Endogenous Metabolic Disorders (18-Mar-2002)

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Endogenous metabolic disorders in small animals that impact the central nervous system (CNS) encompass myriad conditions, including electrolyte abnormalities, endocrine disorders, and organ failure. These conditions have sometimes been referred to as metabolic encephalopathies because of functional CNS perturbations arising from altered energy metabolism, destabilization of neural membranes, hypoxia, endogenous toxin formation, or osmolality shifts.

An outline of this chapter is as follows:

Diabetes Mellitus
Hepatic Encephalopathy
Hypernatremia
Hypocalcemia
Hypoglycemia
Hyponatremia
    Central Pontine Myelinolysis
Hypothyroidism
    Myxedema Coma
Uremic Encephalopathy
Miscellaneous Metabolic Disorders
    Acidosis
    Alkalosis
    Hyperthyroidism
    Hypophosphatemia
    Hypercalcemia
    Potassium Disorders

Diabetes Mellitus
This chronic disorder is associated with impaired utilization of carbohydrates and enhanced lipid and protein use. Neurological signs attributable to the CNS have been associated with two hyperglycemic syndromes: diabetic ketoacidosis (DKA) and nonketotic hyperosmolar hyperglycemia (NKHH). Hyperglycemia results in hyperosmolality and this may lead to cerebral dehydration, with a pathogenesis similar to that of hypernatremia.
Insulin deficiency (either relative or absolute) is the problem in patients with DKA and is related to the hyperglycemia associated with increased gluconeogenesis, enhanced glycogenolysis, and reduced glucose clearance [1], associated with increased levels of diabetogeneic hormones (epinephrine, glucagon, cortisol, and growth hormone) which promote insulin resistance [2-4]. Furthermore, there is increased fatty acid mobilization and fatty acid oxidation (from increased glucagon:insulin ratio), and as a result, elevated serum ketone bodies (e.g., acetoacetic acid and beta-hydroxybutyric acid) from lipolysis. Glycosuria ensues once renal threshold is exceeded, e.g., > 180 - 220 mg/dl in dogs and > 200 - 320 mg/dl in cats [3], leading to osmotic diuresis, polyuria and compensatory polydipsia. Increasing serum levels of ketones will also eventually exceed renal tubular threshold and spill into the urine exacerbating the already existing osmotic diuresis and water loss from hyperglycemia, and potentiate loss of sodium, potassium and magnesium in urine. In summary, the consequences of DKA are severe metabolic acidosis, hyperosmolality, osmotic diuresis, dehydration, and severe electrolytic derangement [2,5,6]. In patients with NKHH, sufficient insulin is produced to prevent lipolysis and ketone body formation, although insufficient to prevent hyperglycemia. This syndrome is seen when blood glucose > 600 mg/dl (sometimes > 1000 mg/dl) and with hyperosmolality > 330 - 350 mOsm/kg [4,5]. Compromised renal function (from primary renal disease or from the hypovolemia) with decreased glomerular filtration and decreased excretion of glucose may be associated with the extreme

hyperglycemia and hyperosmolality [3,5,7]. Neurological signs for both DKA and NKHH are essentially the same as those seen in patients with hypernatremia. In addition, DKA animals are dehydrated and may have a fruity acetone breath odor from the ketosis. In people, seizures are commonly observed in patients with NKHH [8-10], possibly related to excessive activation of glutamate receptors ("excitotoxicity"), including N-methyl-D-aspartate receptor-operated channels [11]. Diagnosis is based on biochemistry panels, serum osmolality, anion gap determination, and blood gas studies [5,12]. Demonstration of both hyperglycemia and glucosuria is an important diagnostic finding, and most dogs and cats with DKA have evidence of hyponatremia [3]. Treatment consists of administration of the following [3,5]:

a. 9% saline solution at 60 - 100 mL/kg/24h. In addition, provide 80% of fluid deficits (% dehydration x kg body weight = fluid deficit in liters) and also adjust for any ongoing fluid losses (e.g., vomiting and diarrhea) to correct cellular dehydration and hypovolemia. For initial fluid replacement, isotonic saline administration at a moderate rate is recommended over hypotonic fluids given rapidly since a rapid decrease in serum osmolality may lead to cerebral edema (especially in patients in whom the serum concentration of sodium fails to rise as that of glucose declines) [4,13]. In one human study, failure of the serum sodium concentration to rise as glucose concentration declined was considered to be a marker for excessive administration of free water [14]. In this report, repair fluid containing an average of 125 mEq/L sodium early in therapy usually prevented a downward trend in the concentration of sodium in serum thereby avoiding a rapid decline in effective serum osmolality [14]. Rehydration over 48 hours was shown to be a safe strategy in people with moderate or severe DKA [15]. After 12 to 24 hours, fluids can be changed to 0.45% saline if hypernatremia or hyperchloremia are present [5].

b. Potassium or phosphate supplementation if required (if unknown, add 20 mEq KCl and 20 mEq KPO_4 to each liter of fluids). During therapy for DKA, serum potassium levels decline in most animals due to rehydration (dilution effect), correction of acidosis (hydrogen moves out of cells in exchange for potassium), insulin-induced cellular uptake of potassium, and continuing urinary losses [16]. Hypokalemia may lead to muscle weakness, cardiac arrhythmias and respiratory failure. Hypophosphatemia occasionally occurs in animals with DKA and has been reported in association with osmotic diuresis and urinary losses. It can lead to muscle weakness, hemolysis, rhabdomyolysis, seizures, cardiac dysfunction and respiratory failure [17]. When serum phosphate levels < 1.0 mg/dl, potassium phosphate at 0.01 - 0.03 mmol phosphate/kg/h should be administered for 6 hours [5,18].

c. Bicarbonate supplementation if serum bicarbonate < 12 mEq/L or total venous CO_2 < 12. Amount of bicarbonate (mEq) = body wt (kg) x 0.4 x (12 - patient's serum bicarbonate level). Note that improved renal perfusion will facilitate urinary loss of ketoacids while insulin treatment will decrease the production of ketoacids.

d. Insulin therapy, e.g., regular crystalline insulin at 0.2 U/kg, IM followed by 0.1 U/kg IM hourly until blood glucose level < 250mg/dL, then use SC regular insulin at 0.1 - 0.4 U/kg every 6 - 8 hours. Note that resolution of ketoacidosis requires insulin therapy.

e. Dextrose supplementation using 5% dextrose (e.g., add 100 ml of 50% dextrose to each liter of fluids) once blood glucose level falls below 250 mg/dl to avoid hypoglycemia.

Note - For more detailed information on therapeutic management of animals with severe diabetic ketoacidosis, readers are referred to the recent publication by Nelson [3]. The overall aim should be to return to normal all abnormal parameters slowly over 36 to 48 hours. Too-rapid correction might lead to cerebral edema [2]. Since DKA usually coexists in dogs and cats with other conditions (e.g., pancreatitis, congestive heart failure, infection, gastroenteritis, renal failure, or insulin antagonistic disorders such as hyperadrenocorticism), treatment should also be directed at these disorders [3,16,18].
For animals with NKHH, primary treatment is aimed at rehydration (e.g., using 0.9% saline at 20 - 30 ml/kg IV as an initial bolus, and then 0.45% saline at 60 ml/kg/day), followed by insulin therapy (see above), and correcting any underlying illnesses including cardiac abnormalities, renal disease, or hyperthyroidism [4]. It is recommended that approximately one-half of the estimated body fluid deficits be corrected over the first 24 hours and the remainder over the ensuing 24 hours [5]. It has been stated that insulin should not be initiated until the patient has received hypotonic fluids for approximately 6 hours to avoid inducing cerebral edema (from rapid decrease in serum glucose) and hypokalemia (insulin induces movement of potassium from the extracellular space to the intracellular space) [5]. Finally, seizures associated with hyperglycemia (usually in NKHH patients) are resistant to anticonvulsant treatment and respond best to insulin and rehydration [1].
Note that besides the two hyperglycemic syndromes, a third diabetic emergency may occur in dogs and cats, namely insulin overdose, resulting in hypoglycemia. The clinical and neurological signs may be similar in all three instances [4]. In people, diabetes also increases the risk of stroke associated with large, medium, and small vessel atheroma formation, as well as arteriolar and capillary microangiopathy [1].

