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Neurotoxic Disorders (6-Feb-2003)

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Introduction

Neurotoxicity in dogs and cats may result from myriad agents, including metals, pesticides, solvents and other chemicals, and bacterial, animal, and plant-derived toxins, as well as therapeutic agents [1]. Drug-induced toxicity may be caused by overdosage, undesirable side effects, or accidental exposure, usually ingestion. In one study [2], the most commonly reported toxins were: lindane-based insecticides (HCB, hexachlorocyclohexane, Isotox, Lintox); pyrethrin and pyrethroid insecticides (permethrin, fenvalerate/DEET); chlorpyrifos, strychnine, lead, metaldehyde (in metaldehyde-based molluscicides), and caffeine (e.g., ingestion of caffeine-based stimulants or chocolate which contains caffeine and theobromine). In general, signs of neurotoxicity may include excitation, depression, tremors, clonic-tonic seizures, hyperactivity, ataxia, circling, salivation, hyperthermia, and coma. Treatment involves decontamination where indicated (e.g., bathing/shampooing), inducing emesis (e.g. apomorphine), correction of any fluid and electrolyte imbalances, repeated administration of activated charcoal with a saline cathartic (sodium sulfate is more efficient than magnesium sulfate) or performing gastric lavage to decrease the amount the animal absorbs, and providing demulscents (milk, kaolin-pectin) for any gastrointestinal irritation [3].
Neurotoxic agents have been arbitrarily grouped as follows:

Metals
- Lead
- Mercury

Automotive products
- Ethylene glycol

Solvents/cleansing agents
- Alcohols
- Chlorhexidine
- Hexachlorophene

Rodenticides
- Anticoagulant Rodenticides
- Bromethalin
- Strychnine
- Thallium

Insecticides, Molluscicides, Repellents
- Amitraz
- Chlorinated Hydrocarbons
- Metaldehyde
- Organophosphates/Carbamates
- Pyrethrins and Pyrethroids

Herbicides
- (2-methyl-4-chloro) Phenoxyacetic Acid

Plants
- Cyanogenic
- Cycad Palms

Bacterial
- Botulism
- Tetanus

Animal
- Tick Paralysis
- Toad Toxicity

Therapeutic agents/drugs
- Aminoglycosides
- Barbiturates
- Caffeine and other Methylxanthines
- Bromide
- Closantel
- Griseofulvin
- Ivermectin
- Levamisole
- Methionine
- Metoclopramide
- Metronidazole
- Pemoline
- Toluene/Dichlorophen
- Tricyclic Antidepressants
- Vincristine
- Zolpidem
- 5-Fluorouracil
- 5-Hydroxytryptophan

Alcohols

Widespread utilization of short-chain alcohols in solvents and alcoholic beverages provides small animals with numerous opportunities for exposure [4]. Toxicosis most commonly occurs following ingestion but may also arise from inhalation

and/or dermal absorption. The actions of short-chain alcohols are believed to result from nonspecific interactions with biomembranes altering the function of membrane-bound proteins, including the GABA-A receptor. Onset of signs typically occurs within an hour of exposure and may last for 24 hours. Clinical signs include behavioral changes such as excitability, vocalizing, and incontinence, ataxia, drowsiness, unconsciousness, loss of reflexes, respiratory compromise, respiratory and cardiac arrest, and death. Therefore, general measures for resuscitation should be followed in the initial treatment of severe alcohol toxicosis, including endotracheal intubation, mechanical ventilation, correction of acid base imbalance with bicarbonate (metabolism of alcohols alters the redox state in the liver, leading to hypoglycemia and lactic acidosis in some cases). Activated charcoal (2 g/kg PO) should be given within 3 hours of an alcohol ingestion and skin should be decontaminated.

Aminoglycosides
Aminoglycoside antibiotics can adversely affect auditory and vestibular mechanisms, especially after prolonged administration of large amounts of the drugs [5]. These drugs concentrate in perilymph and endolymph, thus exposing the cochlear hair cells to high concentrations of the antibiotic agents. 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 [6]. The toxic effects of these drugs are heightened if the tympanic membrane is perforated. However, in one experimental study, gentamicin sulfate did not induce detectable alteration of cochlear or vestibular function in dogs with intact tympanic membranes or after experimental bilateral myringotomy [7]. In other experimental studies, ototoxicity of aminoglycosides may be enhanced by loop diuretics [8], while the severity of ototoxic side-effects can be influenced by nutritional factors [9].

Amitraz
Amitraz, an alpha-adrenergic agonist and a weak monoamine oxidase inhibitor, may induce sedation, depression, ataxia, and muscle weakness in dogs following excessive exposure, such as application to the skin for *Demodex* control and ingestion of tick collars [10]. Other signs may include hypertension, mydriasis, hypothermia, bradycardia, hyperglycemia, hypoperistalsis, vasoconstriction, vomiting, and diarrhea [11-13]. I have also seen brief, generalized seizures in our own Welsh Corgi following treatment for demodicosis. Nerve conduction studies are normal [13]. Treatment with yohimbine at 0.1 mg/kg IV normally reverses the signs. It has been reported that signs can be reversed by low doses of atipamezole (50 µg/kg, IM), a potent alpha 2-antagonist, within 10 minutes after injection [12].

Anticoagulant Rodenticides
A variety of anticoagulant rodenticies are available with one of the best known being warfarin. These agents interfere with vitamin K_1 hydroquinone recycling in the liver leading to impaired synthesis of functional forms of clotting factors II, VII, IX, and X, and development of coagulopathies/bleeding [220]. Intrathecal or intrameningeal hemorrhage may lead to ataxia, stiffness, or seizures. Diagnosis may be made using common coagulation tests (bleeding time, blood clotting time, activated clotting time, prothrombin time, and activated partial thromboplastin time). The PIVKA test may also be useful in identifying a vitamin K_1-responsive coagulopathy. Treatment may involve use of fresh frozen plasma (at 9 mL/kg) or whole blood (at 20 mL/kg) followed by oral vitamin K_1 at a rate of 2.5 mg/kg sid for 2 to 4 weeks.

Barbiturates
Barbiturates inhibit calcium accumulation in neural tissues and thereby inhibit the release of neurotransmitters [1]. Barbiturate anesthetics produce profound respiratory and CNS depression, general anesthesia, hypothermia, hypotension, shock, cyanosis, and coma [1]. Phenobarbital may have several side-effects that include sedation, nystagmus, ataxia, behavioral changes, hyperexcitability, polydipsia, polyuria, and polyphagia [10]. Signs may disappear after several weeks of treatment as animals adapt to the dosage. The hyperexcitability may be difficult to manage and may be the limiting factor in the use of phenobarbital [10]. Treatment of barbiturate poisoning involves use of emetics, activated charcoal, gastric lavage, ventilation support, and fluid therapy.

Botulism
Botulism is a disease resulting from the ingestion of spoiled food or carrion containing a preformed exotoxin produced by spores of *Clostridium botulinum*. The neurotoxin associated with canine disease has been reported to be type C [14-21]. Botulism is an uncommon disease in dogs and naturally occurring disease has not been reported in cats [22], although type C botulism has been reported in dairy cattle from feed contaminated with a dead cat [23]. Most cases in dogs appear to result from eating carrion or contaminated raw meat (botulinum toxin is destroyed by heating at 100ºC for 10 minutes). The

toxin is absorbed from the stomach and upper intestine, circulates in lymphatics and finds it way to the neuromuscular junction of cholinergic nerves where it blocks pre-synaptic release of acetylcholine [24] leading to generalized motor neuron disease and parasympathetic dysfunction [22]. Clinical signs may occur within hours to several days following ingestion of toxin. Clinical signs reflect a progressive, symmetrical disorder, ranging from mild weakness to severe flaccid tetraplegia with absent spinal reflexes and evidence of weakness in muscles of the face, jaw, pharynx, and esophagus resulting in dysphonia, dysphagia, facial paralysis, and megaesophagus. Mydriasis may be present. Early in the course of the disease, or in mildly affected animals, the gait may be stiff and pelvic limbs may be used in a synchronous, bunny hopping fashion. Presence of keratoconjunctivitis sicca in some dogs suggests autonomic dysfunction. Pain perception remains normal and muscle atrophy is not seen. There is no hyperesthesia [22].

Hematological and biochemical parameters are unaffected. Electrodiagnostic studies may reveal a low amplitude of the evoked muscle action potential, decrease in amplitude of the compound muscle action potential with slow repetitive stimulation, slowing of motor and sensory nerve conduction velocities, and sometimes, fibrillation potentials and positive sharp waves, especially in distal limb muscles [25]. These latter changes indicate peripheral nerve dysfunction through some as yet unknown action of the botulinum toxin. Nerve conduction velocity and amplitude can return to normal as clinical improvement occurs.

Diagnosis is suggested by historical, clinical, and electrodiagnostic data. It is confirmed by identification of the toxin in the material ingested or in serum, feces, or vomitus of an affected animal with type-specific antitoxin using the neutralization test in mice [22,26]. ELISA has also been used [27]. Serum should be collected early in the course of the disease [21]. In one report, *Clostridium botulinum* type C was still present in feces and a low toxin titer persisted for 114 days after ingestion of a contaminated duck carcass [20].

The prognosis is usually favorable in dogs, with recovery occurring within 1 to 3 weeks [22], although some affected dogs are euthanized due to other clinical complications [28]. Treatment is primarily supportive. Severely affected animals should be monitored closely to avoid the potential complications of inhalation pneumonia, respiratory paralysis, and urinary tract infections. Padding should be used for recumbent animals, along with assistance with drinking and eating. Penicillin or metronidazole may be used to reduce intestinal clostridial numbers. The use of botulinum antitoxin is controversial [22]. Note that the history, clinical signs, and pattern of onset of lasalocid-induced toxicosis in dogs are similar to those reported for botulism [29].

