameningeal rhabdomyosarcoma that destroyed the trigeminal nerve causing unilateral denervation atrophy of masticatory muscles was reported in a 23 month old dog [530]. When I was at the Neuromuscular Diagnostic

Laboratory at Auburn University, many of the muscle samples that we received from dogs with suspected masticatory myositis (and some dogs with clinical evidence of trismus!) showed non-inflammatory neurogenic atrophy compatible with idiopathic trigeminal neuritis/neuropathy.

Rottweiler Distal Sensorimotor Polyneuropathy
A polyneuropathy has been reported in mature Rottweiler dogs in the US [387]. Clinical signs are characterized by paraparesis that progresses to tetraparesis, spinal hyporeflexia and hypotonia, and appendicular muscle atrophy. While signs may appear acutely, the course tends to be gradually progressive (up to 12 months or longer in some dogs) and may be relapsing. Nerve and muscle biopsies were examined from eight affected Rottweilers, six male and two female, aged between 1.5 and 4 years. Pronounced neurogenic atrophy was present in skeletal muscle samples and there was no evidence of necrosis, phagocytosis or inflammation. Changes in sensory and motor peripheral nerves included loss of myelinated nerve fibers, axonal necrosis, and variable numbers of fibers with inappropriately thin myelin sheaths. Demyelination and remyelination were more apparent in dogs with a chronic clinical course. Regenerating clusters were not common. Ultrastructural findings included occasional myelinated fibers showing myelinoaxonal necrosis, demyelinated fibers often associated with macrophage infiltration, many axons with myelin-like membranous profiles, increased endoneurial collagen, occasional axonal atrophy, and numerous Büngner bands. Many axons had a watery appearance with loss of neurofilaments and microtubules, but no evidence of neurofilamentous accumulation. Onion-bulb formation was rare. Lesions in unmyelinated fibers included increased numbers of Schwann cell profiles and loss of axons in Schwann cell subunits. Morphological and morphometric studies indicated preferential loss of medium- (5.5 to 8 μm) and large-caliber (8.5 to 12.5 μm) fibers which was more severe in distal parts of nerves compared to more proximal regions and nerve roots. Mean nerve fiber diameters for proximal and distal segments were 4.95 ± 2.75 μm and 2.41 ± 0.71 μm, respectively. Numerous positive sharp waves and fibrillation potentials were detected in appendicular muscles by EMG, especially in muscles distal to the elbow and stifle. Few abnormal potentials were noted in proximal limb/paraspinal muscles. Motor and sensory nerve conduction velocities were reduced in some dogs. Hematology, blood chemistries, spinal radiography/ myelography were normal. With the exception of one dog that was serologically positive for Valley Fever and *Ehrlichia canis* (1:80), and another dog that was antinuclear antibody positive (1:160), testing has been negative for immunological disorders (e.g., lupus erythematosus cell preparation, rheumatoid factor, Coombs' test), endocrine dysfunction (e.g., diabetes mellitus, hypothyroidism, hyperadrenocorticism), toxicity (e.g., lead, cholinesterase levels), and infectious disease (e.g., Rocky Mountain Spotted Fever, Borreliosis, ehrlichiosis). CSF protein was marginally elevated in one dog. Pathological findings suggest this condition is a dying-back, distal sensorimotor polyneuropathy. Prognosis appears guarded to poor; despite the fact that some dogs showed a temporary response to corticosteroid therapy. This disorder has morphological and morphometric similarities to hereditary sensory and motor neuropathy (HSMN) type II (or CMT II) in people, a distal axonal neuropathy with normal or near normal nerve conduction velocities with reduced amplitudes, indicating loss of axons [43,225].
Note that this condition appears similar to other distal symmetrical polyneuropathy seen in large-breed dogs.

Sensory Neuropathies
Several sensory neuropathies have been observed in small animals, primarily in dogs. In people, sensory neuropathies may affect one or more sensory modalities - pain, proprioception, touch, and temperature. In animals, only the first two sensory modalities can be determined with any degree of accuracy [388]. Sensory neuropathies in dogs may also be characterized by self-mutilation. In general, paresis and muscle atrophy are not present, and no abnormal spontaneous potentials are detected on electromyographic testing. Nerve conduction studies may demonstrate slowed velocities in sensory but not motor nerves. Spinal cord dorsum potentials (a type of spinal cord evoked potential) can also be used to accurately assess functional severity and distribution of abnormalities in proximal sensory nerves, dorsal nerve roots, and spinal cord dorsal horns in dogs with suspected neuropathy, radiculopathy, or myelopathy involving the brachial or lumbosacral intumescences [86,389]. Electrodiagnostic (EDX) evaluation of H-reflexes (H-waves) provides additional information on dorsal nerve root integrity/function [388].

Sensory Ganglioradiculitis -
A sensory disorder has been reported in adult dogs (with an age range from 1.5 to 9 years) of different breeds and of either gender [353,390-394]. I have also seen the condition in a 2.5 year old Scotch Collie. The terms *sensory neuronopathy, sensory polyganglioradiculoneuritis*, and *ganglionitis* have also been used to describe this condition because of involvement of craniospinal sensory ganglia. Pathologically, the disease is characterized by pronounced degeneration and loss of neurons in dorsal root ganglion cells and in cranial sensory ganglia (such as trigeminal and nodose ganglia), usually accompanied by inflammatory lymphoplasmacytic and macrophage infiltration. The infiltrating cells are primarily T lymphocytes and immunoglobulins are not present on the cell membranes of affected neuron [522]. A marked loss of larger-diameter

myelinated fibers has been observed in dorsal roots and in sensory nerves, and there may be selective loss of myelinated fibers in the dorsal columns of the spinal cord (grossly, the dorsal columns may appear white/opaque), indicative of degeneration secondary to ganglion dysfunction [200,392]. Similar degenerative changes may occur in sensory pathways of cranial nerves, such as the spinal tract of the trigeminal nerve and the solitary tract (containing visceral afferent fibers of facial, glossopharyngeal and vagus nerves). In one case I have seen, axonal necrosis present in multiple nerves was more severe distally. Ventral roots are usually spared or only mildly affected. Denervated Schwann cells of myelinated and unmyelinated fibers are found in the dorsal roots.

The clinical course is usually insidiously progressive over several months or years. Clinical signs are variable and include proprioceptive deficits, generalized ataxia with preservation of muscle strength, depression or absence of tendon reflexes, such the patellar reflex, facial hypalgesia/paresthesia, megaesophagus, head tilt, loss of voice, hearing loss, anisocoria, difficulty in prehending food, dysphagia, stiff gait often with hypermetria, and occasionally, self-mutilation. Muscle atrophy is usually not a feature; however, atrophy of masticatory muscles may be seen in some dogs, attributed to inflammatory involvement of fibers from the motor root of the trigeminal nerve as they course through the trigeminal ganglion [390]. Hematological values, CSF analysis and radiographic studies are within normal limits; however, a mild increase in CSF cellularity and total protein may be present. EMG findings are usually normal. Sensory nerve conduction velocites (NCVs) are slowed or absent, while motor NCVs are normal. Prognosis is guarded to poor. To date, corticosteroids (e.g., prednisone) and procarbazine have been ineffective.