Hepatic Encephalopathy
Hepatic encephalopathy (HE) in dogs and cats is a complex metabolic disturbance of the CNS that may result from

diminished hepatic function, urea cycle enzyme deficiency, or shunting of portal blood around the liver. As a result, the metabolic and detoxification functions of the liver are impaired and/or bypassed and the unaltered constituents of the portal blood go directly into the systemic circulation. Many "toxic" substances derived from intestinal degradation, including ammonia, amino acids (especially the aromatic amino acids phenylalanine, tyrosine, and tryptophan), short-chain fatty acids, mercaptan and various biogenic amines, indoles and skatoles, have been incriminated in causing HE [19,20]. Ammonia, metabolized by astrocytes to glutamine (catalyzed by an astroglia-specific enzyme, glutamine synthetase [21]), has been one of the most studied toxins and is considered to play an integral role in the pathogenesis of HE [1]. Increased intracellular osmolality from too-rapid glutamine accumulation may result in cerebral edema, which also may play a role in development of cerebral hyperemia and increased intracranial pressure in experimental studies of fulminant hepatic failure [22]. Low-grade cerebral edema has been reported in humans with hepatic cirrhosis [23]. Glutamine, short-chain fatty acids, aromatic amino acids, and mercaptans are sodium/potassium ATPase inhibitors [1,24]. Other theories pertaining to the pathogenesis of HE include perturbed monoamine neurotransmission as a result of altered plasma amino acid metabolism; an imbalance between excitatory amino acid neurotransmission mediated by glutamate, and inhibitory amino acid neurotransmission mediated by gamma -aminobutyric acid; and increased cerebral concentration of an endogenous benzodiazepine-like substance [25-27]. It has been stated that there is no evidence that increased levels of "false" neurotransmitters (e.g., octopamine and phenylethanolamine), potentially leading to reduced neuronal excitation and increased neural inhibition, are responsible for the encephalopathy [1].

HE can occur with the conditions listed below.

1. Acute liver failure. Acute hepatic failure may occur in animals of any age. Causes may include toxic injury, metabolic disturbance (e.g., lipidosis in cats), trauma, heatstroke, vascular compromise (e.g., vena cava syndrome or liver lobe infarction), and infectious disease (e.g., infectious canis hepatitis) [28]. The onset of signs is rapid with a fulminant course. Non-specific signs may include depression, anorexia and vomiting.

2. Chronic liver insufficiency (e.g., chronic hepatitis, cirrhosis, hepatobiliary neoplasia, etc.) and acquired portal systemic shunting. Dogs with encephalopathy associated with chronic liver disease are typically middle-aged or older. Weight loss, depression, anorexia, gastrointestinal signs, polydipsia and polyuria may be observed. In these cases, acquired shunts may develop as a compensatory response to portal hypertension and appear as multiple tortuous vessels that usually communicate with the caudal vena cava. Rarely, multiple acquired extrahepatic shunts may develop as a consequence of portal hypertension associated with intrahepatic arterioportal fistulae in young dogs [29]. More recently, a syndrome resembling idiopathic noncirrhotic portal hypertension was reported in 4 young Doberman Pinschers [30]. This hepatopathy, in which there is no intrahepatic arteriovenous fistulae, portal vein atresia or intrahepatic fibrosis, results in portal hypertension, development of portosystemic collateral vessels and HE. Abdominal ultrasonography disclosed a small liver and portosystemic collateral vessels. Radiographic imaging studies confirmed hepatofugal portal circulation. Histopathological features included increased cross-sectional views of hepatic arterioles, hepatic lobular atrophy, mild increase in connective tissue around some large portal triads, with absence of inflammation, disturbed lobular architecture, bile duct proliferation, or intrahepatic cholestasis.

3. Congenital portosystemic anomalies (usually single shunts that may be intrahepatic or extrahepatic and usually not associated with portal hypertension) that shunt portal blood around the liver, allowing mesenteric blood to directly enter the central venous system, most frequently the caudal vena cava or azygous vein [31,32]. The congenital extrahepatic shunts usually involve the portal vein or one of its tributaries, such as the left gastric vein, splenic vein, cranial or caudal mesenteric veins, or gastroduodenal vein [31]. It has been reported that intrahepatic portosystemic venous anomalies are diagnosed relatively infrequently in dogs [33]. These shunts occur when the fetal ductus venosus remains patent or when another portal-to-hepatic-vein communication exists. Shunts tend to be extrahepatic in small breeds, while a single intrahepatic shunt is most common in medium-to-large breeds [34,35]. Congenital portosystemic anomalies usually occur in young dogs less than 1 year of age [36]. There are reports of breed predilection for congenital portosystemic anomalies, including Miniature Schnauzers, Yorkshire Terriers, Cairn Terriers, Australian Cattledogs, Old English Sheepdogs, and Maltese Terriers [19,32,34,37,38]. Affected animals are often stunted and in poor nutritional condition. Clinical signs are intermittent, varying from one day to the next, and are frequently seen a few hours after eating a high protein meal. Signs may include anorexia, depression, weight loss, polydipsia/polyuria, jaundice, and ascites [32]. There may be intolerance to certain drugs, such as tranquilizers or anesthetics. Neurological signs (see below) reportedly occur in approximately 95% of cases with shunts [39]. In animals with congenital shunts the liver is grossly small and often mottled in appearance, while microscopic findings include small hepatic acini with few portal venous branches and arteriolar hyperplasia [32,40]. Marked irregular thickening of the glomerular capillary wall has been observed in dogs with congenital shunts [41]. It has been reported that almost all Irish Wolfhound pups without signs of HE have moderate hyperammonemia and that

approximately 2 - 3% of these dogs have inherited portosystemic shunts associated with high venous ammonia concentrations (>125 µg/dl) and signs of HE [42].

4. Hepatic urea cycle enzyme deficiency. Affected dogs are usually less than 1 year of age and the HE is associated with hyperammonemia without any evidence of hepatocellular destruction or portosystemic shunting [19].

Irrespective of the cause, the neurological signs of HE are similar and are especially related to the prosencephalon (forebrain). Moderately severe cases can be characterized by alterations in behavior or personality, including staring into space, inappropriate vocalizing, aggression, and agitation. More severe changes can induce ataxia, circling, aimless wandering, and head pressing. Advanced neurological alterations can cause depression, blindness, myoclonus, stupor, coma, or seizures.