Bromethalin

Bromethalin toxicosis (e.g., in bromethalin-containing rodenticides) in dogs induces a variety of neurological signs. Dogs given a single oral dose of bromethalin at 6.25 mg/kg developed a toxic syndrome characterized by hyperexcitability, tremors, focal motor and generalized seizures, depression, and death within 15 - 63 hours after bromethalin administration. Clinical signs were dose-dependent, with signs of hind limb ataxia, and/or paresis, and/or CNS depression noted following lower doses. CSF pressure may be increased. Predominant abnormal EEG changes included spike and spike-and-wave EEG patterns, high voltage slow wave (50 - 150 microV, 1 - 6 Hz) activity, photoconvulsive or photoparoxysmal irritative responses, and marked voltage depression (dominant activity less than 10 microV) in all leads [30]. Gross lesions included mild cerebral edema and mild pulmonary congestion. Histologic lesions included diffuse white matter spongiosis, mild microgliosis, optic nerve vacuolation, mild thickening of Bowman's capsule, and occasional splenic megakaryocytes. Ultramicroscopic examination of midbrain stem revealed occasional swollen axons, intramyelinic vacuolization, and myelin splitting at the intraperiod line. Bromethalin was detected in kidney, liver, fat, and brain tissues, using gas chromatography with electron capture detection. Photodegradation of extracted bromethalin may limit accurate quantification of tissue residues. In experimental trials, repeated oral administration (e.g. 3 times daily) of a superactivated charcoal/sorbitol product (Superchar-Vet Liquid®) is reportedly an effective therapy [31,32]. In addition, dexamethasone at 2 mg/kg IV every 6 hours, or prednisolone at 2 to 6 mg/kg, PO, daily, and mannitol solution at 500 mg/kg, IV, every 6 hours to reduce cerebral edema, is recommended [11]. Bromethalin-based rodenticides are also highly neurotoxic to cats. Signs include tetraparesis/paralysis with extensor rigidity, depression, coma, focal motor seizures, anisocoria, positional nystagmus, and opisthotonus [33].

Bromide

Potassium bromide (BR) is a commonly used antiepileptic drug. The recommended oral dosage for BR is 20 - 40 (60) mg/kg /day (one daily dosage). The therapeutic range of BR in dogs is 100 - 200 mg/dl when potassium bromide is used as an add-on drug and 250 - 300 mg/dl when used as monotherapy (see Epilepsy). A variety of neurological signs have been reported in dogs attributable to bromide toxicosis (bromism) including anisocoria, muscle pain, hyporeflexia, hind limb weakness, ataxia, disorientation, depression, recumbency, and stupor. Presumably toxicosis might be expected in some dogs when serum levels exceed therapeutic BR concentrations [215,218]. Toxicosis has also been reported in an epileptic dog with renal insufficiency receiving potassium bromide at a dosage of 29 mg/kg /day [219].

Caffeine
Caffeine is a methylxanthine compound (other related compounds are theophylline, aminophylline, and theobromine) and a CNS stimulant [34]. Methylxanthines enhance catecholamine release and increase calcium entry into cells, and inhibit phosphodiesterase, an enzyme that degrades cyclic AMP (cAMP) [2]. Cardiac acceleration occurs with the increase of cAMP [34]. Intoxication in animals most commonly occurs within several hours following ingestion of chocolate, caffeine-based tablets, or elixirs [1]. One ounce of chocolate contains 5 - 10 mg of caffeine and 35 - 50 mg of theobromine, while baking chocolate is approximately 10 times more toxic [2]. Signs of toxicity in dogs and cats may include vomiting, restlessness, hyperactivity, ataxia, muscle tremors, tachycardia, cardiac arrhythmias, seizures, hyperthemia, polydipsia/polyuria, cyanosis, and coma [1,35,209]. There are usually no histological lesions found in the CNS [2]. Treatment is symptomatic and supportive, including anticonvulsants, antiarrythmic agents, activated charcoal, and fluids.

Chlorhexidine
Chlorhexidine is commonly used as an antiseptic and disinfectant. There have been reports of vestibular dysfunction following use of chlorhexidine (0.5%) or chlorhexidine (1.5%)/cetrimide (15%) in treating otitis externa in dogs and cats with perforated tympanic membranes [36]. Pathological findings included loss of sensory epithelium and fibrosis, and degeneration of afferent nerve terminals and the hair cells in the organ of Corti [1,36]. There is no specific treatment for this toxicosis although immediate flushing of the middle ear with saline may be beneficial [36]. Interestingly, a solution containing 0.2% chlorhexidine did not induce vestibular or cochlear neurotoxicity following installation (over a 3-week period) into the external ear canals of dogs with intact and surgically perforated tympanic membranes [37].

Chlorinated Hydrocarbon Toxicity
Chlorinated hydrocarbon compounds (e.g., endrin, aldrin, dieldrin, heptachlor, lindane, DDT) are used for prevention and control of insect infestations around farms, homes, and on animals, although regulatory agencies have banned the use of may of these insecticides because of accumulating tissue residues and environmental persistence [11]. Dogs and cats may be poisoned by ingestion, inhalation, or absorption through the skin when the insecticide is applied topically [38]. Endosulfan is presently used for garden or farm use and is highly toxic to cats and has been used maliciously to kill dogs [11]. Chlorinated hydrocarbon insecticides are considered to be non-specific stimulants of the central nervous system [38]. Clinical signs can include anxiety, hysteria, facial muscular spasms, jaw champing, spastic gait, ataxia, mydriasis, salivation, and severe generalized seizures. External stimuli may precipitate seizures. Body temperature will usually increase significantly as a result of the seizures. Death may occur within minutes or hours, after several days, or not at all. Neuropathological changes are usually absent [39].
A presumptive diagnosis is based on historical data of recent exposure to the toxin and clinical signs. Prognosis is guarded. Signs of acute toxicosis usually abate in 1 to 2 days. Complete recovery may take weeks. Treatment is symptomatic since there is no known antidote. Seizures may be controlled using intravenous anesthetic barbiturates, given to effect. Purgatives and/or gastric lavage will help remove residual toxin ingested, but maximum benefit is to be expected only during the initial 2 hours after exposure. Soap and water scrubs are indicated for animals exposed by the dermal route. Hyperthermic animals may be bathed in cool water. Forced diuresis with 5% mannitol in 0.9% sodium chloride can enhance urinary excretion.

Closantel
Closantel, a salicylanide derivative and potent uncoupler of mitochondrial oxidative phosphorylation, is primarily used as an anthelmintic against nematodes, trematodes and some arthropods in ruminants. It has also been used in treating dogs infected with demodectic mange and *ancylostoma caninum*. Acute closantel intoxication has been reported in a 13 month old dog that accidentally received 6 times the normal recommended dosage (normal dosage is 5 mg/kg subcutanously followed by 2.5 mg/kg every week until cessation of clinical signs) [210]. Clinical signs of intoxication included depression, blindness, bilateral mydriatic pupils unresponsive to light stimulation, hearing deficit, pelvic limb weakness, hypotonicity, hypersalivation, emesis, diarrhea, and polydipsia/polyuria. Fundic exam revealed markedly swollen optic disks, small papillary/peripapillary hemorrhages, and tapetal hyperreflectivity. Biochemical serum studies revealed marked increase in liver enzymes, muscle CK, and total bilirubin, but decrease in total protein and albumin. The results of clinical and diagnostic findings suggested optic neuritis, myopathy, retinal degeneration, and hepatotoxicosis. Initial supportive treatment included fluid therapy, forced feeding a semifluid diet (Canine/Feline a/d ®, Hills), and prednisolone 2 mg/kg PO bid (followed by alternate day therapy for 1 week and progressive reduction over the ensuing 2 weeks) for the optic neuritis. In order to bind any free closantel (the toxic fraction, since most closantel is bound to plasma proteins, and almost exclusively to albumin), a daily intravenous infusion of 20% albumin was administered (1 ml/kg/day). The dog responded over several weeks and biochemical values returned to normal. Three months after intoxication, the dog appeared clinically normal, although blindness persisted. The histopathology associated with closantel poisoning in dogs is uncertain; however, in sheep with closantel intoxication, spongiform changes are commonly found in the brain, including optic tracts/fasciculi,

and neuronal loss in the ganglion cell layer and outer layer of the retina. The chances of chronic toxicity developing in dogs receiving closantel over several months appears to be quite low.

Cyanogenic Plants
Seizures and semicoma, accompanied by bradycardia, pale and cyanotic mucous membranes, pulmonary congestion, vomiting, and frequent defecation were observed in an 11-week-old puppy after consumption of leaves and stems from the cyanogenic shrub, heavenly bamboo (*Nandina domestica*) [40]. Treatment was supportive, including intubation and oxygenation, epinephrine (1:10,000, IM), prednisolone sodium succinate (100 mg, IV), furosemide (12.5 mg, IV), and ampicillin trihydrate (50 mg, SC). The following morning, the puppy appeared normal.

Cycad Palms
Cycad palms occur in dry sandy soils of tropical and subtropical regions. Ingestion of cycads (also known as sago palms) can result in toxicosis in animals. In a recent survey of 60 dogs with evidence of cycad ingestion, approximately 90% of the dogs were from the southern United States, 39% ingested seeds, 95% developed liver and gastrointestinal tract problems, and 53% had abnormal neurologic signs, including weakness, ataxia, depression, proprioceptive deficits, coma, or seizures [41]. It is not known if the neurological signs were secondary to liver damage or to neurotoxins. High serum bilirubin concentration and alkaline phosphatase and alanine aminotransferase activities were the most common serum biochemical abnormalities. Although clinical signs were observed within 1 day, laboratory values did not change for 24 to 48 hours after cycad ingestion. Mortality rate was 32%, with the remaining dogs responding well to treatment and supportive care such as, emesis, repeated doses of activated charcoal, fluid therapy (e.g., 5% dextrose IV), and seizure control. Sucralfate at 0.5 - 1.0 g, PO, tid, may be used if vomiting is severe or if GI ulceration develops. Dogs ingesting seeds were likely to develop more serious problems.