The pathogenesis of ganglioradiculitis remains to be established, but the evidence points to a cell-mediated immune mechanism [522]. A possible toxic etiology was considered in a 4 year old Labrador Retriever with pathology localized to sensory nerves, dorsal root ganglia and the dorsal columns of the spinal cord [393]. In this dog, liver mercury levels were elevated above normal, although below the range normally associated with mercury poisoning.

Progressive Axonopathy in Boxers -

This putative sensory neuropathy is an inherited autosomal recessive neuropathy of Boxer dogs [395-402]. Pathological findings are seen in nerve roots, peripheral nerves, and in the CNS. Large axonal swellings (spheroids) are found in various brainstem nuclei, especially cuneate and superior olivary nuclei. Spheroids and degenerating fibers are seen in spinal cord white matter, particularly in lateral and ventral funiculi. Minimal changes occur in the dorsal columns. The optic pathways are also involved. In the PNS, small axonal swellings develop at proximal paranodal areas in dorsal and ventral nerve roots as well as in proximal nerves. Axonal swellings are due to accumulation of both disorganized neurofilaments and membranous organelles, mainly vesicles and vesiculo-tubular profiles. Myelin over such swellings is often attenuated. Myelin changes predominate in the nerve roots, whereas axonal degeneration and regeneration are encountered in more distal nerves. In contrast, regenerating axonal clusters are common in cervical ventral roots, throughout the course of the disease. Axonal degeneration in the spinal cord shows no obvious tract or proximal/distal selectivity [397]. Most early axonal spheroids are surrounded by a myelin-associated glycoprotein (MAG)-positive zone but in the larger swellings and longer duration cases this was sometimes absent; however, distorted Schmidt-Lanterman incisures, a feature of the advanced disease, tend to be strongly MAG-positive. [402]. It has been hypothesized that failure of slow axonal transport may occur in roots leading to axonal swellings and secondary hypoplasia of more distal, larger-diameter fibers. Myelin/Schwann cell alterations might occur in response to the axonal changes [399,400]. Immunocytochemical studies revealed that the major axonal cytoskeletal proteins in nerve roots and in spinal cord are markedly disturbed: many spheroids contain increased amounts of actin, and sometimes deficient tubulin in the periphery of the neurofilament accumulations, while the distribution of axonal fodrin in CNS and PNS appears unaltered [401]. In addition, the perikarya of many motor neurons in the spinal cord and brain stem contained phosphorylated 200 kD neurofilaments (phosphorylated neurofilaments are normally localized in the axon rather than the cell bodies).

Onset of clinical signs occurs about 2 months of age. There is a progressive ataxia and weakness, initially in pelvic limbs, but later involving thoracic limbs. Proprioceptive function, muscle tone and tendon reflexes are diminished or absent, while pedal reflexes and pain sensation are preserved. Absent patellar reflexes can be detected at 1 month of age. Muscle atrophy is minimal. Signs slowly progress until animals are 12 to 18 months of age, and then tend to stabilize. Mild cerebellar signs may be evident late in the course of the disease. EDX studies reveal little spontaneous activity in muscle but reduced motor and sensory nerve conduction velocities and reduced evoked muscle action potential amplitudes after about 4 months of age. Eventually, sensory nerves cease to conduct impulses. F-wave latency is increased.

Diagnosis is suggested by signalment, clinical, and electrodiagnostic data, and confirmed by nerve biopsy or pathological evaluation of the CNS. Prognosis is poor. There is no treatment.

A disorder with similar clinical signs, clinical course, and pathological features has been reported in a young Rottweiler puppy (2 affected puppies out of a litter of 11) [200]. Distribution and nature of lesions observed in a 5 month old Pyrenean Mountain dog were also considered similar to those in the Boxers [403], although the characteristic axonal neurofilamentous accumulation was not described.

Sensory Neuropathy in Long-Haired Dachshunds -
This is a neurological disease reported in Long-Haired Dachshund puppies thought to be inherited as an autosomal recessive trait [120,404]. The pathogenesis is unknown. Pathological findings occur in distal sensory nerves affecting both larger caliber myelinated fibers and unmyelinated fibers (UF). Changes include myelinated nerve fiber loss, axonal degeneration, many bands of Büngner, marked increased numbers of axonal organelles (mitochondria, smooth endoplasmic reticulum, and glycogen), prominent endoneurial fibrosis, occasional evidence of small regenerating clusters, and rarely, onion bulb formations. While UF density appeared normal, abnormalities in UFs were frequently seen in distal nerves including increased numbers of intra-axonal neurotubules and/or tubulo-vesicular elements, stacks of lamellar profiles, collections of dense granular material, along with accumulation of mitochondria, smooth endoplasmic reticulum and glycogen, darkening of the axoplasm, empty Schwann cell subunits, Büngner bands, and collagen pocket formations. Paranodal demyelination seen on teased nerve preparations is considered to be secondary to axonal changes. Degenerative changes are noted in the vagus nerve. Less severe, but similar changes occur in mixed nerves. Sensory neurons in the spinal ganglia are normal and dorsal roots appear normal. In the CNS, distal degeneration has been observed in the fasciculus gracilis, suggesting this condition is a distal central-peripheral axonopathy.
Clinical signs are noted in dogs as early as 8 to 12 weeks of age, and are characterized by subtle ataxia, loss of proprioception and placing reactions, especially in pelvic limbs, reduction or loss of pain sensation ("nociception") over the whole body in response to superficial and deep pain stimulation, and dribbling of urine. Self-mutilation of the penis and intermittent vomiting have been noted. Pelvic limbs may splay-out when dogs are lying in sternal recumbency. There is no evidence of paresis or muscular atrophy and patellar reflexes are normal or slightly reduced. EMG studies and motor NCVs are normal. Sensory NCVs are reduced or absent.
Diagnosis is based on signalment, clinical, electromyographic and pathological (nerve biopsy) data. Provided that complications do not occur from vomiting or from self-mutilation (which may necessitate muzzling), it has been stated that most affected dogs live normally [388]. There is no treatment. This canine disorder was considered to have some similarities to human hereditary sensory neuropathy type II (now re-classified as hereditary sensory and autonomic neuropathy type II, an autosomal recessive disorder).
A sensory neuropathy having similar clinical (loss of proprioception and generalized loss of superficial pain sensation, except over the lips and inside the nostrils where pain sensation was blunted but present, and urinary incontinence) and pathological features has been reported in a 2 month old Border Collie puppy [405]. Sensory nerve action potentials were absent.
Another condition that appears similar to that in the Dachshunds has been reported in a 6 year old, male Jack Russell Terrier presented with a chronic history of abnormal pelvic limb posture and a tendency to repeatedly bite its right pelvic limb [406]. At rest, the dog stood with one pelvic limb flexed and the other extended. Neurological examination revealed proprioceptive deficits in pelvic limbs and in one thoracic limb. Postural reaction testing was clumsy in pelvic limbs. The dog continued to dribble urine following micturition. Pain perception was diminished in the distal pelvic limbs up to the level of each stifle. Patellar reflexes were brisk bilaterally and there was no evidence of paresis or muscle atrophy. Electrodiagnostic data were not included in this report. Examination of a sensory nerve biopsy (lateral branch of the superficial peroneal nerve) revealed absence of myelinated fibers, preservation of unmyelinated fibers, abundant endoneurial and epineurial connective tissue, and small numbers of denervated Schwann cells. Future studies are needed to determine if there is involvement of sensory ganglia, and if the condition is inherited.