There are no gross CNS changes in animals with HE. Histopathological findings typically consist of diffuse polymicrocavitation of myelin (status spongiosus) at various levels of the brain, especially in the cerebral cortex (usually involving the peripheral fibers of the corona radiata at the junction of the gray matter), but cerebellum (e.g., cerebellar medulla and peduncles) and brainstem may also be involved, including the internal capsule, thalamus, and hypothalamus, pons, and medulla oblongata). The distribution tends to be bilaterally symmetrical and myelinated bundles of fibers interspersed with gray matter are typically prominent [40]. In the spinal cord, vacuolation occurs in the fasciculus proprius along gray and white matter borders [43]. Ischemic neuronal degeneration of the cerebral cortex has also been reported [44]. The vacuolation is considered to be cytotoxic edema [40] and may be associated with the hyperammonemia since the vacuoles tends to regress when blood ammonia concentration returns to normal (see comments on ammonia and cerebral edema, above) [45]. Experimentally, the vacuoles appear to represent ballooning of myelin sheaths which have split at the intraperiod line [46]. Another morphological feature of HE is presence of Alzheimer type II astrocytes which are most numerous in the neocortex, basal nuclei, and hippocampus. These cells, thought to be derived from protoplasmic astrocytes and characterized by their large, vesicular nuclei, may be in close association with neurons or isolated in the neuropil [40]. Glial fibrillary acidic protein (GFAP) staining is weak or negative, but S-100 expression is retained suggesting that HE results in selective loss of GFAP filaments [40,47]. Polyneuropathy has sometimes been reported in humans with HE [48], some cases of which are associated with alcoholism [49]. Note that polyneuropathies (in people) can develop secondary to liver disease-related vitamin E deficiency [50].

Acute hepatic failure is characterized by marked elevations in alanine aminotransferase (ALT) and total bilirubin, with variable levels of serum alkaline phosphatase (SAP). Chronic liver disease or cirrhosis is typified by variable levels of ALT and total bilirubin, with marked elevations in SAP. Liver enzyme levels can be normal or mildly elevated in animals with congenital shunts. Hypoproteinemia, hypoalbuminemia, hypoglycemia, hypocholesterolemia, and prolonged clotting times can be found in animals with impaired hepatic function, regardless of etiology [32]. Sulfobromophthalein (BSP) retention is often increased, blood urea nitrogen may be abnormally low (due to the inability of the liver to convert ammonia to urea), blood ammonia levels are often increased (approximately 90% of HE patients have an elevated fasting blood ammonia level, e.g. > 95 µg/dl [19]), which may result in the presence of ammonium biurate crystals in the urine sediment from 50 to 100% of affected dogs [34,51]. Fasting (e.g., 12-hour) and post-prandial (e.g., 2-hour) total serum bile acid (TSBA) values are sensitive indicators of hepatic dysfunction, including occult liver disease such as portosystemic venous anomalies or hepatic cirrhosis [52-54]. Results of one study in dogs with suspected liver disease showed that fasting TSBA levels > 20 µm/L and post-prandial TSBA values > 25 µm/L were 100% specific for liver disease [55]. While TSBA levels do not indicate the severity of the hepatic disease or suggest a prognosis [53], comparison of fasting and post-prandial TSBAs may help to discriminate between some hepatobiliary diseases (e.g., animals with significant extrahepatic or intrahepatic shunting often have normal or mildly elevated fasting TSBAs) [56]. Another diagnostic aid regarded as being equal in sensitivity to postprandial SBA in dogs with shunts is the ammonia tolerance test [52]. Increased free cortisol levels have been reported in dogs with portosystemic shunts and HE [57]. In order to confirm the type of liver pathology present, hepatic biopsy is necessary. Clinicopathological features reported in young dogs with a syndrome resembling idiopathic noncirrhotic portal hypertension included erythrocyte microcytosis, normal to mildly increased liver enzyme activities, increased concentrations of TSBAs, reduced plasma indocyanine green clearance, and normal total bilirubin concentration [30]. Electroencephalography in dogs with HE reveals a predominance of generalized slow wave activity with increased amplitude [19]. Results of a CSF study from dogs with congenital shunts showed significantly increased levels of glutamate (e.g., 2 to 3-fold increase), glutamine (6-fold increase) and aromatic amino acids (phenylalanine, tyrosine and tryptophan) compared to CSF of control dogs, while concentrations of GABA and branched chain amino acids (valine, leucine, isoleucine) were within normal limits [58]. In humans, ammonia metabolites alpha-ketoglutarate and glutamine levels in CSF are elevated and glutamine may be one parameter that is related to the degree of HE [59-61].
Diagnosis of HE may be facilitated by use of radiographic imaging techniques, such as positive contrast portography

(considered to be the procedure of choice), computed tomography [62], and transcolonic portal scintigraphy, to demonstrate presence of a small liver and/or anomalous portal vein(s) and large kidneys in dogs with congenital shunts [32,63,64]. Diagnostic gray-scale ultrasonography is another useful technique [65,66]. Experienced surgeons may elect to perform exploratory abdominal surgery. In human medicine, proton magnetic resonance spectroscopy has been used to detect specific metabolic abnormalities (including cerebral increase in glutamine compounds) in the brain (especially in the globus pallidus) in patients with chronic HE [67]. In a recent MRI study in humans with acute HE, cortical lesions resembled those of hypoxic brain damage and were interpreted as acute toxic cortical laminar necrosis [68].

The principal objectives in the specific therapy of HE are listed below.

1. Dietary management. This is aimed at decreasing foods rich in protein, such as meat and egg proteins. Cottage cheese, at 2 g/kg body weight, daily, supplemented with easily digestible carbohydrates (e.g., rice or pasta), can be used to provide most of the caloric needs, along with good quality vitamin (including B vitamins and vitamin A, C, D, E, and K) supplements [28,34]. Note that vitamin K deficiency may develop during liver disease and vitamin K-dependent factors (II, VII, IX, X, and protein C) may be inactivated leading to coagulation abnormalities [56]. Prescription diets (e.g., u/d, k/d; Hill's Pet Products, Topeka, KS) are available to provide protein restricted rations at 1.75 to 2.5 g of protein /kg/day for dogs and 3 to 3.5 g/kg/day for cats [39].
2. Administration of lactulose, a non-absorbable synthetic disaccharide. A recommended dose in dogs is 10 to 40 ml of a 3.35 gm/5 ml solution by gastric tube, three times daily (alternatively, 2.5 to 15 ml for dogs or 1 to 3 ml for cats by mouth, every 8 hours). Dosage can be manipulated so as to produce passage of 2 to 3 soft stools each day. Lactulose results in a marked reduction in the pH of the colonic contents. This, in turn, significantly reduces the formation and absorption of ammonia and other nitrogenous toxins into the portal circulation. Also, the pH gradient causes movement of ammonia into the colon. Dietary supplementation with soluble fiber (psyllium) at 1 - 3 teaspoons daily may also be beneficial [32]. Sodium benzoate is reported to be a safe, cheaper, and effective alternative to lactulose in the treatment of acute portosystemic HE in humans [69].
3. Removal of toxic agents, e.g., bowel cleansing using enemas and/or cathartics; and intestinal antibiotics such as neomycin (20 mg/kg PO bid or tid) or metronidazole (8 mg/kg PO bid). The antibiotics kill colonic bacteria and thereby reduce levels of bacterial nitrogen content and the synthesis of urea.
4. Supportive therapy, e.g., maintaining fluid, electrolyte and acid-base balance).
5. Prevention/control of precipitating factors such as ammonia-producing processes such as GI bleeding (e.g., administration of H_2 receptor antagonists), constipation, and azotemia. In humans with portosystemic encephalopathy, other precipitants include infection, hypokalemia, hypoglycemia, hypoxia, and certain medications (e.g., sedatives and analgesics) [1].