Ethylene Glycol Toxicity
Ethylene glycol (EG) is a commercial antifreeze automotive product with limited toxicity, but its metabolites, including glycolic acid are extremely toxic to dogs and cats. In a recent report from the ASPCA National Animal Poison Control Center, exposures were commonly (57%) from container spill, engine flush, or engine leak and were in or around the home (66%) [42]. Interestingly, among cases with a known final outcome, 59% did not show clinical signs and death/euthanasia was reported in 28%. In an earlier study, a mortality rate of 43% was reported in dogs and cats [43]. As little as 1 tablespoonful of 50:50 radiator fluid can be lethal in cats, while 4.5 ounces may be lethal in a 20-pound dog [11]. Signs of depression, vomiting, knuckling, ataxia, seizures, and coma may be observed within a few hours of exposure. Affected animals may be hypothermic. The condition is associated with severe metabolic acidosis, serum hyperosmolality, and eventually, renal failure with polydipsia, polyuria, calcium oxalate monohydrate and dihydrate crystalluria, and isosthenuria [44]. Glycolic acid is metabolized to formic acid, oxalic acid and oxalate. The oxalate combines with calcium to form oxalate crystals in renal tubules (especially proximal), urine, and within the lumen or perivascular space of cerebral capillaries [39]. Microscopically, the crystals appear pale yellow and there is evidence of nephrosis with attenuated epithelial cells and dilated tubules [39]. The birefringent crystals may be found in urine after 3 hours in cats and after 5 hours in dogs. Anion gaps > 40 - 50 mEq/L may be diagnostic. A moderate hypocalcemia may be found in serum. Ultrasonographic changes vary from mild to marked increases in renal cortical echogenicity [45]. Ethylene glycol colorimetric spot tests are available for use with urine and serum. A test for rapid (10 min) analysis of biological fluids for EG and glycolic acid also has recently been reported [46].
Treatment consists of administration of activated charcoal and sodium sulfate, correction of dehydration and acidosis, and maintaining fluid therapy. Fomepizole (4-methylpyrazole), an alcohol dehydrogenase inhibitor, is considered safe and effective for dogs if started within 8 hours of exposure [44,47]. The dose is 20 mg/kg, IV, initially as a loading dose, followed by doses of 15, 15, and 5.0 mg/kg at 12, 24, and 36 hours. This drug is not recommended for cats [48]. Instead, 20% ethanol (also an inhibitor of EG metabolism) is given at 5 mL/kg in saline IV, and 5% sodium bicarbonate at 6 mL/kg IV every 6 hours for 5 treatments, then every 8 hours for 4 treatments [11]. For dogs, the ethanol dosage is 5.5 mL/kg in saline IV, together with 8 mL/kg of 5% sodium bicarbonate, IP, each given every 4 hours for 5 treatments, then every 6 hours for 4 treatments. In cases of severe renal failure, peritoneal dialysis and hemodialysis may be options to ameliorate the azotemia, fluid, electrolyte, and acid-base abnormalities [49,50]. Prognosis is guarded. In one study in which EG intoxication was confirmed in 37 dogs, 21 were azotemic or became azotemic within 18 hours after admission, and only 1 of the 21 survived [47]. However, dogs treated with Fomepizole within 8 hours of EG ingestion had a good prognosis. Note that ultrasonographic detection of the "halo" sign (a pattern of greater than normal cortical and medullary echogenicity with persistence of areas of lesser echo intensity at the corticomedullary junction and central medullary regions) in anuric animals with EG intoxication was considered to warrant a grave prognosis.

5-Fluorouracil
5-Fluorouracil (5-FU) is a pyrimidine analog and an antimetabolite. It destroys rapidly dividing cells and is used to treat many neoplastic conditions. 5-FU creams and solutions are used for topical treatment of solar and actinic keratoses and some skin tumors in people [1,51]. In a report of 26 cases of accidental 5-FU ingestions by dogs reviewed from phone calls to the Illinois Animal Poison Information Center from January 1, 1987 to December 31, 1988, 12 were classified as "toxicosis", 13 as "suspected toxicosis", and one as "exposure" [51]. Dogs were the only species involved in 5-FU cases received during this time. Ingestion of more than 20 mg/kg of 5-FU was associated with the development of toxicosis. None of the 12 dogs that ingested oral doses in excess of 43 mg/kg (estimated) survived. Clinical signs associated with 5-FU poisoning in the dog were death, seizures, vomiting (with and without blood), tremors, diarrhea (with and without blood), ataxia, and depression. Cardiac arrhythmias, and respiratory depression have also been noted [51]. Clinical signs generally developed within 45 to 60 minutes after exposure, and deaths occurred 6 to 16 h after ingestion. Hyperesthesia, hyperexcitability, nervousness, muscle tremors, and cerebellar ataxia have also been reported in dogs and cats following intravenous 5-FU treatment or accidental ingestion [1]. Treatment should include dermal decontamination, GI tract decontamination/protection (e.g., sucralfate 0.5 - 1.0 gm, PO, tid), fluid therapy, anticonvulsants (e.g., pentobarbital sodium 3 - 15 mg/kg IV slowly to effect, or phenobarbital 3 - 30 mg/kg IV slowly to effect), and GI protectants. It is recommended that induction of emesis or administration of activated charcoal be delayed until seizures are controlled and the airway protected so as to avoid aspiration [51].

Griseofulvin
Griseofulvin treatment of ringworm in pregnant cats has resulted in multiple congenital malformations in kittens [52]. Malformations of the brain included exencephaly, malformed prosencephalon, caudal displacement, and hydrocephalus. Skeletal malformations included cranium bifidium, spina bifida (C1 through C4, and sacral), abnormal atlantooccipital articulation, cleft palate, absence of maxillae, and lack of tail vertebrae. Cyclopia and anophthalmia with absence of optic nerves and rudimentary optic tracts were also observed. Atresia ani, atresia coli, lack of atrioventricular valves in the heart, and absence of external nares and soft palate were other abnormalities present.

Hexachlorophene Toxicity
Hexachlorophene (pHisoHex ®) is used as a germicide in soaps, shampoos and disinfectant solutions. Dogs and cats may be exposed by percutaneous absorption of hexachlorophene following skin application, or dogs may eat soap containing hexachlorophene [53-57]. Nursing puppies have been poisoned following hexachlorophene application to the mammary glands of the bitch [55]. Clinical signs in dogs are usually characterized by acute onset of tremors, especially of the head, that can increase with excitement. Tremors may disappear during inactivity or sleep. Neuromuscular twitchings, spasms, opisthotonus, severe seizures, and death have been reported in some affected animals [56]. Irreversible visual impairment and permanent mydriasis were reported in Beagles following dermal application of an ointment containing 3% and 10% hexachlorophene over a 12-week period [58]. In cats, dilated pupils, vomiting, weakness, ataxia and spastic or flaccid paralysis, along with signs of hypovolemic shock (hypothermia, pale mucous membranes, tachycardia, tachypnea, and dyspnea) have been reported [53,59]. Significant elevations in cerebrospinal fluid pressure have been recorded in cats following experimental hexachlorophene toxicity [59].
Grossly, mild brain edema has been reported associated with flattening of the cerebral gyri and prolapse of a portion of the cerebellum through the foramen magnum [54,56]. Microscopically, the toxin produces spongiform changes, seen as a vacuolar myelinopathy, in the white matter of the brain, cerebellum and spinal cord, along with astrocytosis and microgliosis [53,56]. Comparative studies have shown that the vacuoles are associated with intramyelinic edema with splitting of myelin sheaths at the intraperiod line [60,62]. Neuronal cell bodies appear to be unaffected. Vacuolar lesions may also be seen in peripheral nerves [39,63]. Lesions in the CNS may regress after exposure to hexachlorophene is stopped [63].
Prognosis is guarded. Some animals recover spontaneously within a few weeks following removal of the exposure to hexachlorophene [55]. Paralyzed cats that have not reached the stage of severe central nervous system depression usually recover if exposure is stopped; however, clinical recovery may take 4 to 6 weeks. Gastric lavage or saline cathartic treatment may help animals that have ingested the toxin. In experimental studies with cats, hexachlorophene toxicosis has been reversed by slow intravenous injection of 30% urea (2 gm/kg) in a 10% aqueous glucose solution [59]. Cats are especially sensitive to phenol intoxication because of their inability to conjugate glucuronic acid with phenolic compounds. Since hexachlorophene is a polychlorinated biphenol, its use in cats should be contraindicated [53]. Barbiturates reportedly are ineffective in controlling seizures in dogs with experimental hexachlorophene toxicity [56].

5-Hydroxytryptophan
5-Hydroxytryptophan (5-HTP) is sold as an over-the-counter dietary supplement. Within target cells of the CNS,

cardiovascular system, GI tract and respiratory tract, 5-HTP is rapidly converted to serotonin. In a recent survey involving 21 dogs with evidence of accidental 5-HTP ingestion, clinical signs of toxicosis, resembling serotonin syndrome in humans, developed in 19 of 21 (90%) dogs. Neurologic signs included seizures, depression, tremors, hyperesthesia, and ataxia. Gastrointestinal tract signs included vomiting or diarrhea, signs of abdominal pain, and hypersalivation. Other clinical signs were hyperthermia and transient blindness. Three dogs died. No important clinical laboratory or necropsy findings were reported. The doses of 5-HTP ingested ranged from 2.5 to 573 mg/kg of body weight; the minimum toxic dose reported was 23.6 mg/kg, and the minimum lethal dose was 128 mg/kg. Onset of signs ranged from 10 minutes to 4 hours after ingestion, and signs lasted up to 36 hours. Of 17 dogs with clinical signs of toxicosis that received prompt and aggressive treatment, 16 recovered. Treatment consisted of decontamination, seizure control, thermoregulation, fluid therapy, and supportive care. Cyproheptadine, a serotonin antagonist, is also recommended at 1.1 mg/kg, PO or rectally, every 1 to 4 hours until signs resolve [64,65].