Sensory Neuropathy in English Pointers -
This sensory neuropathic disease, inherited as an autosomal recessive trait, has been reported in English Pointer dogs [407-409]. An apparently similar, recessively inherited entity has been reported in Czechoslovakian Shorthair Pointer dogs in Europe and has been called toe necrosis, hereditary neurotrophic osteopathy, and ulcero-mutilating acropathy [410]. Changes in the primary sensory neurons are observed pathologically, including presence of small spinal ganglia with reduced numbers of cell bodies (from 20 - 50%), a disproportionately large population of small sensory cell bodies, degeneration of unmyelinated and myelinated fibers in the dorsal roots and peripheral nerves, and reduced fiber density and myelin staining in the dorsolateral fasciculus (Lissauer's tract) of the spinal cord in which pain and temperature fibers travel. Ultrastructurally, there is evidence of bands of Büngner, denervated Schwann cell subunits, collagen pockets, lysis of neurotubules and filaments in unmyelinated fibers, and little evidence of axonal regeneration of myelinated or unmyelinated fibers [407].
The pathogenesis of this disease is presently unclear; however a deficiency in growth and/or differentiation of primary sensory neurons may be involved. The loss of primary sensory neurons is associated with a notable reduction in staining of substance P, an excitatory agent that mediates nociception (i.e., pain sensation) [411]. This loss is most apparent in the dorsolateral fasciculus and superficial laminae of the spinal dorsal horns. In older dogs, a loss of P substance was also found in the spinal nucleus of the trigeminal nerve. This finding, in addition to appearance of scattered fiber degeneration in the

dorsal columns of the mature Pointer, suggested that fiber degeneration may progress slowly with age to include sensory systems not affected in early postnatal life [411].
Clinical signs are characterized by nociceptive (pain) loss and acral mutilation. This nociceptive loss is more apparent in distal parts of limbs, so that acral analgesia is replaced by hypalgesia proximal to the carpus and tarsus. No nociceptive loss is found about the face. Although blunting of digital pain has been detected prior to weaning, clinical signs usually become apparent at 3 to 8 months when affected dogs suddenly begin to lick and bite their paws. Acral changes include swollen reddened paws, ulcerations, lacerations, paronychia, painless fractures, and autoamputations.
There is no evidence of proprioceptive loss, ataxia, or depressed tendon reflexes. EMG studies and sensory and motor nerve conduction studies are normal. Diagnosis is based on signalment and clinical data, and normal electrodiagnostic results. Histopathological evaluation of nerve or spinal ganglia biopsy samples may support the clinical diagnosis. Prognosis is poor because of high potential for osteomyelitis secondary to autoamputation. There is no treatment for the underlying sensory neuropathy.
This sensory neuropathy appears to have clinical and pathological similarities to several of the hereditary sensory and autonomic neuropathies (types I through V) described in people [43,412].

Sensory Trigeminal Neuropathy -
Sensory trigeminal neuropathy has been reported in a 2 year old, female Rough Coated Collie dog [413]. The cause was not determined. Pathological lesions included marked loss of nerve fibers in the trigeminal nerves and their spinal tracts. Motor fibers of the mandibular nerves were unaffected. These changes were not associated with inflammation and were considered to be secondary to loss of neurons in the trigeminal ganglion (Gasserian ganglion). The motor nucleus of the fifth nerve was normal. Clinical signs of acute onset of excessive salivation, coughing and dysphagia were believed to be associated with bilateral loss or absence of tactile sensation and deep pain from the face, tongue and oral mucosa. The condition in this dog remained relatively unchanged over an 18 month period.

Idiopathic self-mutilation -
Idiopathic self-mutilation or behavioral self-mutilation has been seen in both dogs and cats. Affected animals are often of nervous or high-strung breeds such as Siamese, Burmese, Himalayan or Abyssinian cats, and Doberman Pinscher, German Shepherd, Great Dane, and Irish Setter dogs [414]. In dogs, this self-mutilation may manifest itself as continued licking, biting or scratching of one or more areas usually near the carpus or hock, and has been termed *acral lick dermatitis* (ALD), *lick granuloma, acral pruritic nodule, neurodermatitis,* and *canine obsessive/compulsive disorder* (also see Behavioral disorders). EDX studies have provided evidence of both mild sensory axonal polyneuropathy in some affected dogs [415], as well as apparent motor ventral root involvement in 9 of 16 dogs with lick granuloma [416] The tricyclic antidepressant drug, clomipramine (Anafranil ®), dosed at 1 to 3 mg/kg PO daily, results in significant improvement in the dogs' licking behavior [417-419]. Other effective drugs against ALD include citalopram, fluoxetine, and naltrexone [420-422].
A feline orofacial pain syndrome has been described in cats (the majority of cases are in Burmese cats) characterized by acute onset of exaggerated licking and chewing movements with pawing at the mouth sometimes leading to severe self-mutilation [517]. Signs may be seen in kittens around 14 weeks of age (associated with vaccination and mouth ulceration), in kittens around 5 months of age (associated with teething), or in older cats (from 1 to 16 years of age), sometimes associated with stress or dental disease. The attacks can be episodic (eg, lasting between 5 minutes and 2 hours) or continuous (necessitating paw bandaging or an Elizabethan collar to prevent mutilation). Some cats show spontaneous remissions and recurrences. The syndrome may be similar to trigeminal neuralgia and glossodynia (burning or painful tongue) in people. Treatment using anti-epileptic drugs (diazepam or phenobarbitone) are effective in many cases.
I have seen degenerative changes in sensory and in mixed nerves (perhaps affecting only the sensory portion) from 2 dogs (an 8 month old male Spitz and a 6.5 year old male Miniature Doberman Pinscher) presented for bilateral self-mutilation of the digits in the pelvic limbs. Axonal necrosis was dominant in the Spitz, whereas, demyelination and remyelination were the main features seen in the Miniature Doberman. Mild dorsal column pallor (fasciculus gracilis) was observed in the Spitz (suggesting this condition might have been a form of sensory ganglioradiculitis), but no inflammation was present in dorsal roots or ganglia in which there was mild loss of neurons. No spinal cord or ganglia changes were noted in the Miniature Doberman. Neurological examination and EMG testing were normal in both dogs, while sensory but not motor nerve conduction velocity was markedly reduced in the Miniature Doberman.
Self-mutilation has also been noted in animals with nerve injury, e.g., lumbosacral stenosis and trauma [423,424], and auto-mutilation was observed in an epizootic of tibial and peroneal neuropathy in a kennel of Walker Hound puppies thought to be toxin-induced (see toxic neuropathies) [425].

Storage Disease Neuropathies
Readers are referred to Chapter 2 and Storage Diseases for neuropathies associated with different storage disorders, including gangliosidosis, fucosidosis, globoid leukodystrophy, glycogenosis type IV, mannosidosis, and sphingomyelinosis (phenotypic variant of Niemann-Pick disease type A).