Surgical closure of a portosystemic shunt helps to reverse hepatic atrophy, results in an increased hepatic mass, and corrects imbalances in carbohydrate, lipid, and protein metabolism that are not affected by medical management [70]. Today, total surgical ligation of a single portosystemic shunt is the preferred method of choice [32], although partial ligation/surgical attenuation may be indicated in many cases because of the risk of portal hypertension [71,72], which is characterized by abdominal distension and pain, bloody diarrhea, ileus, endotoxic shock, and peracute cardiovascular collapse [32]. For treatment of single, extrahepatic, portosystemic shunts, this complication may be overcome by gradual vascular occlusion (over 30 to 60 days) using a specialized ameroid constrictor device [73]. Alternatively, the use of transvenous coil embolization and cellophane banding for gradual occlusion of intrahepatic and extrahepatic shunts have been described [74,75]. Use of a portocaval venograft and ameroid ring for the occlusion of intrahepatic portocaval shunts in dogs also shows promising short-term results [76]. Note that following surgical correction of shunts, TSBA levels may not return to normal, even in clinically normal dogs [77]. Transcolonic portal scintigraphy, as well as ultrasound-guided injection of (99M)Tc-macroaggregates into a splenic vein, have been used to evaluate immediate and long-term changes in shunt blood flow after partial ligation of single extrahepatic portosystemic shunts [78,79]. If shunting persists, complete surgical ligation or ameroid constrictor placement is indicated [32].

The prognosis for animals with HE is guarded; however, successful long-term medical and surgical treatment have been reported in young and old dogs with portosystemic shunts [34,37,80,81]. In one study, the outcome of surgical management of intrahepatic portosystemic shunts in dogs was graded as excellent in 75% and grave in 25% [33]. In contrast, a recent study reported that animals with intrahepatic shunts had a significantly lower probability of survival than animals with extrahepatic portocaval or portoazygos shunts [72]. Prognosis appears to be better in dogs with complete surgical ligation [82,83]. Seizures, including status epilepticus, may occur in dogs, especially in older dogs (e.g., >18 months of age) following ligation of portosystemic shunts [84,85]. The recommended antiepileptic drug therapy for these dogs is potassium

bromide at 100 mg/kg PO qid for 24 hours, followed by maintenance therapy at 30 mg/kg daily [86]. Benzodiazepine therapy should be avoided. Another complication following ligation, usually with a grave prognosis, is portal vein thrombosis [87]. Acute pancreatitis, cardiac arrhythmias, hemorrhage, pulmonary edema, fever and positive blood cultures, as well as intraoperative hypothermia and hypoglycemia are other perioperative complications [33,88,89]. Coagulopathies (including disseminated intravascular coagulation, which can be related to release of thromboplastin and defective clearance of activated clotting factors by the liver) can also be a complication of hepatic necrosis [90].

Primary congenital portosystemic shunts are also an important cause of HE in cats [91,92] and the majority are single extrahepatic shunts [32,93]. Most cats are of mixed breeding, although Persians and Himalayans may be at risk. In contrast to dogs, affected cats present with intermittent clinical and neurological signs, e.g., stunted growth, seizures, ataxia, visual disturbance, tremors or twitching, pupillary dilatation, and behavioral changes, usually accompanied or preceded by ptyalism. Other signs including poor condition, diarrhea, ascites, and polydipsia/polyuria are uncommon [32]. Many affected cats have golden or copper-colored irises [36]. Clinical signs are often first noted in kittens around 10 to 12 weeks of age; however, signs may be first seen in well grown, adult cats. Note that portosystemic shunts can occur in cats without signs of HE but with a history of vague gastrointestinal signs [94]. In one survey of 52 cats with congenital shunts, common biochemical findings were hyperammonemia, increased BSP retention, and high fasting and postprandial TSBA concentrations [95]. In contrast to dogs, only a small percentage of cats have ammonium biurate crystalluria. There appears to be no advantage in performing an ammonium chloride tolerance test in cats that have unequivocal fasting hyperammonemia [96,97]. Surgery appears to be the treatment of choice, and prognosis may be favorable, providing recanalization of the shunt does not occur [96-98], although the outcome of surgical ligation of portosystemic shunts is cats is considered to be less favorable than in dogs [99,100]. In a recent report of per rectal portal scintigraphy in cats, it was concluded that this imaging technique was useful in the diagnosis of congenital portosystemic shunts, facilitated a quantitative assessment of the effects of surgical ligation of the shunting vessel, and might be a more accurate indicator of the degree of shunting after surgery than blood ammonia and TSBA levels [63].

Hypernatremia

Sodium (Na) is the major extracellular ion (osmole) in the body, including the CNS. Blood sodium levels reflect the ratio of Na to water in the extracellular fluid and account for most of the osmotically active particles in serum. Serum osmolality is defined as the concentration of a solution expressed in osmoles of solute particles per kilogram of solvent. Serum osmolality (normally 290 - 310 mOsm/L) can be calculated by the following formula [101]:

$$2 \times ([Na] + [K]) + glucose/18 + BUN/2.8$$

Hypernatremia occurs when serum Na levels exceed the normal range (>156 mEq/L in dogs and >161 mEq/L in cats) [101,102]. It is indicative of a relative increase in total body Na relative to total body water. Causes of hypernatremia include [101-107]:

a. Excess water loss, e.g., diabetes insipidus (central or nephrogenic), burns, fever, osmotic diuresis (acute/chronic renal failure, diabetes mellitus, diuretics, or IV solute administration such as mannitol, glucose or urea), osmotic diarrhea (lactulose therapy, malabsorption syndromes, infectious enteritides) and hot weather.
b. Excess salt intake, e.g., salt poisoning [107], administration of IV hypertonic solutions (NaCl), sodium bicarbonate, or saline emetics. Water loss and salt gain may occur with hyperaldosteronism and hyperadrenocorticism.
c. Insufficient water intake, e.g., lack of access, inability to drink (mechanical inability to prehend or swallow is a potentially serious complication of hypertrophic feline muscular dystrophy), or CNS disease resulting in primary adipsia (absence of thirst), or mental depression, or congenital adipsia. Essential hypernatremia due to failure of the hypothalamic osmoreceptors to respond appropriately to an increase in serum osmolality is rare in small animals [101]. Note that in normal animals stimulation of thirst and antidiuretic hormone (ADH) release by increasing serum osmolarity is the physiologic protection against development of hypernatremia and hyperosmolality. The ADH results in increased renal water reabsorption and increase in urine osmolality.

As with hyponatremia, hypernatremia may be further classified into hypovolemic, normovolemic, and hypervolemic forms [7]. Hypernatremia represents hyperosmolality, and as a consequence, an osmotic gradient is created that results in water movement out of cells into the extracellular fluid. Mild to moderate hypernatremia usually causes minimal clinical signs; however, marked hypernatremia may induce cerebral signs, such as depression, weakness, irritability, confusion, propulsive

circling, dementia, seizures, coma, and death in dogs and cats as a result of cellular dehydration of neurons [102,106]. Additionally, in people and in experimental animals, shrinkage of brain tissue may cause tearing of vessels, leading to intracranial hemorrhage (e.g., subarachnoid, subdural, intraparenchymal), infarction, venous thrombi, and cerebral edema [108-110]. Neurological signs might not occur until serum Na levels exceed 170 - 175 mEq/l (>350 mOsm/kg) [101,103]. The effects of rising serum osmolality on the nervous system was demonstrated in experimental studies (rabbits) in which predictable signs occurred: lip licking, restlessness, and heightened response to touch were noted with serum osmolality between 350 - 375 mOsm/kg; nystagmus, ataxia, and trunk/limb trembling appeared when osmolalities were in the 375 - 400 range; and finally, when osmolality exceeded 400 mOsm/kg, synchronous/asynchronous jerking movements, limb spasm, reduced responsiveness and death occurred [111]. The severity of the neurological signs is not only dependent on the degree of hyperosmolality but especially on its rate of increase, with signs being most severe in animals with rapidly developing hyperosmolality [102,105]. If the serum is chronically hyperosmolar, the brain compensates by increasing intracellular osmolality by movement of Na, potassium, chloride, and glucose into cells and by production of solutes called osmolytes or idiogenic osmoles (these include amino acids such as glutamine, glutamate, aspartate, creatine, and taurine, as well as myo-inositol and glycerophosphoryl-choline) which help normalize brain water content [112-115].