Ivermectin

Ivermectin, approved for the prevention of canine heartworm infection (at 6 μg/kg, monthly), and believed to be a gamma-aminobutyric acid (GABA) agonist, can produce severe CNS dysfunction in some dogs. In mammals, GABA acts as an inhibitory neurotransmitter at pre- and postsynaptic neurons within the CNS. Signs include depression/disorientation, muscle fasciculations, ataxia, dilated pupils, drooling, rarely seizures, and coma. Mydriasis, depressed menace response, and apparent blindness (reversible with time) may also be observed, along with vomiting, diarrhea, hyperthermia, bradycardia, and sinus arrhythmia [1]. Collies appear idiosyncratically sensitive to the drug [66-68], although toxicosis has been seen in other breeds [69], perhaps associated with the blood-brain barrier acting as an ineffective ivermectin barrier [1]. Treatment is supportive, including activated charcoal and a saline cathartic, fluids, shock doses of corticosteroids (in severely affected dogs), and picrotoxin and physostigmine only in comatose dogs [1]. It has been reported that ivermectin and milbemycin commercial formulations have similar margins of safety and that milbemycin toxicosis appears to be dose-dependent in Collies with a demonstrated sensitivity to ivermectin [70].

Lead Poisoning

Accidental lead poisoning is one of the more common intoxications of dogs and cats [71-80]. It may occur from many sources including linoleum, putty, roofing felt, golf balls, old car batteries, lead weights, ingestion of contaminated soil, improperly glazed ceramic water bowls, and toys; however, lead-based paints are the most frequent source of poisoning [78,81]. Lead is believed to inhibit sulfhydryl groups of essential enzymes of cellular metabolism. One important consequence of this is inhibition of heme synthesis resulting in the circulation of immature erythrocytes [82]. Dietary factors, such as high-fat- low-calcium diets, may facilitate absorption of lead from the alimentary tract [83]. The majority of absorbed lead is deposited in bones, followed by liver and kidney, brain and spinal cord [84]. Lead can disrupt the blood-brain barrier by damaging capillary endothelial cells with resultant cerebral edema and hemorrhage. In the brain, morphological changes range from diffuse capillary proliferation to status spongiosus and cerebral cortical necrosis. In studies of experimental lead toxicosis of dogs, microscopic lesions were present in up to 89% of the lead-treated dogs [85,86]. Cerebrocortical lesions comprising spongiosis, vascular hypertrophy and gliosis predominated. These lesions were bilateral, had a predilection for gyri and were located mainly in the parietal and frontal cortex. There were bilaterally symmetrical spongiform changes in the brain stem. The cerebellum had spongiform changes in the roof nuclei and in the lingula there was spongiosis of the Purkinje cell layer and vacuolation of Purkinje cells. Axonal degeneration was evident in a sciatic nerve of only one dog. While peripheral neuropathy may occur sporadically with spontaneous lead poisoning, the inability to experimentally produce a polyneuropathy in dogs given chronic oral low level lead in another study [87], further suggests that dogs may be resistant to the toxic neuropathic effects of lead.

Lead poisoning is more commonly reported in dogs than cats [77]. Affected animals may be of any age (e.g., from 8 weeks to 16 years). In case reports of lead toxicoses from 2 major animal poison control centers in Europe and North America, 60% of dogs were less than 2 years old [81]. The incidence is reportedly higher in summer and early fall [81]. Clinical signs of central nervous system dysfunction usually are preceded or accompanied by gastrointestinal malfunction [74,78]. Signs may be acute or chronic. The most common gastrointestinal signs in dogs and cats are vomiting, anorexia, diarrhea, and in some animals, abdominal pain. Common neurological signs in dogs and cats include depression, generalized seizures, hysteria (barking and/or whining continuously, aimless running and snapping at objects), ataxia, blindness, head pressing, and jaw champing. Abdominal pain and hysteria may be more common in animals less than 1 year of age. Megaesophagus and partial laryngeal paralysis, believed to be due to lead-associated neuropathy, have been seen in a cat [88]. Megaesophagus may also be observed in dogs with lead poisoning. In some cats, clinical signs may be non-specific (e.g., weight loss). Low-level lead intake in young dogs can cause an early increase in blood pressure [89].

Diagnosis is suggested by finding rubricytosis and numerous nucleated erythrocytes in a stained blood smear [90]. The presence of basophilic stippling in red blood cells, anemia, increased packed cell volume, presence of diffuse radiopaque

material in the gastrointestinal tract, and radiopaque bands in x-rays of long bone metaphyses of young dogs [84], also supports the diagnosis (chronic low dose lead intoxication results in bone storage and altered normal bone physiology [91]). Elevated urinary levels of delta aminolevulinic acid has been reported to have limited value as a diagnostic aid in canine lead poisoning [75,92]. Furthermore, recent studies suggest that theta-aminolevulinic acid dehydratase and zinc protoporphyrin were of poor predictive diagnostic value as markers of lead intoxication in dogs [93,94]. In some animals, leukocytosis, elevated liver enzyme levels, and increased serum concentrations of glucose and cholesterol may be found. Levels of 40 μg or more of lead/100 ml of whole blood is considered definitively diagnostic of lead poisoning [71,77]. There is no direct correlation between severity of clinical signs and blood level content. Electroencephalographic changes reported in nonsedated dogs were marked by intermittent high-amplitude slow wave activity [95].
Treatment with the chelating agent, calcium disodium ethylene diamine tetraacetate (EDTA), using a dose of 25 mg/kg IV, qid for 2 to 5 days, often results in rapid recovery within 36 to 48 hours. Oral administration (same dosage) has also been effective [96]. Alternatively, oral penicillamine may be given in a dose of 100 mg/kg, daily, for 1 to 2 weeks. Treatment is repeated over another 5-day period if signs persist. The prognosis is favorable in the majority of lead poisoning cases treated with chelating agents [78,97]. Recent studies in dogs with naturally acquired lead poisoning indicated that succimer (meso-2,3-dimercaptosuccinic acid), administered orally for 10 days (10 mg/kg of body weight, PO, q 8 h), also effectively reduced blood lead concentrations and eliminated clinical signs of lead poisoning [98]. Succimer is also effective in cats [214]. Succimer may also be given rectally as a solution in patients that are vomiting.

Levamisole
Levamisole is used as an anthelmintic, microfilaricide, and immunostimulant [1,99,100]. Clinical signs of toxicity may be seen at approximately 4 times the normal therapeutic dose (which is 10 to 11 mg/kg), although toxicity has been reported following a single oral dose of levamisole hydrochloride given at the rate of 12 mg/kg [101]. Levamisole is a nicotine-like ganglionic stimulant producing both muscarinic and nicotinic effects at cholinergic receptors [1]. Clinical signs and lesions of levamisole toxicosis include: nausea, vomiting, increased salivation, frequent urination and defecation, colic, dizziness, headache, muscle tremors, ataxia, anxiety, hyperesthesia with irritability, clonic convulsions, depression, rapid respiration, dyspnea, cardiac arrhythmias, prostration, collapse, hemorrhages in the subepicardium and thalamus, enteritis, hepatic degeneration and necrosis, and splenic congestion. Most of these signs and lesions are similar to those observed in nicotine poisoning [102]. Levamisole causes an electroencephalographic arousal and multiple foci of EEG irritation [101,102]. Treatment is largely supportive, including GI tract decontamination, seizure control, fluid therapy, and ventilation support [1].

Mercury Poisoning
Dogs and cats are susceptible to mercury poisoning [39,103-105] a condition that has been termed Minamata disease (methyl mercury poisoning) in people. Elemental mercury is transported in blood plasma, proteins and hemoglobin, and may be incorporated rapidly into the brain [106]. While rarely seen in clinical practice, methylmercury (MM) poisoning or methylmercurialism usually occurs after consumption of contaminated fish, especially in cats [107-109] although it has also been reported in dogs [110]. Neurologic signs in dogs and cats following oral exposure have included abnormal symmetrical use of pelvic limbs, hypermetria, ataxia, paresis, abducted pelvic limbs, loss of postural reactions, proprioceptive impairment, blindness, opisthotonus, grand mal convulsions and terminal recumbency [111]. Serum biochemical findings were limited to hypercholesterolemia in dogs. Significant species difference in susceptibility to MM-induced neuronal lesions was the relative resistance of the feline spinal cord, canine cerebellar cortex and canine peripheral nervous system. Subacute exposure produced marked cerebral cortical involvement in dogs and cats, marked cerebellar cortical lesions, marked CNS perivascular inflammatory cell cuffing in cats, marked leptomeningitis in dogs and moderate lesions in the brain stem and cerebellar roof nuclei in both species. Chronic exposure of a dog to 120.4 μg Hg/kg/day for 55 weeks produced a marked loss of neurons and reactive astrocytosis in the cerebral cortex in the absence of clinical signs of toxicity. Twice weekly exposure to 0.64 mg Hg/kg as MM for 6 to 9 weeks in 5 dogs produced milder clinical signs, hypercholesterolemia, lipoproteinemia, and hydrocephalus. Neuronal loss and gliosis were most severe in the cerebral cortex with minimal involvement of the brain stem. Cerebellar lesions observed in cats include focal atrophy of the granular layer, focal spongiosus of the molecular layer and degeneration and loss of Purkinje cells in the cerebellum [112]. Demyelination in the fiber tracts of the dorsal funiculus, mainly the fasciculus cuneatus and in the lateral and ventral corticospinal tracts were also noted [112]. Terminal blood MM levels were in excess of 18 μg/ml, while brain methylmercury levels ranged from 21.0 to 28.4 μg/g. The liver and kidney contained the highest total levels of mercury of 50 to 80 μg/g, of which 23 to 37% was inorganic [112]. Increased levels of mercury in the brain does not necessarily result in behavior abnormalities or pathology [113]. In acute exposure to ingested mercury salts, oral administration of milk and eggs to bind mercury to protein has been recommended [11].

Metaldehyde
Metaldehyde toxicosis usually follows ingestion of metaldehyde-based molluscicides [2]. The incidence of toxicosis is more common in coastal and low-lying areas. Metaldehyde is degraded to various aldehydes in the stomach which may give a formaldehyde odor to the contents [114]. Signs include tachycardia, salivation, tremors, vomiting, hyperesthesia, nystagmus (especially in cats), ataxia, opisthotonus and seizures, hyperthermia, diarrhea, and depression. Death from respiratory failure may follow from 4 to 24 hours after ingestion. Delayed deaths may follow liver failure (after 3 to 4 days). Stomach contents should be submitted in suspected poisonings. Treatment includes activated charcoal, anticonvulsants, and fluid therapy with sodium lactate to correct the severe acidosis that develops in poisoned animals [11].