Toxic Neuropathies
Clinically-related, drug-induced neuropathies are not well defined in dogs and cats. Vincristine-associated peripheral neuropathy was reported in a 12 year old, female, Golden Retriever that received 16 weekly doses of vincristine (0.5 mg/m^2) as part of a regimen for treatment of mycosis fungoides [426]. The dog was presented for sudden onset of a shuffling pelvic limb gait, intermittent collapse, and difficulty negotiating turns and stairs. Neurological examination revealed mild ataxia in the pelvic limbs, depressed pelvic limb postural reactions, and depressed patellar and pelvic limb withdrawal reflexes. EMG testing revealed fibrillation potentials and positive sharp waves consistent with denervation. Sciatic motor NCV was decreased. Evoked muscle potentials were polyphasic and had reduced amplitude and prolonged duration. Severe nerve fiber degeneration, nerve fiber loss (both small- and large-caliber fibers), and marked endoneurial fibrosis were seen in a nerve biopsy sample. The neuropathy improved after vincristine was discontinued. Results of a repeat nerve biopsy taken 10 weeks after cessation of vincristine administration showed fewer degenerating nerve fibers and presence of demyelination-remyelination. The dog appeared neurologically normal at this time. In experimental studies in cats, focal axonal swellings (giant axon formations) due to distorted accumulations of neurofilaments and secondary paranodal demyelination were found primarily in the proximal portions of peripheral nerves, with only a few giant axon formations seen distally along with variable axonal degeneration [427]. In people, a neuropathy typically occurs in all patients receiving vincristine for a sufficient period and signs/EDX testing suggest a symmetrical distal sensorimotor polyneuropathy [105]. Loss of myelinated fibers and axonal degeneration in unmyelinated fibers have been observed [428]. In people, itraconazole may aggravate vincristine-induced neurotoxicity [429,430]. Cis-platinum, another antineoplastic agent, has been implicated in peripheral neuropathies in human patients, usually resulting in large fiber sensory neuropathy and axonal degeneration/demyelination [431,432]. The neurotoxicity is dose-limiting and cumulative. Neurological signs (ataxia, lower motor neuron paresis in pelvic limbs) have been noted in some dogs following use of this drug, although a distinction between toxic neuropathy and paraneoplastic neuropathy was not made [433].
As chemotherapeutic treatment of tumors becomes more aggressive, there is a real possibility that clinicians will be presented with further cases of drug-induced neuropathies. There is also a risk of neuropathies being induced by tumor irradiation (see radiation therapy). In an experimental study of intraoperative radiation therapy, peripheral neuropathy resulting from direct effects of irradiation on nerve and secondary effects on nerve vasculature was apparent clinically (e.g., hind limb paresis associated with significant loss of large-caliber nerve fibers and endoneurial/perineurial/epineurial fibrosis) 1 to 19 months following irradiation [434,435]. This toxicity appears to be dose-limiting, with intraoperative doses < 15 Gy not resulting in clinically significant peripheral nerve injury [436,437]. The nerve toxicity appears to be enhanced by hyperthermia [438].
Thallium poisoning, from ingestion of thalium-containing rodenticides or insecticides, may produce degenerative changes in peripheral nerves (distended myelin sheaths with swelling and fragmentation of axons) and ganglionitis, with clinical signs of trembling, muscle spasms, paresis or paralysis of hind limbs, severe pain, and megaesophagus [439]. Experimental studies in cats indicate that thallium induces a central-peripheral sensory distal axonopathy [440]. Thallium in rodenticides has been banned in the US since 1965; however, sporadic cases of acute and chronic thallium poisoning continue to be reported [441,442] (see thallium). Experimental neuropathies (resulting in dying-back disorders) have been induced in cats using a variety of neurotoxic hexacarbons and acrylamide [443]; however, these neuropathic toxicities are rarely encountered in clinical practice. Neurotoxic organophosphates may induce a delayed peripheral neuropathy in cats (16 - 18 days after injection) associated with focal, distal but not terminal axonal degeneration [444] (see organophosphate/carbamate toxicity). Experimental administration of beta, beta'-iminodipropionitrile (IDPN) to cats induces neurofilament-filled axonal swellings in proximal and distal regions of peripheral nerves [445]. Lead intoxication does not appear to produce a toxic neuropathy in dogs [446] (see lead poisoning). Experimental pyridoxine (vitamin B6) intoxication in dogs results in degeneration of primary sensory neurons (affecting peripheral nerves, dorsal roots, dorsal funiculus, and spinal tract of the trigeminal nerve) and clinical signs of ataxia-dysmetria and proprioceptive deficits [447-449]. Iatrogenic peripheral vestibular disease and/or deafness may result from use of various antibiotics and chemical agents that cause degeneration of vestibular and auditory peripheral receptors (see deafness and vestibular disease).
An epizootic of peroneal and tibial neuropathy was reported in a kennel of Walker hounds in eastern North Carolina [425]. Approximately 40 puppies were involved. Signs of pelvic limb monoparesis, areflexia, muscle atrophy, and deficient postural reactions, were first seen in 2 week old puppies. Signs progressed to severe paresis and self-mutilation of digits. Limb analgesia was also noted. Histopathological findings were largely restricted to distal tibial and peroneal nerves and included nerve fiber loss, especially the larger-caliber fibers, and occasional scattered demyelinating fibers.

Ultrastructurally, axonal neurofilaments were often whorled and denser than normal. Dilated granular endoplasmic reticulum were prominent in Schwann cell cytoplasm. The cause was not determined; however, a toxic-induced neuropathy secondary to a contaminant in the well water was suspected.

Traumatic Neuropathy

Trauma to peripheral nerves is a common cause of neuropathies in animals [450]. Nerve injuries may result from mechanical blows, gunshot wounds, fractures, pressure, and stretching (see brachial plexus avulsion). Sciatic nerve injury in dogs and cats often follows fracture of the ileal body or acetabulum, or from sacroiliac fracture-dislocation with cranial displacement of the ilium [424,451-453]. Facial nerve injury may occur during total ear canal ablation and lateral bulla osteotomy in the dog [454]. Bilateral mandibular nerve injury has been reported in dogs thought to result from carrying large objects in the mouth (probably from mandibular nerve neuropraxia, see below) [455]. A transient facial nerve paralysis (presumably resulting from nerve compression) was reported in a 50 kg Doberman Pinscher x Great Dane dog following prolonged anesthesia [168]. Neck trauma in cats may lead to Horner's syndrome and subclinical ipsilateral laryngeal hemiplegia by damage to the vagosympathetic trunk [294]. Sciatic nerve entrapment by muscle or fibrous tissue has been reported in small animals following femoral fracture, ischial or acetabular fracture, and femoral head and neck excision [452,456-458]. Bilateral entrapment was found in a dog with hip dysplasia [457]. Note that nerve root entrapment and compression commonly occur in dogs with cauda equina syndrome (see lumbosacral stenosis). Another common cause of nerve compression and/or entrapment is peripheral nerve neoplasia (see peripheral nerve tumors). In cats with hyperlipidemia, peripheral nerve fascicles are subjected to compression by xanthomata which leads to secondary axonal degeneration and nerve fiber loss. Nerve root injury and spinal cord hemorrhage has been reported in a dog in association with tearing of the dura mater following an episode of violent struggling [459].