Pathological studies of brain lesions associated with hypernatremia are somewhat sparse. In one case involving hypernatremia and adipsia in a 4.5 month old female Dalmatian puppy with diabetes insipidus associated with inadequate ADH secretion, a nuclear scan of the cranial vault was normal, as were skull radiographs and CSF analysis [106]. Pathological studies revealed extensive dysplastic malformation involving midline structures of the frontal lobes and rostral diencephalon. These included absence/reduction of the corpus callosum at rostral/caudal levels, frontal lobe fusion in the median plane ventrally including caudate nuclei and prorean gyri (both of which blended caudally with the rostral hypothalamus), and absence of rostral part of the fornix, its columns, septum pellucidum, and septal nuclei. The pituitary gland was normal. The dysplasia was considered to involve the nuclei normally related to thirst regulation and ADH formation. In a 7 month old female Miniature Schnauzer with seizures, hypernatremia and adipsia associated with defective osmoreceptor function, suggesting this was a case of essential hypernatremia (the dog did not have diabetes insipidus), astrogliosis and neuronal degeneration were detected in thalamic and hypothalamic regions but were considered to be nonspecific lesions related to the seizures [116]. The authors of this report added an addendum that they had seen two additional young female Miniature Schnauzers with thirst deficiency and neurological signs associated with hypernatremia. In one of these dogs necropsied, no pathological changes were found in the thalamic/hypothalamic region. In a further canine case characterized by seizures and hypodipsic hypernatremia associated with defective osmoregulation of ADH, pathological changes including hydrocephalus, atrophy of the septum pellucidum, and neuroaxonal dystrophy of the cuneate nuclei were observed at necropsy [117]. Pressure atrophy of osmoreceptors in the hypothalamus secondary to hydrocephalus was postulated. The underlying cause of the pathological changes was not determined. In a report of a fatal hypernatremia from salt ingestion in a 8 year old male Airedale Terrier, CNS lesions included intracranial hemorrhage, thrombosis, and vascular stasis with engorgement of vessels, along with diffuse white matter vacuolation [107]. The authors considered that the cerebral edema might have followed prolonged seizural activity or was due to isotonic water intoxication (Plasma-Lyte was administered initially followed by 5% dextrose solution).

For treatment, a solution of 5% dextrose can be administered intravenously for acute hypernatremia [12]; however, oral administration of fluids is recommended for treating chronic hypernatremia since rapid correction may lead to cerebral edema (water intoxication), seizures, and death because of the accumulated intracellular idiogenic osmoles [105,118] (see also the pathophysiology associated with too-rapid correction of hyponatremia). A caveat is that excessive ingestion of water mixed with food may result in hyponatremia and neurological deterioration associated with cerebral edema [238]. The water deficit may be calculated [12,105] using the following formula:

$$\text{Water deficit (L)} = 0.6 \times \text{lean body weight (kg)} \times (\text{patient's Na/normal Na} - 1)$$

For animals with acute-onset symptomatic hypernatremia, a decline of serum Na around 1 mEq/L per hour can be safely performed; however the rate of decline in animals with chronic hypernatremia should not exceed 0.5 mEq/L per hour [101]. Of course, therapy for hypernatremia should also be directed at the underlying cause. Prognosis for acute hypernatremia is guarded. Adipsic animals may be maintained for several years by combining water with food [106,116,238]. Diuretics (e.g., furosemide) are recommended for animals with hypernatremia caused by excessive salt intake to prevent development of pulmonary edema during fluid therapy [103,107].

Hypernatremic Myopathy - Episodic weakness and signs of depression were reported in a 7 month old Domestic Shorthaired

cat with episodic hypernatremia (serum Na concentration ranging from 182 to 215 mEq/L; normal is 148 to 161 mEq/L) secondary to hypodipsia (failure to drink water) [119]. This rare condition was accompanied by hyperosmolality (ranging from 381 to 431 mOsm/L) and evidence of hypopituitarism (adrenocorticotrophic and growth hormone deficiencies, along with blunted thyroxine response to thyroid-stimulating hormone). The most prominent clinical sign was ventral flexion of the neck. No other neurological abnormalities were detected. Electromyographic testing revealed prolonged insertional activity, fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges. Nerve conduction velocities were normal. These abnormalities were more severe during episodes of hypernatremia. Serum creatine kinase activity was increased, while CSF analysis was normal. Examination of several muscle biopsies were normal. Contrast-enhanced computed tomographic studies of the brain demonstrated marked hydrocephalus, although no hypothalamic or pituitary lesions were detected. The episodic weakness might have been associated with muscle membrane alterations associated with displacement of intracellular potassium by high levels of extracellular sodium. Interestingly, the clinical signs, serum CK levels, electrodiagnostic data, and muscle biopsy findings were very similar to those seen in cats with hypokalemic myopathy. Forced water intake and dietary sodium restriction (using a low-salt feline diet) corrected the hypernatremia and signs of muscle dysfunction. After restoration of eunatremia, secretion of pituitary hormones became normal. It was suggested that hypothalamic dysfunction, possibly related to hydrocephalus, induced both hypodipsia and transient hypopituitarism [119].

Hypocalcemia
Ionized calcium is important for presynaptic neurotransmitter release from synaptic vesicles and stabilization of nerve and muscle membranes [1]. As a result of reduction in extracellular fluid concentration of calcium ions, and since divalent cations have a stabilizing effect on nerve and muscle membranes [120], the nervous system becomes increasingly excitable due to increased neuronal membrane permeability to sodium. Nerve fibers discharge spontaneously resulting in skeletal muscle contraction and tetany.

Total serum calcium is approximately 50% ionized, 40% protein bound (especially to albumin), and 10% complexed with anions such as citrate or phosphate [121]. Only ionized calcium is biologically active in bone formation, neuromuscular activity, blood coagulation, and cellular biochemical processes. The proportion of ionized calcium is affected by acid-base balance: ionized calcium levels are decreased by alkalosis and increased by acidosis. Total serum calcium and protein-bound calcium are decreased in hypoproteinemia, but ionized calcium levels remain normal. Accordingly, clinical signs of hypocalcemia do not occur in hypoalbuminemic conditions. The correction formula based on serum albumin concentration is [122]:

$$\text{Corrected total calcium level (mg/dl)} = \text{measured calcium (mg/dl)} - \text{albumin (g/dl)} + 3.5$$

(Note that assessment of ionized calcium levels are preferable to such formulas and today are readily available in commercial laboratories and are inexpensive).

Serum calcium levels usually represent a balance between bone formation and bone resorption which is regulated by parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol, and calcitonin. Except for acid-base imbalance and hypoalbuminemia, hypocalcemia usually indicates hormonal imbalance [121]. Dietary intake of calcium rarely affects serum levels directly.