Methionine
Methionine is an essential amino acid and nutrient, a lipotrope, and a urine acidifier [65]. It has been used as a nutritional supplement in food animals. Accidental ingestion may lead to neurotoxicity and metabolic acidosis. The toxicity of methionine is partially related to its metabolism to ammonia and to increased production of mercaptan-like compounds. Toxicity is especially apparent in dogs with pre-existing liver disease. Signs include excessive salivation and vomiting, ataxia, depression, lethargy, circling, head pressing, aimless pacing, aggression, somnolence, blindness, seizures, stupor and coma [1]. In experimental studies, cats given DL-methionine (0.5 to 1 g/kg of body weight/day) developed severe hemolytic anemia and excessive oxidation of hemoglobin leading to a marked increase of methemoglobin concentration and Heinz-body formation [115]. Treatment is supportive, including emetics, activated charcoal, saline cathartic, and fluids containing bicarbonate [1].

(2-Methyl-4-chloro) Phenoxyacetic Acid
Ten hours following ingestion of an accidentally spilled herbicide that contained an octanoic acid ester of bromoxynil (3,5-dibromo-4-hydroxybenzonitrile) and an isooctyl ester of (2-methyl-4-chloro) phenoxyacetic acid (MCPA), an 8 year old Golden Retriever showed signs of vomiting, abdominal pain on palpation, ataxia, anorexia, and generalized weakness [116]. Appendicular muscles were firm on palpation and persistent muscle contraction (myotonia > 1 minute duration) was found on muscle percussion, using a reflex hammer. Electrical activity indicative of myotonia was identified on EMG evaluation. With supportive treatment, the dog eventually recovered from suspected MCPA toxicosis.

Metoclopramide
Metoclopramide, a derivative of para-aminobenzoic acid, has GI stimulatory and antiemetic properties, and has been employed clinically for gastric stasis disorders, gastroesophageal reflux, vomiting, nausea, and to allow intubation of the small intestine [117]. In the CNS, metoclopramide antagonizes dopamine at receptor sites and also sensitizes tissues to the effects of acetylcholine. Neurotoxicity may occur at therapeutic levels with dogs and cats showing signs of movement disorders such as slow to rapid twisting movements of the face, neck, trunk or limbs, as well as CNS depression, nervousness, restlessness, or frenzied behavior (especially in cats) [1]. Signs usually resolve within a few days after terminating metoclopramide medication. Diphenhydramine (2 - 4 mg/kg PO, IM, or IV, tid) may reduce the movement disorders. Most of the sign dissapear in 2 - 3 days after stopping medication [10].

Metronidazole
Metronidazole is used in small animals for treating giardiasis, trichomoniasis, and certain anaerobic infections. It appears that most neurotoxicoses in dogs and cats result from long term administration, and usually at high dose rates (e.g., exceeding 66 mg/kg/day, in dogs) [1]. In one report, five dogs receiving metronidazole at doses ranging from 67 to 129 mg/kg of body weight per day, for 3 to 14 days, showed signs of acute neurological dysfunction severe generalized ataxia and vertical, positional nystagmus, usually preceded by anorexia and intermittent vomiting [118]. Increased levels of protein were noted in 2 of 3 dogs from which CSF was collected. Two dogs were euthanatized because of severe neurological dysfunction. Three dogs slowly improved and eventually recovered completely after several months. Axonal degeneration was seen in vestibular tracts of one dog, while bilateral leukomalacia was found in another dog near the radix of the vestibular nerve. It was concluded that currently recommended dosages of metronidazole for dogs were excessive, and a total daily dosage of 30 mg/kg was recommended [118]. In another report involving a 2 year old Plott Hound-cross dog (receiving metronidazole at 89.5 mg/kg/day for 5 weeks) with progressive ataxia, nystagmus and knuckling, who was disoriented, had intermittent excitatory episodes, consisting of paddling, muscle spasms and vocalization, with involuntary urination during defecation, neurological abnormalities were reversed within 2 weeks after discontinuation of metronidazole therapy [119]. Interestingly, in a recent report from Sweden, adverse CNS signs were associated mainly with metronidazole administration to Collies [120]. In one retrospective study involving 20 dogs with metronidazole toxicosis (ranging from 60 - 65 mg/kg over 37 - 45 days), recovery was enhanced by administration of diazepam (the average intravenous/oral

dosage was 0.43 mg/kg tid for 3 days) [212]. It was postulated that this positive effect might result from diazepam competitively displacing metronidazole from GABA receptors. In cats, receiving metronidazole from 58 to 222 mg/kg, daily, for up to 6 months, neurological abnormalities seen include disorientation, ataxia, seizures, and blindness [121,122]. The neurological signs in all cats resolved within days of initiating supportive therapy and withdrawal of the drug.

Organophosphate/Carbamate Toxicity

Organophosphate and carbamate compounds are widely employed for control of external parasites in dogs and cats and for control of insects in the home and garden. Cats are relatively susceptible to acute toxicosis by the organophosphate compound chlorpyrifos [123]. Toxicosis may develop following ingestion of liquid concentrates or granules of these compounds or from excessive skin/hair coat dusting or painting [63]. Organophosphates and carbamates are acetylcholine esterase (ChE) enzyme inhibitors: -organophosphates are irreversible inhibitors of the enzyme, whereas carbamates are reversible inhibitors of ChE. This results in an accumulation of the neurotransmitter acetylcholine, causing:

a. overstimulation of the parasympathetic nervous system and subsequent development of muscarinic signs, e.g., salivation, lacrimation, urination, and defecation (SLUD), as well as pronounced gastrointestinal sounds, bradycardia, and pupillary constriction,
b. nicotinic signs associated with skeletal muscle stimulation, e.g., muscle fasciculations, tremors, twitching, spasms that may result in a stiff gait or rigid stance, and eventually weakness and paralysis, and
c. variable involvement of the central nervous system due to central cholinergic overstimulation (anxiety, restlessness, hyperactivity, anorexia, and generalized seizures).

The role of various serum and liver esterases in the pathogenesis of acute organophosphate toxicosis remains to be determined [63]. Death from asphyxia may result from severe central respiratory depression, bronchial fluid accumulation and bronchoconstriction. Clinical signs occur usually within minutes or hours. It has been reported that toxicity by the organophosphate compound, fenthion (Spotton®, Prospot®) usually results in a predominance of nicotinic signs (with no muscarinic signs), including muscle tremors, muscle weakness (particularly the neck muscles), and collapse after exercise [124]. In experimental intoxication with dichlorvos, muscle hemorrhage and necrosis was noted and was believed to be secondary to continual muscle fasciculations/contractions and possibly to the metabolic disturbances (metabolic acidosis and tissue hypoxia) produced in muscle as a result of ChE inhibition [125]. The myopathy associated with organophosphate toxicosis seems to be associated with excessive entry of calcium ions into muscle cells [126]. In a clinical report, acute polymyopathy in a 7 year old German Shepherd dog was attributed to the muscular hypertonia, tremors and seizures which developed during the acute phase of carbamate poisoning [127]. After two days of generalized muscular rigidity, the dog adopted a characteristic fetal position thought to be explained by the imbalance between the injuries to the extensor and flexor muscles. The polymyopathy, the diagnosis of which was based on EMG findings, myoglobinuria, and elevated serum muscle enzymes (muscle biopsy was normal), resolved gradually over the course of a week. A delayed neurotoxicity may occur in cats days or weeks after minimal exposure to organophosphates. In an experimental study, cats developed clinical signs of delayed neurotoxicity 16 to 18 days after di- isopropylfluorophosphate injection [128]. A histologic survey of the central and peripheral nervous systems revealed that the topographic distribution of axonal degeneration was characteristic of a dying-back neuropathy. In teased- fiber preparations from the left recurrent laryngeal nerve, the axonal degeneration that was initially focal and nonterminal subsequently spread in a somatofugal direction to involve the entire distal axon. Nerve fiber varicosities and paranodal demyelination preceded the axonal degeneration. The varicosities were associated ultrastructurally with intra-axonal and/or intramyelinic vacuoles, along with accumulations of axonal agranular reticulum [129]. Neurotoxic esterase is considered to be the target enzyme in the production of organophosphorus-induced delayed neurotoxicity (OPIDN) [130,131]. Affected animals manifest signs of a **neuropathic syndrome**. Dogs appear to be relatively resistant to delayed neurotoxicity [132]. Clinical signs associated with carbamate toxicity are likely to be less severe and shorter in duration [63]. ChE activity in domestic animals has been recommended as a potential biomonitor for nerve agent and other organophosphate exposure [133]. In this regard, it should be noted that physostigmine is a reversible ChE inhibitor and has a short duration of action. It crosses the blood-brain barrier readily; hence, it is a centrally acting carbamate. Pretreatment with physostigmine rapidly improves the incapacitating effects of organophosphate intoxication in various animal species [134]. Physostigmine carbamylates to a portion of ChE enzyme and thus protects the enzyme from irreversible binding with organophosphate.