Additional iatrogenic causes of nerve injury include crushing, cutting, compression by casts or splints, and injecting agents into, or adjacent to the nerve. In one study involving 57 dogs and 26 cats with femoral fractures that were fixed with intramedullary pins, 12 (14.5%) exhibited signs of sciatic nerve entrapment [460]. Normograde intramedullary pinning of the femur is less likely to induce sciatic nerve injury, particularly in midshaft and distal fractures [461]. In an experimental study evaluating the effects of injection of various agents normally administered intramuscularly, the degree of nerve injury varied with [462,463]:

a. The agent injected; e.g., iron-dextran, meperidine, and cephalothin induced minimal damage, while maximal nerve injury followed injection of penicillin, diazepam, chlorpromazine, and steroid agents (especially hydrocortisone and triamcinalone, while minimal damage was seen with dexamethasone) [462].
b. The site of injection, e.g. severe injury followed intrafascicular injection but there was minimal injury following extrafascicular injection.
c. The quantity of drug injected.
d. The caliber of the fibers, e.g., large, heavily myelinated fibers were more susceptible to injection injury than smaller, thinly myelinated nerve fibers.

The mechanism of injury appears to be a direct neurotoxic effect on both axons and Schwann cells, with disruption of the blood-nerve barrier and with changes occurring in nerves within 30 minutes of injection [464,465].

Nerve damage may be defined in terms of structural damage. *Neurotmesis* is complete severance of all structures of the nerve with Wallerian degeneration (axonal necrosis and myelin fragmentation) of the distal stump. *Axonotmesis* consists of damage to the nerve fibers resulting in degeneration; however, the endoneurial and Schwann cell sheaths remain intact and provide a framework for axonal regeneration. *Neuropraxia* is an interruption in the function and conduction of a nerve without structural damage.

The regenerative ability of a nerve is directly proportional to the degree of continuity of connective tissue structures within the nerve. In neuropraxic and axonotmesic lesions where the endoneurial connective tissue and Schwann cells remain intact, the potential for axonal regeneration is good. In neurotmesis, axonal regeneration is usually frustrated by lack of connective tissue scaffold or growth tubes. Also, scar tissue tends to interfere with sprouting axons, resulting in neuroma formation. Once an axon has grown past the point of injury and penetrates a Schwann tube in the distal nerve stump, remyelination occurs. Axonal regeneration occurs at a rate of 1 to 4 mm per day. Clinical signs of spinal nerve dysfunction are outlined in Table 2.

Table 2. Clinical Signs of Spinal Peripheral Nerve Trauma			
Nerve	**Spinal Cord Origin**	**Muscles Innervated**	**Clinical Signs of Dysfunction**
Suprascapular	C6 - C7	Supraspinatus Infraspinatus	Loss of shoulder extension; muscle atrophy with prominent spine of scapula
Axillary	C7 - C8	Deltoideus Teres major Teres minor	Reduced shoulder flexion; deltoid atrophy; reduced sensation over lateral surface of shoulder
Musculo - cutaneous	C6 - T1	Biceps brachii Brachialis Coracobrachialis	Reduced elbow flexion; loss of bicipital reflex; reduced sensation over medial surface of forearm
Radial	C6 - T2	Triceps brachii Extensor carpi radialis Ulnaris lateralis Lateral digital extensor Common digital extensor	Reduced extension of elbow, carpus, and digits; loss of extensor postural thrust and limb support (with radial nerve damage above the elbow); loss of triceps reflex; reduced sensation over dorsal surface of paw and craniolateral surface of forearm
Median	C7 - T2	Flexor carpi radialis Superficial digital flexor	Reduced flexion of carpus and digits; reduced sensation over palmar surface of paw
Ulnar	C8 - T2	Flexor carpi ulnaris Deep digital flexor	Reduced flexion of carpus and digits; reduced sensation over caudal surface of forearm
Femoral	L4 - L6	Iliopsoas Quadriceps Sartorius	Inability to extend stifle or bear weight on affected limb; loss of patellar reflex; reduced sensation over medial surface of paw, hock, stifle, and thigh (via sensory saphenous nerve)
Obturator	L5 - L6	External obturator Pectineus Gracilis	Inability to adduct hip or thigh (animal "does the splits" on a smooth surface)
Sciatic	L6 - S1	Biceps femoris Semimembranosus Semitendinosus	Inability to flex stifle; loss of flexor reflex (for other dysfunction see branches of sciatic nerve - tibial and common peroneal nerves)
a) Tibial	(L6) L7 - S1	Gastrocnemius Popliteus Deep digital flexor Superficial digital flexor	Inability to extend hock or flex digits; reduced sensation over plantar surface of paw; loss of gastrocnemius reflex
b) Common Peroneal	L6 - L7 (S1)	Peroneus longus Lateral digital extensor Long digital extensor Cranial tibial	Inability to flex hock or extend digits; knuckling of dorsal paw; reduced sensation over craniodorsal surface of paw, hock, and stifle
Pudendal	S1 - S3	External anal sphincter Striated urethral muscle	Loss of anal reflex and bulbocavernosus reflex (males only); reduced sensation of perineum
Pelvic (parasympathetic)	S1 - S3	Smooth muscle of bladder and rectum	Urinary incontinence

Modified from Braund KG. Clinical syndromes in veterinary neurology. St Louis: Mosby, 1994 [16].

Diagnosis of traumatic neuropathy is usually based on history and clinical signs. EDX data may be helpful in evaluating nerve integrity, severity of damage, and in monitoring progress/regeneration. Approximately 5 to 7 days post-injury are required before increased insertional activity and spontaneous potentials (e.g., positive sharp waves and fibrillation

potentials) are detected. Nerve integrity may be easily assessed by nerve stimulation proximal and distal to the site of the lesion. Exploratory surgery is another method for direct evaluation of peripheral nerve damage.
Treatment may involve surgical anastomosis (neurorrhaphy) or neurolysis (freeing of a nerve from inflammatory adhesions). Experimental studies in dogs suggest that too early mobilization following neurorrhaphy will impede nerve regeneration by delaying revascularization and enhancing scar formation [466]. In those instances where nerve damage is chronic, high, or severe, muscle relocation and muscle tendon transfers are recommended, including arthrodesis of the tibiotarsal joint in pelvic fracture cases where the lumbosacral joint or sciatic nerve is severed [424,456,467].
Prognosis is guarded with peripheral nerve injury. Lesions characterized by neuropraxia and axonotmesis have a better prognosis than those of neurotmesis. Also, the closer the nerve injury is to the muscle it must reinnervate, the better the prognosis. Self-mutilation that results from abnormal sensation in an affected area produced by regeneration of sensory nerves can be a major complication and a poor prognostic sign. In one study involving 34 dogs and cats with nerve injury associated with fracture-dislocation of the pelvis, 81% had good/excellent limb function 16 weeks after the injury, and the outcome was the same for animals with or without surgery [424]. The authors of this report suggested that surgery be performed on animals with signs of severe pain or moderate to severe nerve injury so as to relieve the nerve entrapment, avoid further nerve damage, and assess prognosis (e.g., the affected nerve may be severely attenuated, frayed, stretched, lacerated or transected). Loss of limb function or self-mutilation occurred in 15% of animals in this study. A poor prognosis is given if limb function has not improved in 3 to 4 months in animals with lumbosacral trunk/high sciatic nerve injury [424]. Physical therapy, such as a whirlpool bath, may help to overcome circulation problems and delay muscle atrophy (see rehabilitation).

Vascular Neuropathy
Readers are referred to chapter 2 and Myopathic Disorders for a review of vascular neuropathy (see ischemic neuromyopathy).

Vestibular Disease
Various forms of vestibular disease have been identified in dogs and cats, and they may involve peripheral receptors within the inner ear or the centrally located nuclei and tracts within the brainstem.