Hypocalcemia may be seen with:

1. Hypoparathyroidism. In normal animals, an inverse linear relationship exists between parathyroid hormone (PTH) and serum calcium levels, e.g., a fall of serum calcium levels below 10.5 mg/dl stimulates PTH secretion, while calcium levels > 10.5 mg/dl result in suppression of PTH secretion [122]. With hypoparathyroidism, there is a decrease in serum calcium concentration and an increase in plasma phosphate levels (associated with loss of PTH actions on mobilizing calcium and phosphate from bone and retention of calcium and enhancing phosphate secretion by the kidneys). Primary hypoparathyroidism results from absolute or relative deficiency of parathormone and is infrequently seen in dogs and cats [123-131]. Animals have been classified as having 'idiopathic hypoparathyroidism' in the absence of trauma, malignant or surgical destruction, or other obvious damage to the neck or parathyroid glands [122,132,133]. The histological interpretation is lymphocytic parathyroiditis since the glands are microscopically atrophied with infiltration/replacement by lymphocytes, plasma cells, fibrous connective tissue and capillary proliferation. Commonly reported canine breeds include Poodles, Miniature Schnauzers, Retrievers, German Shepherds and Terriers [122].

2. Nutritional hyperparathyroidism (typically a disease of young growing animals) occurs secondary to dietary calcium deficiency, hypovitaminosis D, or dietary phosphate excess. This is an uncommon condition, especially in cats, due to the wide availability of commercial balanced diets, that usually results from animals fed foods such as beef heart or

liver that have low calcium-to-phosphorus ratios (note that all-meat diets are extremely low in calcium and have a low phosphorus concentration resulting in a low calcium:phosphorus ratio [134]). In an attempt to maintain mineral homeostasis, the low dietary calcium results in a transient decrease in serum calcium, inducing increased PTH release which leads to accelerated bone resorption and reduction in bone mass as calcium is removed from bone, increased renal calcium reabsorption and phosphorus excretion, increased renal synthesis of active vitamin D (calcitriol), and eventually the development of skeletal disorders including osteopenia (marked decrease in bone opacity), vertebral lordosis/kyphosis, bone pain, and pathologic fractures, including the vertebrae. Note that affected animals usually have normal serum levels of calcium and phosphorus [122], although in one recent report, 4 of 6 affected young cats were hypocalcemic [134]. In this study, serum PTH levels were markedly elevated, 1,25(OH)2-vitamin D3 (calcitriol) levels were mildly increased, while 25(OH)-vitamin D3 concentration was mildly decreased [134].

3. Renal disease (acute and chronic) - associated with decreased renal hydroxylation of vitamin D, soft-tissue calcification, reciprocal decrease in calcium serum levels secondary to hyperphosphatemia, and skeletal resistance to the effects of parathormone [121]. Note that uremic acidosis results in an increased proportion of ionized calcium in serum that may prevent signs of tetany in a hypocalcemic animal [122].

4. Acute pancreatitis in which ionized calcium may be bound to free fatty acids in necrotic fat [121,122,135]. The hypocalcemia is usually mild and subclinical in dogs with pancreatitis and any co-existing acidosis (frequently present in acute pancreatitis) will increase the levels of ionized calcium [122].

5. Post-parturient eclampsia (most common in small dogs; less common in cats and large dogs) [121,122,136].

6. Ethylene glycol toxicity in dogs and cats [122,137].

7. Intestinal malabsorption in dogs [121,122].

8. Commercial phosphate-containing enemas (resulting from acute, severe hyperphosphatemia following colonic absorption of the enema solution) [138].

9. Miscellaneous causes include trauma to the parathyroid glands, thyroid medullary carcinoma, various primary and metastatic bone tumors, and some forms of chemotherapy [122]. There has been a report of acute hypocalcemia in 2 dogs associated with infarction of parathyroid gland adenomas that were previously responsible for causing persistent hypercalcemia. [139]. In experimental studies in which gnotobiotic dogs were infected by canine distemper virus, some infected dogs had low serum calcium concentrations associated with ultrastructural evidence of parathyroid gland inactivity, degeneration, and viral inclusions [140]. Hypocalcemia has also been seen following administration of sodium bicarbonate for salicylate intoxication in a cat [141].

In dogs and cats, hypocalcemic tetany may occur when serum calcium levels are less than 6 mg/dl, or when ionized calcium levels are less than 2.5 mg/dl [121]. Clinical signs of hypocalcemia are characterized by abrupt onset of intermittent neurological or neuromuscular disturbances. Signs include nervousness, panting, pacing, muscle spasm and cramping, often seen in leg muscles, focal muscle twitching, trembling, stiff-stilted gait, intense facial rubbing with the paws or on the ground, ataxia, tonic-clonic spasms, episodic rigidity and falling, tetraparesis, and sometimes seizures and status epilepticus. In a recent report on nutritional secondary hyperparathyroidism, 4 of 6 cats were presented for evaluation and treatment of seizures (3 of these cats were hypocalcemic) [134]. Hypocalcemic animals are frequently febrile. Nictitating membranes may be raised in cats. Some animals manifest mental dullness and appear disoriented. Typical electrocardiographic findings include deep, wide T waves, prolonged Q-T intervals, and bradycardia [122]. Diagnosis of hypocalcemia is based on clinical signs and serum ionized calcium levels.

Hypocalcemic tetany requires prompt and immediate replacement of calcium, e.g., calcium gluconate as a 10% solution at 1 - 1.5 ml/kg or 5 - 15 mg/kg, IV, slowly over a 10 to 30 minute period [122]. Following control of the tetany, the same dose can be given subcutaneously (diluted in an equal volume of saline) every 6 to 8 hours while waiting for oral vitamin D and calcium supplementation to take effect (this usually requires a period of 24 to 96 hours). Once serum calcium levels are stable, the subcutaneous injections can be gradually tapered (serum calcium levels should be maintained above 8 mg/dl). Oral calcium supplements should be given to animals initially with primary hypoparathyroidism, e.g., calcium carbonate tablets at 0.5 - 1 g/day (cats) and 1 - 4 g/day (dogs) in divided doses, for several weeks or months, according to serum calcium levels. After this period calcium in balanced diets is usually sufficient. Vitamin D therapy, however, is usually permanent for animals with primary hypoparathyroidism. Vitamin D increases serum calcium by promoting intestinal absorption.

Suggested dosages are [122]:
- Vitamin D2 (ergocalciferol) at 4000 - 6000 U/kg/day initially for several weeks, followed by a maintenance dose of 1000 - 2000 U/kg once daily to once weekly, depending on monitored serum calcium levels; or
- Dihydrotachysterol at 0.02 - 0.03 mg/kg/day initially for several weeks, followed by a maintenance dose of 0.01 - 0.02 mg/kg q24 - 48h. This preparation raises serum calcium levels faster than vitamin D2 and its effects dissipate quicker once administration is stopped.

Treatment of animals with nutritional secondary hyperparathyroidism entails short- term parenteral calcium gluconate injections as clinically indicated, a balanced diet, and cage rest [122,134].

Prognosis will depend upon the underlying cause of the hypocalcemia. Correct dosage and owner compliance may result in excellent prognosis for animals with uncomplicated primary hypoparathyroidism; however, animals with spinal fractures have a guarded prognosis [134]. Note that uncontrolled motor activity as a result of seizures and/or excessive muscle jerking in animals with vertebral osteopenia will place these animals at high risk for spinal cord damage secondary to spinal fracture [134]. Iatrogenic hypoparathyroidism in cats resulting from neck surgery is often transient and lifelong treatment is not always necessary [122]. The prognosis for uncomplicated cases of nutritional secondary hyperparathyroidism is good [134].