Diagnosis is suggested by historical data, clinical signs and response to therapy. Whole blood cholinesterase levels can be determined using several substrates, including acetyl-, butyryl- and propionylthiocholine [217]. Red blood cell ChE levels reduced by 25% or more will confirm exposure [11]. At post mortem examination, brain tissue submitted for ChE activity is the most definitive diagnostic measure available for lethal organophosphate toxicosis [123]. Atropine, a muscarinic cholinolytic agent, at a dosage of 0.2 to 0.4 mg/kg body weight, IV, slowly over 5 minutes, usually results in a dramatic

cessation of muscarinic signs within 3 to 5 minutes. Repeated administration of atropine, SC or IV, at lower dosages is often required, especially in cats. Atropine blocks the effects of accumulated acetylcholine at muscarinic parasympathetic nerve endings. However, it does not affect the skeletal muscle (nicotinic) signs. Repeated doses of atropine can be given using one-half the initial dose. Overatropinization can cause tacchyarrhythmias, pyrexia, behavioral excitation and signs of delirium. Additionally, a ChE-reactivating oxime, such as pralidoxime chloride (2-PAM, Protopam Chloride) may be used to counter the nicotinic cholinergic signs. This compound acts by forming a relatively non-toxic complex with the organophosphate compound that can be excreted in urine, and also reactivates acetylcholine esterase. 2-PAM works best in the presence of atropine, the dose of which may be reduced when 2-PAM is used (e.g., 0.04 to 0.4 mg/kg once, or as needed). The dose of 2-PAM (given as a 10% solution) is 10 to 20 mg/kg for cats and 40 mg/kg for dogs, given IV slowly, or with fluids over a 30 minute period [11]. Signs of muscle weakness and fasciculations usually disappear within 30 minutes. If signs remain, repeat the dosage within an hour and then give every 8 hours, for 24 to 48 hours, or until recovery. Treatment with 2-PAM should begin within 24 to 48 hours and this agent may be especially beneficial in animals exposed to fenthion and chlorpyrifos with their slow rate of elimination [11]. The dose can be reduced in animals that are severely depressed, weak and anorectic one or more days after exposure. Oximes are of not benefit in treating carbamate toxicosis and may worsen the animal's condition. Orally administered activated charcoal in cats and dogs (0.5 to 4.0 gm/kg), in combination with a saline cathartic (e.g., 70% sorbitol), will help reduce absorption following ingestion of organophosphate/carbamate compounds. Seizures in cats and dogs may be controlled using diazepam (2.5 to 5.0 mg/kg IV as needed) or a barbiturate such as phenobarbital (10 to 20 mg/kg IV as needed). Supportive care is very important, especially in cats, and includes monitoring for hypo- and hyperthermia, oral or parenteral potassium supplementation if hypokalemia is detected, and parenteral fluid, electrolyte and nutritional support (e.g., hand-feeding, tube-feeding, or use of pharyngostomy tubes) [123]. Such care may extend over several weeks.

Diphenhydramine (Benadryl®) may be effective in treating organophosphate-induced neuromuscular weakness in dogs and cats, that is refractory to other forms of therapy [135,136]. Initial treatment should be initiated IV or IM (IM only in cats) at 4 mg/kg every 4 to 6 hours until clinical improvement occurs, followed by oral treatment at 4 mg/kg, tid. Diphenhydramine blocks the nicotinic and muscarinic effects of compounds such as fenthion (Spotton®). Experimental studies have shown that early and prolonged treatment using a high-dose regimen of methylprednisolone prevented the development of OPIDN in cats [137].

Variations in clinical presentations may occur with organophosphate compounds. In one report, two cats with chronic exposure (3 weeks) to chlorpyrifos (Dursban®), an organophosphate available as a soil insecticide and a parasiticide for use on cattle, presented with paraparesis, generalized hyperesthesia, anorexia, depressed postural reactions and bilaterally dilated pupils that were partially responsive to light stimulation [138]. It was considered that both cats lacked muscarinic signs but showed evidence of nicotinic and central nervous system stimulation. Serum ChE activity was low in both cats and electromyographic studies revealed presence of fibrillation potentials and high frequency discharges, especially in more distal muscles of the pelvic limbs. Administration of 2-PAM, 20 mg/kg, IV, bid, for 5 or 6 treatments, as well as atropine sulfate, 0.05 mg/kg, SC, every 6 hours for 2 days, resulted in complete clinical recovery. Interestingly, diazepam induced signs of acute organophosphate toxicity (miotic pupils, hypersalivation, generalized muscle fasciculations, and depression) in both cats - the mechanism of action was not determined.

Pemoline

Extreme agitation, hyperactivity, and vomiting that began within 24 hours after ingestion of approximately 750 mg of pemoline, a CNS stimulant used in humans for treating attention deficit-hyperactivity disorder in adolescents, was reported in a 3 year old German Shorthaired Pointer [139]. The dog was tachycardic, hyper-responsive, pyrectic, disoriented, and had mydriasis. These signs were consistent with excessive stimulation of the CNS and sympathomimetic effects resulting from pemoline toxicosis. Plasma pemoline concentration was markedly elevated (32 hours after ingestion the plasma concentration was 368 µg/ml, compared with a therapeutic concentration of 1.7 to 7.0 µg/ml reported for children). Several sedatives were administered intravenously to alleviate clinical signs and to allow administration of activated charcoal and fluids. Clinical signs resolved approximately 72 hours after ingestion of pemoline.

Pyrethrin and Pyrethroid Insecticides

These compounds are used as parasiticides and formulated for use in dogs and cats as shampoos and dips. Pyrethrins are natural insecticides while pyrethroids (e.g., permethrin and fenvalerate) are synthetic compounds and classified as type I (no alpha cyano-3-phenoxybenzyl group) or type II (with alpha cyano-3-phenoxybenzyl group) [2,140]. These insecticides are thought to interfere with sodium channels (type I pyrethroids and pyrethrins), enhance sodium ion conductance, and block post-synaptic GABA-A receptor-chloride ionophore complexes (type II pyrethroids). Cats may be more susceptible to pyrethrin/pyrethroid poisoning than dogs [11]. Signs of toxicosis may occur within hours of exposure (but may be delayed) and include tremors, salivation, ataxia, vomiting, depression, hyperexcitability, hyperactivity, seizures, dyspnea, and death

[2]. Treatment is symptomatic and supportive, including dermal decontamination, emesis induction within 1 hour (e.g., apomorphine at 0.03 mg/kg IV or 0.04 mg/kg IM), activated charcoal (2 g/kg, qid), magnesium sulfate or sodium sulfate (0.5 g/kg PO as a 10% solution in water), anticonvulsants, oxygenation (if necessary), and fluid therapy. The syndrome is generally reversible, with most animals recovering within 72 hours [33].

Strychnine Poisoning

Strychnine is a rodenticide poison used for "control" of squirrels, gophers, rabbits and other wild carnivora [63]. Dogs, and infrequently cats, become poisoned when they eat strychnine baits, especially in rural areas, although dogs also may be poisoned maliciously in rural and urban areas [63,141-144]. In one report on 261 cases of strychnine poisoning in dogs in Canada [145], strychnine poisoning occurred more often in younger dogs, with 61% of the cases being in animals less than 2 years old. Large breeds of dogs and male dogs were affected more often. In this study, the German Shepherd was the most common breed of dog affected.

Strychnine acts at the brainstem and spinal cord level by stereochemically and competitively blocking the motor inhibitory neurotransmitter, glycine. Some supraspinal signs may also be associated with strychnine inhibition of gamma-aminobutyric acid (GABA). Clinical signs of poisoning are induced by uncontrolled impulses reaching skeletal muscles and are characterized by retraction of the corners of the mouth, drawing together of the ears, stiffness of muscles of the neck, chest and abdomen, stiffness of gait and assumption of a "sawhorse" stance followed by tonic extension of the limbs, opisthotonus, vocalization, and difficult respiration. Affected animals are hypersensitive to auditory, visual (e.g., bright light), and tactile stimuli [11]. Consciousness is not lost during initial "seizural" attacks. After several minutes, the attack(s) may subside only to be followed by further episodes. Eventually, the respiratory muscles may be unable to function. Apnea can lead to cerebral anoxia, loss of consciousness and death. The entire course may last from 30 minutes to 1 to 2 hours, if the animal is untreated. Atypical signs, including absence of seizures or tetanic spasms, and time course (e.g., 10 hours) have been reported in dogs [216].

A presumptive diagnosis is based on a history of ingestion and characteristic clinical signs. In one report, chemical analysis of tissues and ingesta containing strychnine indicated that the highest concentrations were in stomach contents, followed by the liver, and the kidney [145]. Vomitus and urine can also be screened. The dimethoxy derivative of strychnine, brucine (2,3-dimethoxystrychnidin-10-one), may be detected in serum [216]. Prognosis is guarded, depending on the amount of poison ingested and/or promptness of treatment. The main objectives of treatment are to keep the muscles relaxed and to prevent asphyxia. The drug of choice in dogs has been pentobarbital, at 30 mg/kg, IV (or via intraperitoneal or intrathoracic routes if the animal is difficult to manage or is having seizures). Thiobarbiturates, such as thiopental sodium or thiamylal sodium, given IV to effect, are recommended for cats. Muscle relaxants recommended include glyceryl guaiacolate ether given in an intravenous dose of 110 mg/kg in either a 5 or 33 1/3% solution [146]. This drug controls "seizures" for up to 60 minutes. It can be safely repeated as needed. Methocarbamol (Robaxin®) also can be used, at a dose of 150 mg/kg IV, and repeated as needed. Supportive treatment includes prompt gastric or enterogastric lavage using 1 to 2% tannic acid or 1:2000 potassium permanganate and enemas, followed by administration of activated charcoal. Forced diuresis with 5% mannitol in isotonic saline and acidification of urine with 150 mg/kg body weight of ammonium chloride PO, will enhance urinary elimination of strychnine.

If the animal survives 24 hours, prognosis for complete recovery is very good. The clinical signs and necropsy findings closely resemble plastic explosive type 4 (PE4 containing cyclonite) toxicity [147]. Roquefortine (a diketopiperazine alkaloidal tremorgenic mycotoxin) and strychnine poisoning may be difficult to differentiate clinically [148].

Tetanus

Tetanus is a bacterial disease caused by *Clostridium tetani* that can affect all domestic animals and people. Disease occurs as a result of localization of tetanus spores in an anaerobic environment, such as a necrotic wound with suppuration, with conversion to a vegetative, toxin-producing form. Infection most frequently occurs following an injury, but may also develop after surgical procedures, such as ovariohysterectomy [149-152]. Organisms produce the exotoxin tetanospasmin within 4 to 8 hours, which travels via peripheral nerves (alpha motor neurons) to the CNS [153]. A trans-synaptic migration of tetanus toxin occurs in spinal cord motor neurons. Small amounts of toxin may be spread hematogenously to the CNS. Tetanus neurotoxin appears to prevent synaptic vesicles from fusing with the cell membrane and prevents the release of neurotransmitters [154,155]. It is active at the neuromuscular junction, autonomic terminals, and in inhibitory neurons in the CNS, with the central effects usually predominating the clinical picture. Toxin causes disinhibition on gray matter gangliosides [106] and binds the release of inhibitory neurotransmitters from interneurons (glycine) and from descending upper motor neuron pathways (gamma aminobutyric acid) resulting in release of spinal cord and brainstem motor neurons from inhibition and subsequent hyperexcitability [156,157]. In people, at high concentrations, tetanus toxin acts like botulism toxin in that it inhibits the release of acetylcholine at cholinergic synapses [106].