A. Peripheral Vestibular Disease may be congenital, idiopathic, or associated with otitis media-interna. There are also several miscellaneous causes of peripheral vestibular disease.
Idiopathic Vestibular Disease - This is an acute peripheral vestibular syndrome, without evidence of inflammatory lesions, that is seen in cats of all ages and in older dogs [468,469]. In one study of 75 affected cats, 80% were diagnosed in the months of July and August [468]. Both dogs and cats have signs of peripheral vestibular involvement including head tilt, asymmetrical ataxia, and horizontal or rotatory nystagmus. More severe signs of falling, rolling, and vomiting (especially in dogs) are seen occasionally. The signs appear suddenly, often causing severe incapacitation. In a few days, the affected animal tends to stabilize and improves gradually over several weeks. Residual deficits, such as a mild head tilt, may be seen. It is important to exclude an infection as the cause since the idiopathic syndrome and acute labyrinthitis (see below) have identical clinical signs; however, facial nerve dysfunction and Horner's syndrome are never seen in animals with idiopathic disease. In the idiopathic disease, the external, middle, and inner ear are grossly normal. Otoscopic and radiographic examinations are normal. The canine disease must also be differentiated from brain stem disease (e.g., central vestibular disease). The syndrome has also been mistaken for an acute vascular accident (i.e. infarction or hemorrhage) of the brain stem. The signs of the idiopathic syndrome are only those of peripheral vestibular dysfunction. Postural reactions and other cranial nerves are not affected. In the early stages, postural reactions may be very difficult to test and the peripheral nature of the syndrome may not be obvious until the second or third day.
The peracute onset of clinical signs and absence of otitis media/interna, based on otoscopic and or radiographic examinations, suggest a diagnosis of idiopathic vestibular disease. Analysis of CSF is normal. The etiology remains uncertain. No microscopic lesions have been documented in the labyrinth, vestibular nerve and ganglion, or within the brainstem.
Prognosis for spontaneous remission is good; however, recovery may take 2 or 3 weeks. Recurrences may be noted, especially in dogs. A variety of treatments have been tried, including antibiotics, anti-inflammatory agents, anti-motion sickness drugs, and others. There is no evidence that any treatment alters the course of the disease. If infection cannot be absolutely excluded, antibiotics are recommended, but aminoglycosides should be avoided.

Otitis Media-interna refers to an inflammation of the middle and inner ears and is a common cause of peripheral vestibular dysfunction in dogs and cats [468]. The most common route of infection to the middle and inner ears is from the external ear

canal with attendant otitis externa and subsequent rupture of the tympanic membrane. The nasopharynx is also a source of retrograde infection by way of the eustachian tubes. A third source of infection of the middle-inner ear structures is hematogenous spread. Most infections are caused by bacteria including *Staphylococcus* sp., *Streptococcus* sp., *Proteus* sp., *Pseudomonas* sp., *Enterococcus* sp., and *Escherichia coli*. Foreign bodies such as grass awns may initiate inflammation and predispose to secondary microbial infection. Yeast (e.g., *Candida* sp. and *Malassezia canis*) and fungal infection (e.g., aspergillosis, cryptococcosis) [470,471] are observed infrequently. Animals predisposed to chronic otitis externa and chronic ear mite infestations would appear to have an increased risk of developing otitis media-interna; however, in one survey, no breed was disproportionately represented, compared to the hospital population examined [468]. Nevertheless, the psoroptid mite *Otodectes cynotis* reportedly can damage the tympanic membrane and invade the middle and inner ears, especially in cats, resulting in secondary infection of these structures [472]. Occasionally, middle ear infection occurs secondary to trauma (e.g., traumatically ruptured tympanic membrane associated with petrosal bone fracture), inflammatory polyps, granulomas (e.g., cryptococcal), and tumors (see below).

Varying degrees of vestibular disturbance reflect otitis media-interna. Signs may range from ipsilateral head tilt, nystagmus (frequently rotatory), positional strabismus (ventral or ventrolateral), and ataxia of trunk and limbs, such as torticollis, circling, falling, and rolling. These dramatic signs may become less pronounced within 2 - 3 days. Postural reactions, preservation of strength, and initiation of voluntary movement are similar to those described for idiopathic vestibular disease. Mild hypertonia and hyperreflexia may occur in limbs on the side of the body opposite the vestibular lesion. Pain may be noted around the external ear and when the animal opens its mouth. An aural discharge, sometimes bloody, head shaking, and pawing or rubbing of the ears may be noted. Frequent yawning has been observed and affected animals may be lethargic, anorexic and febrile. Attendant middle ear inflammation may disturb function of the facial and sympathetic nerves which course through the middle ear, resulting in ipsilateral facial paresis/paralysis and Horner's syndrome, respectively. During the course of the disease, irritation of the sympathetic fibers may induce mydriasis. Since the facial nerve contains the parasympathetic preganglionic neurons that modulate lacrimal gland secretion, animals with otitis media-interna may have decreased tear production and develop ipsilateral keratitis sicca. Facial nerve dysfunction may be seen in approximately 50% of animals with otitis media/interna [473]. Ipsilateral hemifacial spasms have been reported in dogs with otitis media [186] and signs, including blepharospasm, elevation of the ear, and deviation of the nose, are probably due to facial nerve irritation. Another structure that may be involved in otitis media-interna is the cochlear nerve, dysfunction of which results in deafness.

Occasionally, otitis media-interna is bilateral and affected animals may assume a wide-based stance with head close to the ground and swinging from side to side, or alternatively, assume a crouched posture on the ground with limbs spread apart [89]. Nystagmus is not present and the oculocephalic response (normal vestibular nystagmus) is absent in bilateral disease. Such animals may also be deaf and show bilateral facial paralysis.

The diagnosis of otitis media-interna is based on clinical signs, otoscopic examination, radiography/imaging, and surgical exploration [474]. Examination of the pharynx (visually or using a retroflexed pediatric gastroscope) may reveal inflammation that may have spread to the middle ear via the auditory tube [472], polyps originating from the auditory tube or tympanic cavity [475], or granulomas protruding from the choanae [470]. Cats with tumors of the middle and inner ear often have signs of pain when opening the mouth [182]. Otoscopy may reveal an otitis externa and evidence of erosion or rupture of the tympanic membrane. Fluid in the middle ear produces outward bulging of the tympanic membrane which may appear opaque and hyperemic. Fluid behind the membrane may appear clear or discolored. Fluid and/ or inflammatory exudate should be sampled for culture, cytology, and sensitivity testing from the external and middle ear by aspiration if the tympanic membrane has ruptured, by myringotomy (surgical incision of the tympanic membrane performed caudal to the malleus in the posteroinferior quadrant of the tympanic membrane [472]), or by exploratory surgery. Radiographic examination (recommended skull radiographic views include oblique lateral, open-mouth and ventrodorsal projections [472] of the petrous temporal bones may reveal middle ear inflammation as suggested by fluid density and sclerosis of the bulla. Normal detail of the bony labyrinth may be lost. The presence of a nasopharyngeal mass on lateral radiographic views is suggestive of inflammatory polyps in cats [182]. Lysis or active periosteal reaction involving the bulla or petrous part of the temporal bone is usually associated with neoplasia. In some instances, radiographs may be normal, despite significant middle ear inflammation [474] and special imaging techniques, e.g., CT and MRI may be more sensitive in detection of fluid in the middle ear disease [476]. Soft tissue changes in the early stages of the disease may be detected better with MRI [477]. Positive contrast ear canalography is considered to be a more sensitive method for detecting tympanic membrane rupture and otitis media than either otoscopy or survey radiography [478].