Hypoglycemia

Glucose is the major nutritive carbohydrate substrate of the brain which requires about 100g glucose/day for normal functions [1,86]. This dependence on glucose, along with the brain's limited glycogen stores, results in rapid CNS dysfunction when hypoglycemia is present and permanent neurological sequela if the condition is prolonged [1]. Counterregulatory (i.e. glucose-raising) hormones (in particular, epinephrine and glucagon, but also norepinephrine, growth hormone, and cortisol) are released once blood glucose reach critical levels, e.g., < 40 mg/dl with induction of gluconeogenesis [142-144]. If the glucose levels decline slowly, the CNS is able to utilize alternative non-glucose organic substrates, such as ketoacids, intermediaries of glucose metabolism, and certain amino acids [1,145,146]. In people, neuronal damage consecutive to severe and prolonged hypoglycemia occurs mainly in the cerebral cortex, hippocampus and caudate-putamen as a result of active extracellular release of excitatory amino acids [147-149]. Neuropathological studies have been limited in dogs, although early signs of acute neuronal necrosis were reported exclusively in the superficial layers of the cerebral cortex, in addition to spongy changes in the dentate gyrus of the hippocampus in a 5 year old female Collie dog with hypoglycemia [150]. In another dog, there was extensive bilateral polioencephalomalacia observed in the cerebral cortex and basal nuclei [151]. Hypoglycemic Toy-breed puppies with hepatic steatosis (fatty liver) have ischemic neuronal changes in the cerebral neocortex [152]. The apparent selective vulnerability of certain neurons to hypoglycemia mimics that seen in hypoxic-ischemic conditions (e.g., cardiac arrest) and seizures [153]. Curiously, it has been reported that cats appear to have high resistance to brain injury caused by hypoglycemia [154]. Hypoglycemia plus hypoxia has been equated with tissue ischemia [40].

A common cause of hypoglycemia in dogs is a functional islet cell tumor (synonyms are hyperinsulinism, beta cell tumor, and insulinoma) [155]. These tumors occur in middle-aged to older dogs, of either gender, and are associated with increased insulin or proinsulin secretion by functional, neoplastic beta ells ("islet" cells) of the pancreas, independent of the negative feedback effects caused by hypoglycemia [156-160]. While a wide variety of breeds may be affected, Labrador Retriever, German Shepherds, Irish Setters, Standard Poodles, Collies, Boxers, and Fox Terriers may have a higher incidence than other breeds. Insulinomas occur less frequently in cats [161-164]. Clinical signs of hypoglycemia may reflect both neuroglycopenia (generalized seizures, weakness, ataxia, collapse, lethargy, transient blindness, and abnormal behavior, e.g., hysteria) and sympathoadrenal stimulation (muscle tremors, nervousness, restlessness, and hunger) [6]. The adrenergic signs precede neurobehavioral signs in humans and thus function as an early warning system [165]. Signs are often intermittent initially but become more frequent as the disease progresses. There is a strong correlation between onset of clinical signs of hypoglycemia and fasting, excitement, exercise, or eating [6,166]. Food consumption may stimulate excessive insulin secretion by the tumor resulting in postprandial hypoglycemia 2 to 6 hours later [6]. Polyneuropathy may be another complication of insulinoma in dogs [157,167-173]. Clinical signs range from paraparesis to tetraplegia, facial paresis/paralysis, hyporeflexia, hypotonia, and muscle atrophy, usually in conjunction with seizures, etc. Histopathological findings in nerves from affected dogs include severe axonal necrosis, nerve fiber loss, and variable demyelination. Muscle changes reflect neurogenic atrophy.

Results of CBC and urinalysis are usually normal. Hypoglycemia is the only consistent abnormality identified in serum biochemical profiles in animals with insulin-secreting tumors [6]. In one study involving 71 dogs with insulinomas, the mean initial blood glucose concentration was 46 mg/dl [6]. A serum insulin concentration > 20 µU/ml in a dog with a blood glucose level < 60 mg/dl is strong evidence for the diagnosis of an insulinoma. Some dogs may be euglycemic, necessitating hourly evaluations of blood glucose concentrations during a 4- to 12-hour fast. In one study, a fast of 8 hours was successful in demonstrating hypoglycemia in 26 of 28 trials in 25 dogs with insulinomas [174]. Some researchers no longer recommend use of insulin:glucose ratios because of false-negative and false-positive results [6,175,176]. Abdominal radiographic studies are usually normal. Since tumor metastasis to the lungs is extremely rare [6], thoracic radiographs are of limited help in evaluating metastatic disease. Abdominal ultrasonography may sometimes identify a pancreatic, peripancreatic, or hepatic mass [6,177]. Ultrasound may also detect biliary obstruction caused by the tumor [177]. Scintigraphy has been used to identify tumors and metastases (often to liver and mesenteric lymph node) in dogs [178,179]. In one report, somatostatin receptor scintigraphy using indium In-111 pentetreotide was performed [178].

Definitive diagnosis is obtained by surgical exploration, biopsy and histopathological examination of the tumor. Insulin-

secreting tumors can often be visualized or palpated by the surgeon [6]. As islet cell tumors in dogs and cats are frequently malignant with metastasis occurring early in the course of the disease, usually to regional lymphatics and lymph nodes (e.g., duodenal, mesenteric, hepatic and splenic nodes), liver, mesentery, and omentum [6], careful inspection of these sites is imperative. Surgical removal is the treatment of choice [6,180]. Immunohistochemical studies of 20 islet cell tumors in dogs revealed that 8 of the 20 tumors had positive immunoreactivity for insulin, 9 for glucagon, 14 for somatostatin, and one for gastrin [159]. Three tumors were pure insulinomas, but no pure somatostatinomas, glucagonomas, or gastrinomas were identified. Most tumors and metastases had mixed positive immunoreactivity; one neoplastic cell type predominated with lesser numbers of other cell types. The authors noted that the tumor staining pattern did not correlate consistently with function, as determined by blood glucose and serum insulin assays. Positive immunoreactivity has also been shown for insulin, somatostatin, and islet amyloid polypeptide in an islet cell tumor in a cat [162].

With inoperable cases (e.g., animals with extensive local tumor spread or metastatic disease, older animals, or animals that are anesthetic risks) medical therapy for chronic hypoglycemia evolves around frequent feedings of diets high in proteins, fats, and complex carbohydrates, in conjunction with prednisone at 0.25 - 0.5 mg/kg/day, PO, in two divided doses (dogs), and/or diazoxide, from 10 to 60 mg/kg, divided into 2 doses daily (not to exceed 60 mg/kg/day for dogs) [6,181,182]. Prednisone antagonizes the effects of insulin at the cellular level and promotes gluconeogenesis, while diazoxide inhibits the release of insulin, inhibits tissue use of glucose, enhances epinephrine-induced glycogenolysis, and increases the rate of mobilization of free fatty acids. Neither drug has any effect on tumor growth or metastasis. In a dog with an insulinoma-related peripheral polyneuropathy, frequent feeding and treatment with corticosteroids resulted in recovery from a non-ambulatory to an almost completely normal clinical state, despite the persistence of hypoglycemia and hyperinsulinism [183]. Frequent feedings and prednisone (5 mg, sid or bid, PO) have been used in successfully treating a cat with chronic hypoglycemia associated with insulin-secreting pancreatic islet cell carcinoma [163]. Variable results have been obtained with the long-acting somatostatin analogue, octreotide acetate (SMS 201 - 995; Sandostatin®) in dogs with insulinoma [184]. The long-term prognosis for animals with islet cell tumors is guarded to poor. In canine surgical cases, a mean post-operative survival time is reported to be 12 to 14 months [6,174]. In dogs treated only medically, the mean survival times drop to around 90 days, with few dogs surviving a year [6]. One surgically-treated cat survived 7 months [162], while a medically managed cat survived 18 months [163]. Postoperative complications can include acute pancreatitis and diabetes mellitus (which may develop as a result of chronic beta cell suppression by the excessive insulin levels). Sometimes the diabetes persists, necessitating a low-carbohydrate diet and/or insulin administration. Dogs that remain hypoglycemic after surgical removal are considered to have functional metastases [6].