Considerable species differences exist in susceptibility to tetanus. The dog is much less susceptible than the horse, and

tetanus is seen less commonly in cats than in dogs. Clinical signs usually are observed within 4 to 12 days of infection [158-162], although extensor rigidity and ptyalism were observed in one dog 3 weeks after a routine ovariohysterectomy [151]. Frequently seen signs include stiffness of gait with extensor rigidity in all limbs, dyspnea, and spasms of the masticatory and pharyngeal muscles resulting in trismus and dysphagia. The tail may be elevated, facial muscles may be contracted to give a sneering expression ("risus sardonicus") with wrinkling of the forehead and puckering of the skin around the eyes, and the third eyelid may be protruded. Earflaps are usually held in an erect fashion, although low carriage has been noted early in the condition in some animals [163]. Animals may assume a "sawhorse" stance. In severe disease, the animal may be recumbent and opisthotonic. Affected animals are hypersensitive to external stimuli and reflex muscle spasms may occur. Autonomic involvement, such as bradyarrhythmias [164], or tachycardia/tacchyarrhythmias [165], may result from increased vagal tone or adrenergic stimulation, respectively. Death results from respiratory failure.

Localized tetanus may also be seen in dogs and cats with a localized limb injury and is usually characterized by stiffness in one limb before gradually spreading to involve the opposite limb and eventually, the entire body [162]. Tetanus in cats and dogs may remain localized to one of the thoracic limbs, which is held in rigid extension and caudally deflected (elbow extension and carpal flexion or extension) due to continuous involuntary muscle spasms [166,167]. Intermittent spasms may be superimposed upon the tonic rigidity. In one of the affected cats, the neck became twisted to the side [166]. The affected limb does not appear to be painful. Localization to both thoracic limbs, along with mild trismus and forehead wrinking, has been seen in one affected cat [213].

Potential complications include bony fractures from spasms or seizures, dyspnea from laryngeal spasms, inhalation pneumonia from dysphagia, and decubital ulcers. Urinary and fecal retention may be associated with anal and urethral sphincter/bladder spasms. In such instances, urinary stasis may lead to hemorrhagic, purulent cystitis [168,169]. Gastric and intestinal bloating may also occur [169]. Transient megaesophagus and/or hiatal hernia have been reported in association with gastro-esophageal reflux and regurgitation [170,171]. It has been reported that the hiatal hernia developed approximately 2 weeks after the beginning of clinical signs of tetanus [171,172]. Tetanus has been reported as a complication in dogs during parturition [173] and pregnancy [174].

To my knowledge, structural changes in the CNS or PNS have not been reported in dogs or cats. In people, degenerative changes may be found in the cerebral cortex and brainstem, along with hemorrhage, demyelination, and gliosis in chronic cases [106]. Diagnosis of the severe form of tetanus is largely based on characteristic clinical data. Mild forms of the disease may be difficult to diagnose since there are no specific ancillary aids available. There is a lack of the usually observed electrical silence following needle insertion in electromyographic studies. Nerve conduction studies are normal. Megaesophagus and/or hiatal hernia in animals with tetanus can be diagnosed radiographically [170].

Since tetanus is often mild or localized in dogs and cats, prognosis is usually favorable with treatment, which consists of penicillin G (e.g., 20,000 to 100,000 units/kg, qid, IV, as the aqueous potassium or sodium salt or IM, as the procaine salt), and immediate administration of tetanus antitoxin (TAT) (e.g., 100 to 1,000 IU/kg IV) [160]. Antibiotic therapy is aimed at any remaining vegetative *C. tetani* organisms in the wound, while the antitoxin is given to neutralize any toxin that remains unbound to the CNS. A test dose (e.g., 0.1 - 0.2 ml) of TAT can be given SC 20 minutes prior to the intravenous dosage and the animal observed for any anaphylactic reaction. If a wound is present, radical debridement and excision of all infected or necrotic-appearing tissue should be performed, along with peroxide irrigation to reverse the anaerobic state, and local intramuscular instillation of 1,000 units of TAT and 1,000,000 units of procaine penicillin G, in and around the wound site. Metronidazole is also effective (at 10 mg/kg, PO, tid, in dogs, and at 250 mg, PO, sid or bid, in cats). Antibiotic therapy should be continued for at least 10 days. Chlorpromazine (e.g., 0.5 - 2.0 mg/kg IM, IV, or PO, bid or tid, in dogs and cats) and pentobarbital (e.g., 3 - 15 mg/kg, IV or IM, every 2 - 3 hours, in dogs and cats) can be used to control reflex spasms and convulsions. Tracheostomy may be needed if laryngeal spasms are severe [22]. Esophagostomy or gastrostomy tubes or gastric tube feeding may be necessary if trismus prevents feeding or if megaesophagus and/or hiatal hernia are present along with gastro-esophageal reflux and regurgitation [22,171]. Prompt treatment usually results in a favorable prognosis [150,161,171], although complete remission of clinical signs in dogs and cats with generalized or localized tetanus may take 3 to 5 months [166]. A guarded to poor prognosis has also been reported in severely affected animals [22,169]. Megaesophagus and/or hiatal hernia tend to resolve with resolution of the tetanus [170], although, in one report, all dogs with this complication that were fed normally, died [171]. Nursing care is important to monitor nutritional and fluid balance.

Thallium

Thallium poisoning, from ingestion of thallium-containing rodenticides, may produce vomiting, bloody diarrhea, salivation, anorexia, depression, paralysis, trembling, dyspnea, and death in 3 - 5 days [175]. Degenerative changes have been observed in peripheral nerves [176]. Today, thallium toxicosis is relatively rare as rodenticides containing it are banned in the USA. Thallium toxicosis can be confirmed by detection of thallium in the urine, using colorimetric analysis. Treatment involves use of diphenylthiocarbazone (dithizone) to increase the rate of thallium excretion from the body, administration of antibiotics, fluid therapy, warm-water enemas, and oral administration of activated charcoal slurries [177,178].

Tick Paralysis

This is a flaccid, afebrile ascending motor paralysis in animals and people, produced by a neurotoxin generated by some but not all strains of certain species of ticks. Not all infested animals become paralyzed. Cats in the U.S. appear to be relatively resistant to tick paralysis, although signs of paralysis have been reported [179]. In North America, the common wood tick, *Dermacentor variabilis*, and *Dermacentor andersoni* (the Rocky Mountain wood tick) are incriminated most often. In Australia, especially along the east coast, *Ixodes holocyclus* is the most important species. Other species that occasionally cause paralysis are *Ixodes cornuatus* and *Ixodes hirsti*. *Ixodes scapularis*, the principal vector of the agent of Lyme disease (*Borrelia burgdorferi*) in the Northeast, Midwest, and Southeast of the United States, can also cause tick paralysis in dogs [180]. This tick is also a primary vector of the agent of human and rodent babesiosis. *Ixodes pacificus* has also been incriminated in dogs in the Grass Valley area (Nevada Co.) of northern California [181,182]. In Australia, *Ixodes holocyclus* is the vector for Lyme disease and spotted fever, caused by *Rickettsia australis* [183]. There is circumstantial evidence that some dogs bitten by *Ixodes holocyclus* develop signs of chronic illness similar to Lyme disease [183]. With tick paralysis, adult ticks, especially females, produce a salivary neurotoxin that circulates in the host animal and interferes with acetylcholine liberation at the neuromuscular junction and/or impulse propagation along motor axon terminals. In Australia, heavy infestations with nymphs or larvae may result in paralysis [184].

Onset of clinical signs is gradual, paralysis first becoming evident as an incoordination in the pelvic limbs, resulting in an unsteady gait. Altered voice, cough, and dysphagia can be early signs. Dogs become recumbent in 24 to 72 hours. Reflexes are lost but sensation is preserved. Jaw muscle weakness and facial paresis may be present. Death may occur within several days from respiratory paralysis. Electromyographic studies reveal absence of spontaneous potentials and lack of motor unit action potentials. No muscle response follows direct nerve stimulation. Motor and sensory nerve conduction velocity may be slower that normal. Prognosis is usually good with recovery occurring in 1 to 3 days following tick removal or dipping the animal in an insecticide solution. Administration of a systemic insecticide (e.g., cythioate, 3 - 6 mg/kg, PO) can be used to kill any hidden ticks on dogs. Assisted ventilation is necessary in cases with respiratory failure.