Prognosis is usually favorable with prolonged oral and topical antibiotics chosen from positive culture and sensitivity studies. When culture and sensitivity are not available, chloramphenicol (25 - 50 mg/kg PO tid in dogs and bid in cats), cephalexin (22 mg/kg PO tid); cefadroxil (22 mg/kg PO bid) or trimethoprim-sulfadiazine (15 mg/kg, PO or SC bid) can be used, over a 4 to 6 week period. For cases of cryptococcal peripheral vestibular disease (e.g., *Cryptococcus neoformans*), itraconazole at 50 to 100 mg PO every 24 hours for several months has been beneficial in cats [470]. Artificial tears can be

used for animals with keratitis sicca. Because of potential ototoxicity, especially in cases where the tympanic membrane has been damaged, topical agents (e.g., iodophors, aminoglycosides, cetrimide, iodine, chloramphenicol and chlorhexidine) should be used with caution. Indeed, topical antibiotics are considered insufficient for the treatment of otitis media-interna [476]. Drainage of the middle ear using a bulla osteotomy (e.g., from a ventral approach) may be required in the event of fluid buildup in the tympanic bulla. Note that the tympanic bulla in cats consists of dorsolateral and a ventromedial cavities divided by an incomplete bony septum, and both compartments should be surgically drained [479]. In more chronic cases refractory to treatment, surgical debridement and total ear canal ablation-lateral bulla osteotomy or ventral osteotomy (especially used for disease processes confined to the middle and inner ear) can be successfully performed [181,182,480]. Short-term complications may include Horner's syndrome, facial nerve paralysis, and otitis interna [182]. In some animals, neurological signs may recur, while in other patients, minor residual neurological deficits (e.g., head tilt or ataxia) may persist. Ventral bulla osteotomy and curettage, along with removal of retained epithelium and debris, can successfully treat cases of recurrent otitis media that develop after total ear canal ablation and lateral bulla osteotomy [481]. Removal of nasopharyngeal polyps by traction and/or bulla osteotomy is usually successful [475]. Treatment of middle ear tumors may involve surgical resection, radiation or chemotherapy. Prognosis is guarded to poor [182,482].

Additional potential complications include development of osteomyelitis of the osseous bulla and petrous temporal bone, extension of infection to the meninges or brain parenchyma leading to meningoencephalitis [89] or to pontine and cerebellomedullary abscesses [483], complications that occurs more often in cats [484], and cholesteatoma formation. A cholesteatoma is a form of epidermoid cyst that is lined by stratified squamous keratinizing epithelium. It appears as a laminated structure composed of layers of keratin, and rests on a fibrous stroma of inflammatory granulation tissue. In one study of otitis media, 7 of 42 dogs had an accompanying cholesteatoma within the middle ear [47]. In this study, the masses appeared to be formed from pockets of the tympanic membrane which became adherent to the inflamed middle ear mucosa. Clinical signs in some affected dogs included head tilt, poor balance, deafness, and difficulty and pain when eating or yawning. None of the dogs had Horner's syndrome or facial nerve disorder. Radiographically, the cholesteatomas were sometimes responsible for extensive resorption and remodeling of adjacent bone, including the temporomandibular joint and retroglenoid process. Treatment is by surgical resection (e.g., via osteotomy).

Congenital Vestibular Disease - Signs of peripheral vestibular disease without deafness have been observed in several breeds of puppies [89,485,486] including English Cocker Spaniels, German Shepherds, Tibetan Terriers, and in Burmese kittens. Signs may be noted from birth to 3 or 4 months of age, and typically include a pronounced head tilt, circling, and often falling and/or rolling. Nystagmus is not a feature in these young animals. The cause of this disorder is unknown. Pathological studies have failed to produce any evidence of either inflammation, degeneration or malformation. Prognosis is guarded since clinical signs may regress completely, recur, or remain static. There is no treatment.

A congenital condition, characterized by early onset of deafness and vestibular disease, has been reported in Doberman Pinscher puppies [57]. Twenty-one dogs from ten different litters were examined for signs of vestibular disease, at ages between birth and 10 weeks. Signs included rolling or falling, head tilt, circling, and inaccurate control of head movements with occasional bumping against objects. Vision was normal and no head tremors were observed. As the puppies grew older, signs usually became less pronounced and affected animals showed only mild head tilt and a tendency to circle when excited; however, relapses occasionally occurred. Vestibular testing (such as rotational and post-rotational nystagmus, and caloric stimulation) was abnormal in all dogs, bilaterally. Righting reflexes were poor in young dogs, but improved with age. Hearing, as assessed by the brainstem auditory evoked response (BAER) method, was absent in all puppies 3 weeks of age or older. Otoscopic and radiographic studies indicated that the tympanic membranes and tympanic bullae were normal. Histopathologic studies revealed that all affected dogs had a non-inflammatory neuroepithelial degeneration of the cochlea with a progressive loss of the auditory sensory hair cells, resulting in almost complete loss of the organ of Corti by 11 weeks of age. Microscopic examination of the vestibular system from several affected dogs showed either absence of otoconia or some degree of otoconial abnormality in one or more maculae. Pedigree analysis indicated that this vestibular/hearing disorder in Doberman Pinschers had an autosomal recessive mode of inheritance.

Diagnosis is usually straightforward and the prognosis for clinical improvement of the vestibular disease is good. This improvement may result from central compensation due to sensory and visual input. However, the deafness is severe, bilateral, and permanent. While hearing is very difficult to assess accurately using response to sounds, such as clapping, BAER testing can provide early diagnosis of deafness, allowing breeders and owners to identify affected parents and avoid further breeding.

A similar condition has been seen in Beagle and Akita puppies and in Siamese kittens [89]. Almost identical clinical signs have been reported in two related litters of Doberman Pinscher puppies with congenital peripheral vestibular disease attributed to lymphocytic labyrinthitis [487]. Multiple lymphocytic aggregates were found in the lamina propria beneath the ciliated columnar epithelium of the middle ear. No lesions were found in the brain. Analysis of CSF was normal. Signs of unilateral or bilateral vestibular disease developed when puppies were between 3 and 12 weeks of age. Several of the

puppies were deaf and some showed thoracic limb hypermetria. Vestibular signs improved in some dogs but persisted unchanged in others.
Congenital nystagmus, without vestibular disease, occurs sporadically in puppies. The nystagmus is usually pendular and spontaneously resolves. It has also been seen in Belgium Sheepdogs with incomplete development of the optic chiasm [488]. Nystagmus may also be observed in some Siamese cats and it may persist for life [89]. It has also been seen in some cats with Chediak-Higashi syndrome in which it is associated with congenital cataracts, photophobia, pale irises, and albinotic or depigmented fundi [489].
Miscellaneous Causes of Peripheral Vestibular Disease - Neoplasia is an infrequent cause of peripheral vestibular disease, however, older cats and dogs appear at risk for tumors involving the middle or inner ear [182]. While a variety of tumors, including anaplastic carcinoma, lymphoblastic lymphosarcoma, osteosarcoma, fibrosarcoma, chondrosarcoma, squamous cell carcinoma, basal cell tumors, sebaceous adenocarcinoma, papillary adenoma, and ceruminous gland adenoma and adenocarcinoma have been reported in dogs and cats (involving bony or soft tissue structures), squamous cell carcinoma and ceruminous gland adenocarcinoma may be the most common tumor of the middle ear in cats [490,491]. In dogs, however, papillary adenomas and extension of adnexal or ceruminous gland tumors originating in the external ear appear to be more common in this location [492]. Rarely, middle ear tumors may directly extend into the brainstem [482]. Neurofibromas involving the vestibulocochlear nerve are very rare. Prognosis is poor. Iatrogenic peripheral vestibular disease may result from use of aminoglycoside antibiotics, which can cause degeneration of vestibular and auditory peripheral receptors (see deafness). Cats are especially susceptible to the vestibular effects of streptomycin. Cranial trauma may cause signs of peripheral vestibular disease secondary to fractures in the petrous temporal bone or tympanic bulla. Signs of peripheral vestibular disease accompanied by facial paresis/paralysis, but without otitis media, occur sporadically in dogs, a few of which have had hypothyroidism and pituitary chromophobe adenoma [89]. Thyroid hormone replacement therapy has been ineffective in these cases.

Inflammatory Polyps are another cause of peripheral vestibular disease. Polyps are smooth, non-neoplastic masses that arise from the lining of the tympanic cavity, auditory tube, or nasopharynx [490,493]. They are typically pedunculated and fixed by a thin stalk to their point of origin. The polyps are often associated with obstructive disease and may cause rupture of the tympanic membrane. Inflammatory polyps are commonly associated with otitis media [475]. They are thought to occur as a result of chronic middle ear infection or from ascending infection from the nasopharynx. Polyps tend to be single masses and are especially common in young adult to middle-aged cats, with no apparent gender or breed predisposition. They are infrequently observed in dogs [494]. Clinical signs include head shaking, aural discharge, head tilt, facial paralysis, vestibular dysfunction, Horner’s syndrome, and sometimes, presence of a mass in the external ear canal. Masses in the nasopharynx may cause dysphagia and stertorous respiration, respiratory distress, and phonation change [490,495]. Polyps are composed of fibrous connective tissue stroma containing numerous capillaries and inflammatory cells, including macrophages, neutrophils, lymphocytes and plasma cells, covered by pseudostratified columnar ciliated or non-ciliated respiratory epithelium. This epithelium is continuous with the tympanic cavity, eustachian tube and nasopharynx. Some polyps are covered by squamous epithelium if lesions originate from deeper portions of external ear canal. Focal mucosal ulceration may be seen. They are differentiated from neoplastic masses by direct visualization, cytology and histopathology. Skull radiographs may indicate changes similar to those seen in otitis media. They may also be seen as soft tissue masses in the pharyngeal region and within the tympanic bulla. Imaging (e.g., CT) can also be used to define the regional extent of the polyp [496]. Treatment is usually uncomplicated and involves simple traction-avulsion of the mass through the external meatus (sometimes necessitating lateral ear canal resection) or from the nasopharynx (retraction of the soft palate or incision may be required to visualize the eustachian tube). Bulla osteotomy facilitates polyp removal from the tympanic bulla. Prognosis is usually good, although a temporary Horner’s syndrome was commonly observed in one study following bulla osteotomy [475]. Less frequently, self-limiting facial and hypoglossal neuropathies may also develop following surgery [521]. Recurrences can occur. In one study, recurrence rate following removal by traction-avulsion was approximately 40% and was more likely in cats with aural polyps and in those with more severe aural signs. Interestingly, none of the cats treated with prednisolone after traction-avulsion suffered a recurrence. Results of another study suggest that traction-avulsion is a reasonable treatment for inflammatory polyps if the bullae are radiographically normal [523].

B. Central Vestibular Disease - Signs of central vestibular disease in animals are similar to those seen with peripheral vestibular disease. However, in central disease, there may be evidence of other cranial nerve dysfunction due to involvement of various brainstem nuclei (e.g., trigeminal or abducent), altered mental status, vertical or positional nystagmus, cerebellar signs, and evidence of paresis and/or proprioceptive deficits resulting from brainstem involvement of descending and ascending long tracts. Also, animals with central vestibular disease have a tendency to roll in one direction [89]. Central signs do not include Horner's syndrome but facial paresis/paralysis, secondary to involvement of the facial nucleus, may be observed. Unilateral lesions in the brainstem usually produce an ipsilateral hemiparesis and postural reaction deficiencies

(associated with lesions in the general proprioceptive and/or upper motor neuron systems). However, central lesions occasionally result in a "paradoxical" vestibular syndrome in dogs in which the lesion is located on the opposite side to that expected from the clinical signs (head tilt, strabismus, body tilt). The lesion, typically a space-occupying one in the area of the cerebellopontine angle, such as tumor or granulomatous mass, is considered to be located on the same side of the body in which proprioceptive/postural reaction deficits are detected [89,497-499,529]. Presumably, presence of unilateral deficits of other cranial nerves would be another indicator of the side on which a lesion is located. This syndrome may occur if vestibular pathways in either the caudal cerebellar peduncle (particularly the supramedullary juxtarestiform body) or the flocculonodular lobe of the cerebellum are involved [89,498]. The paradoxical vestibular syndrome occurs less frequently in cats [500,501].

Causes of central vestibular disease include inflammatory diseases, such as distemper and granulomatous meningoencephalomyelitis (GME), bacterial meningitis/meningoencephalitis [502] and rickettsial meningoencephalitis (e.g., Rocky Mountain spotted fever) [503], feline infectious peritonitis [504], toxoplasmosis and neosporosis, migrating parasites, such as *Cuterebra* larvae in cats [89], and mycotic meningoencephalomyelitis (e.g., cryptococcosis and *Acremonium* sp. [505], along with vascular disease, thiamine deficiency (especially cats), storage diseases [506], trauma, drug toxicity (e.g. metronidazole in dogs and cats) and tumors, particularly those located at the cerebellopontine angle. Surface tumors may include meningioma, choroid plexus papilloma, medulloblastoma, neurofibroma, trigeminal neurofibrosarcoma/schwannoma, and lymphosarcoma [89,529]. Dogs may be at risk for meningiomas and choroid plexus papillomas, while in cats, meningiomas and lymphomas are common [89,476]. Parenchymal tumors that may cause central vestibular dysfunction include the focal/neoplastic form of GME, gliomas, or metastatic tumors [89,507]. Forebrain tumors may result in central vestibular disease secondary to caudal transtentorial herniation [476].

Diagnostic aids in evaluating central vestibular disease include otoscopy, CSF analysis for inflammatory diseases (including cellularity, protein, antibodies, protein electrophoresis, etc.), advanced imaging studies (e.g. CT or MRI) for tumors, skull radiographs for skull fractures and tympanic bulla evaluation, BAER studies to evaluate hearing and integrity of central brainstem pathways, and surgical biopsy/resection (intracranial, ear canal, or bulla osteotomy) [473,476,508]. Specific treatments are based on the underlying cause of the vestibular disorder, for example antimicrobial therapy for infectious agents, surgical removal/resection, radiation therapy and chemotherapy for tumors, and thiamine administration for thiamine deficiency.

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