In Australia, tick paralysis is a far more serious and life-threatening condition [185-188]. Central effects include sympathetic stimulation that can produce peripheral vasoconstriction, arterial hypertension, increased pulmonary capillary hydrostatic pressure, pulmonary congestion and edema, tachyarrhythmias, and pupillary dilation. Respiratory embarrassment, in addition to diaphragmatic and intercostal paralysis, may stem from intoxication of medullary respiratory centers. Furthermore, hypoxia, hypercarbia, and respiratory acidosis may accompany respiratory failure. Clinical signs usually begin with pelvic limb weakness that progresses to paralysis within a few hours. Ascending paralysis soon involves the forelimbs. Mydriatic pupils are poorly or unresponsive to light. Other signs may include voice change, depressed gag reflex, megaesophagus, salivation, regurgitation and/or vomition, labored breathing, dyspnea, and cyanosis. Death occurs within 1 to 2 days if dogs are untreated. Similar signs are seen in cats with tick paralysis due to *Ixodes* sp. Focal forms of tick paralysis, such as asymmetrical facial paralysis and anisocoria, have been seen in some dogs, while others may only present with vomiting and loss of voice [184,189]. Short-term, acquired humoral immunity develops in animals following exposure to the toxin. Treatment involves removal of ticks, neutralization of circulating toxins, and supportive therapy. Painting ticks with pyrethroids and leaving the tick to die in situ may reduce mortality and analphylactoid reactions in sensitized patients [190]. Intravenous polyclonal hyperimmune serum (e.g., 0.5 - 1.0 ml/kg, IV) is suggested for dogs. For affected cats, administration of hydrocortisone (30 mg/kg, IV) followed by slow intravenous injection of serum (5 - 10 ml) is recommended [184]. This antiserum treatment is expensive and effective only in the early stages of paralysis [191]. In a recent survey from Australia, adverse reactions following tick antitoxin serum were reported in 3% of dogs and 6% of cats, with only a small percentage of these reactions associated with anaphylaxis [192]. The majority of adverse reaction were attributed to the Bezold-Jarisch reflex, a vagally mediated reflex initiated by chemical stimulation of cardiac receptors in the posterior wall of the left ventricle. Bradycardia, hypotension, reduction in total peripheral resistance and a slight reduction in myocardial contractility occurs with activation of these receptors [192]. A 1:1,000 solution of epinephrine should be available if animals show signs of anaphylaxis. Recommended dosage is 0.01 ml/kg IV or IM up to a maximum of 0.2 - 0.5 ml; repeat every 15 to 20 minutes if needed [192]. Due to the cholinergic nature of the Bezold-Jarisch reflex, atropine (at 0.1 - 0.2 mg/kg IV) will attenuate or abolish its clinical manifestations. A combination of phenoxybenzamine hydrochloride (e.g., 1 mg/kg as a 0.1% solution, given IV, over 15 minutes, every 12 to 24 hours) and acepromazine (0.05 - 0.10 mg/kg, IV, every 6 to 12 hours) produces sedation, helps relieve the respiratory distress, and resolves any cardiac arrhythmias [184,193]. Phenoxybenzamine hydrochloride, an alpha-adrenergic blocking drug, is thought to attenuate the arterial hypertension [188,193]. Some severely affected animals may require supplemental oxygen or intermittent positive pressure ventilation. Affected animals should be kept in a quiet, air-conditioned environment [184]. Food and water should be withheld until animals are walking and have not vomited for 24 hours. Weekly dips, use of collars impregnated with insecticide (e.g. permethrin) [190], or regular use of the organophosphate agent cythioate (3 mg/kg, PO, every 3 days) will help prevent tick paralysis in Australia. In a recent report from Australia, a correlation was noted between use of Lufenuron (a member of the benzoylphenylurea group of compounds used in dogs and cats for flea control) and lack of

envenomation/paralysis caused by *Ixodes holocyclus* [194]. Despite treatment, prognosis can be guarded with this form of tick paralysis. In a recent survey of 577 dogs affected by tick paralysis, younger dogs were more likely to survive, and respiratory and gait scores reflected disease severity and were good prognostic indicators, in that dogs with mild disease recovered more quickly, whereas those with severe disease that received an additional dose of tick antitoxin serum were significantly less likely to survive [195].
Sensitive biological assays of toxin/antitoxin potency have been developed to assist in research on characterization of salivary toxins of the Australian paralysis tick *Ixodes holocyclus* and on immunity to tick paralysis [196]. The aim of current research is to develop a recombinant veterinary vaccine based on the tick neurotoxin peptide sequence. A successful vaccine would provide cost-effective, long-term protective immunity against tick-induced paralysis [191].

Toad Toxicity
This condition occurs in animals that bite or mouth various species of toads that contain bufotoxins within their parotid glands. Toxic species include the Colorado River toad (*Bufo alvarius*) and the marine toad (*Bufo marinus*). Toxicity is common in dogs in Florida and in Australia, especially in Queensland, where there is a seasonal incidence, primarily from September/October through April [197]. In one report from Florida, most dogs were treated during the spring and summer [198]. Toads tend to breed during the warmer and wetter months and hibernate during the colder and dryer months. Terrier breeds are commonly affected associated with their inquisitive nature and their tendencies to pursue hopping toads [197]. Cats are infrequently reported. Clinical signs develop within minutes of mouthing the toad and include profuse salivation, head shaking, ataxia, vomiting, polypnea, hemorrhagic diarrhea, and seizures in severe cases. Some dogs are presented in status epilepticus. Other neurological signs may include stupor, nystagmus, extensor rigidity, and opisthotonus [198]. Common EKG findings with *Bufo Marinus* include sinus arrhythmia, tachycardia, and occasionally ventricular fibrillation [198,199]. Abnormal cardiac depolarization and arrhythmias have been experimentally shown using resibufogenin and bufalin from toad venom [200]. Bufalin, from the *Bufo marinus* toad, is structurally and functionally similar to digitalis glycosides [201]. Death may occur within 30 minutes. Treatment involves washing the buccal mucosa with a swab or hose to dilute the toxin, intravenous diazepam (e.g., 0.25 to 1 mg/kg, IV), intravenous atropine (e.g., 0.04 mg/kg) and, if required, intravenous pentobarbital (e.g., 2.5 to 7.5 mg/kg, IV). Propranolol (e.g., 1.5 to 5.0 mg/kg, IV, rapidly, followed by a repeat dose in 20 minutes, for dogs and cats) is recommended, especially if ventricular fibrillation develops [199]. Prognosis will depend on the potency of the toxin, quantity absorbed, and size of the patient. It is usually favorable when animals are treated promptly [198], but may be guarded once seizures are seen [197].

Toluene/Dichlorophen
Toluene/dichlorophen anthelmintics (effective against ascarids, hookworms, and some tapeworms of dogs and cats) may cause adverse effects in healthy cats and dogs following oral administration of less than 1.5 times the recommended product dose [202]. Clinical signs usually are observed within 6 hours of dosing and include ataxia, aberrant behavior, mydriasis, vomiting, depression, muscle tremor, and hypersalivation. In this report, the four most common products associated with toxicosis in cats were Daltrek Tri-Wormer, De-Vos Control III Worm Caps, Zema Pulvex Multi-Purpose Worm Caps, and Vermiplex. In dogs, commonly involved products were Happy Jack's Trivermicide Worm Capsule, Farnam Triple Wormer, Zema Pulvex Multi-Purpose Worm Caps, Anchor Canine Wormer, and Performer Brand Dog Wormer. In most cases, clinical signs disappear within a few hours to a day with general supportive care.

Tricyclic Antidepressants
Tricyclic antidepressants (TCAs), a class of psychotherapeutic medications, are widely prescribed for human patients, thereby increasing the potential for accidental oral ingestion by companion animals [203]. Animals ingesting TCA in an amount exceeding 15 mg/kg are in grave danger. TCAs block re-uptake of biogenic amines (e.g., epinephrine), have anticholinergic (atropine-like) effects, and quinidine-like action on the cardiovascular system. Clinical signs in animals include hyperexcitement and vomiting followed by ataxia, lethargy, and muscular tremors. Bradycardia and cardiac arrhythmias should be anticipated in the later stages of the TCA toxic syndrome [203]. In a review of over 450 cases reported to the Illinois Animal Poison Information Center between 1985 and 1989, more than 7% of affected animals eventually died [203]. Initial therapy includes intubation, oxygen administration, enterogastric lavage, and activated charcoal via a stomach tube. Animals in a hyperactive state should receive diazepam (0.5 mg/kg IV or IM, repeated as needed, every 10 minutes for three doses), followed by activated charcoal (2 gm/kg, every 3 - 4 hours, PO) and a suitable cathartic, such as sorbitol (0.5 gm/kg, PO) or sodium sulfate (Glauber’s salts) at 0.25 gm/kg, PO. Magnesium sulfate (Epsom salts) is not recommended because of the TCS-induced decrease in GI motility. Intravenous sodium bicarbonate at 2 - 3 mEq/kg, over 15 - 30 minutes, should be given if acidosis, hypotension, tachycardia, or other cardiac abnormalities are noted. Blood pH should be maintained above 7.5.

Vincristine
Vincristine is a vinca alkaloid widely utilized in cancer chemotherapy. Its major clinical limitation is due to a drug induced sensory-motor neuropathy, the pathogenesis of which is poorly understood. In cats with experimental vincristine neuropathy, major pathological lesions were focal axonal swellings (giant axon formations) due to malaligned accumulations of neurofilaments and secondary paranodal demyelination [204]. These were primarily confined to the proximal portions of the peripheral nerves. Wallerian degeneration involved a small number of nerve fibers in the distal regions. Muscle spindles were affected and motor nerve conduction velocities were reduced by 30% [205]. We reported a vincristine-induced peripheral neuropathy 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 [206]. 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. Electromyographic testing revealed fibrillation potentials and positive sharp waves consistent with denervation. Sciatic motor nerve conduction velocity was decreased. Evoked muscle potentials were polyphasic and had reduced amplitude and prolonged duration. Severe nerve fiber degeneration, nerve fiber loss, and 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 people, vincristine-induced neurotoxicity is aggravated by itraconazole [207,208].

Zolpidem
Zolpidem is a nonbenzodiazepine hypnotic and sedative of the imidazopyridine class used for treating short-term insomnia in humans. The drug increases the frequency of chloride channel opening and inhibits neuronal excitation. A retrospective review of zolpidem ingestion in 33 dogs that were reported to the ASPCA Animal Poison Control Center between January 1998 and July 2000 revealed that ingested dosages ranged from 0.24 to 21 mg/kg [211]. Clinical signs reported included ataxia, hyperactivity, vomiting, lethargy, panting, disorientation, nonspecific behavior disorder, hypersalivation, tachycardia, tremors, apprehension, vocalization, weakness, and hyperesthesia. In most instances, clinical signs developed within 1 hour and typically resolved within 12 hours. Treatment includes induction of emesis within the first 1 to 2 hours (or gastric lavage), use of activated charcoal in conjunction with a catharctic, such as sorbitol, and fluid administration. Note that supportive treatment (e.g., phenothiazines or barbiturates) may be used to treat signs of stimulation and hyperactivity; however, the use of diazepam or other benzodiazepines should be avoided.

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