Miscellaneous Causes of Hypoglycemia - Hypoglycemia has been reported in association with various non-islet cell tumors in dogs, including hepatocellular carcinoma, hepatoma, hemangiosarcoma, hepatic leiomyosarcoma, splenic hemangiosarcoma, salivary gland adenocarcinoma, metastatic oral melanoma, metastatic mammary carcinoma, primary pulmonary adenocarcinoma, and lymphatic leukemia [185-187]. In the dog, non-islet cell tumor hypoglycemia has been attributed to excess production of IGF-II (insulin-like growth factor II) circulating in a molecular form that can easily cross the capillary wall to exert its insulin-like effects on target tissues [188]. Removal of the tumor can result in return of normal blood glucose levels and remission of clinical signs [186].

Transient, juvenile hypoglycemia may occur in neonatal puppies and in toy and miniature-breed puppies less than 3 months of age as a result of cold, starvation, or gastrointestinal disease. It may also be seen with liver insufficiency (e.g., portal shunt). These disorders usually respond to a dietary carbohydrate source. Feeding puppies and the bitch with a protein-rich diet reportedly prevented the juvenile hypoglycemia seen in the Yorkshire Terrier breed and other toy breeds [189]. A 50% dextrose solution, at a dose of 0.5 to 1.0 ml/kg administered slowly over 10 minutes, IV, may be given for temporary control of seizures in animals with a hypoglycemic crisis [190]. The cause of transient hypoglycemia is unknown but it may be related to enzyme immaturity leading to depletion of primary energy sources, such as ketones or glucose [191]. Another cause of juvenile hypoglycemia is glycogen storage disease (see glycogenoses).

Hypoglycemia can result from excessive insulin administration to animals with diabetes mellitus [4], and cats may be at greater risk of insulin overdose than dogs, especially if the cats are obese and receiving insulin doses > 6 U/injection, administered once or twice daily [192]. Interestingly, in some affected diabetic dogs and cats, sympathoadrenal signs were either not seen or not recognized [192]. Treatment of such cases includes administration of a slow bolus of 50% dextrose at 0.5 g/kg, diluted 1:4, followed by a continuous infusion of 5% dextrose to maintain normal blood glucose levels, and the animal fed as soon as it is able to eat unassisted [4]. In adult dogs, hypoglycemia may also occur with severe hypoadrenocorticism, liver disease (e.g., impaired glucose production and glycogen storage), sepsis, glycogenoses, and as a complication of pregnancy accompanied by ketonuria [6,193]. Spontaneous hypoglycemia has been reported in a 9 year old cat with chronic renal failure [194]. Hypoglycemia in highly nervous hunting dogs is also well recognized. Attacks are characterized by apparent disorientation, weakness and generalized seizures. Recovery is rapid; however the affected animal's hunting ability is compromised. Frequent feedings with protein-rich foods and/or candy bars may prevent the attacks. The

cause has not been determined.

Hyponatremia

Hyponatremia is a metabolic state in which serum sodium (Na) levels are < 146 mEq/L in dogs and < 151 mEq/L in cats [102]. True hyponatremia is associated with serum hypoosmolality (< 290 mOsm/L) which suggests total body water in excess of Na [1,101]. Hyponatremia generally results from retention of ingested or administered water and usually indicates a defect in renal water excretion (e.g., inappropriate reabsorption of water in proportion to Na, or failure to reabsorb sodium by the kidney) and with urine specific gravity > 1.003 [102]. Electrolyte loss in excess of water may cause hyponatremia but this is uncommon. Hyponatremia with normal or increased serum osmolality is termed *pseudohyponatremia*. Hyperosmolar pseudohyponatremia may be associated with administration of hypertonic mannitol or parenteral hyperglycemia [195], urea nitrogen, or toxins that attract water into the intravascular space and dilute serum Na concentration. Differential diagnosis might include diabetes mellitus, ethylene glycol toxicity, and renal failure [101]. Isoosmolar pseudohyponatremia is often seen with hyperlipidemia and hyperproteinemia [102]. True hypoosmolar hyponatremia can be further subdivided, based on extracellular fluid volume, into [1,102]:

a. Hypervolemic (e.g., congestive heart failure, liver failure, nephrotic syndrome, hypoalbuminemic states
b. Normovolemic (e.g., syndrome of inappropriate antidiuretic hormone secretion, primary polydipsia, water intoxication, hypothyroidism, adrenal insufficiency [196], or renal failure;
c. Hypovolemic (e.g., renal or extrarenal disease, such as gastrointestinal, third space or cutaneous losses).

Neurological signs of hyponatremia are related to the rapidity of onset of the hyponatremia [12,105]. In acute hyponatremia, water flows down the its concentration gradient and enters brain cells producing cerebral edema and increased intracranial pressure [1]. Signs range from generalized weakness and mental depression to stupor, coma, seizures, and dementia [197]. Treatment is aimed at increasing serum Na levels and treating the underlying cause of the hyponatremia. Administration of hypertonic saline (e.g., 3 - 5%) should be given to animals in which serum Na is < 115 mEq/L. The Na deficit may be calculated using the following formula [101]:

Na deficit (mEq/L) = (140 - measured Na) x body weight (kg) x 0.3

The replacement fluid should be given slowly over 12 to 24 hours. Normal isotonic saline can be given to hypovolemic animals, while water restriction (i.e. limiting water intake to less than urine output) can be performed for animals with normovolemia or hypervolemia associated with excessive water intake or renal retention. In instances where severe neurological signs are seen associated with normal or excessive intravascular fluid, furosemide (at 2 - 4 mg/kg IV) can be used to promote renal water excretion [101].

Treatment of chronic cases of hyponatremia may present a different challenge. Paradoxically, the neurological condition of some patients with severe hyponatremia may actually deteriorate as their electrolytes get better. In hyponatremic people in whom correction of the hyponatremia occurs too rapidly (e.g., correction of hyponatremia by more than 12 mEq/L per day), a demyelinating condition termed central pontine myelinolysis is well recognized in which nerve cells and axons are spared but there is loss of oligodendrocytes [197,198]. This disorder is characterized by symmetrical myelinolytic foci in the pons and sometimes (in approximately 10% of cases) in extrapontine areas such as thalamus, subthalamic nucleus, striatum, internal capsule, amygdaloid nuclei, lateral geniculate body, white matter of cerebellum foliae, and deep layers of the cerebral cortex and adjacent white matter [199]. Results of an immunohistochemical study of central pontine myelinolysis in people indicated reduced immunoreactivity of myelin basic protein, myelin- associated glycoprotein, transferrin, and carbonic anhydrase C, and dystrophic astrocytic alterations based on labeling of glial fibrillary acidic protein and S-100 protein [200]. The exact pathogenesis of this myelinolysis still has not been determined but is certainly appears to be associated with the electrolyte derangement [201]. One hypothesis is that chronic hyponatremia (e.g., 2 - 3 days) may allow the brain to compensate for the imbalance in the osmotic gradient by active extrusion of intracellular electrolytes (sodium, potassium, and chloride) followed by organic osmolytes ("idiogenic osmoles"), including amino acids glutamine, glutamate and taurine, as well as myoinositol, phosphocreatine/creatine, and glycerophophorylcholine [114,202], and thereby reduce the brain edema. Although the adaptive solute loss from the brain helps protect against cerebral edema in severe hyponatremia, it also places the brain at risk to dehydration when serum sodium levels are returned to normal, since with rapid correction of chronic hyponatremia, compensatory influx of electrolytes is not matched by the slower moving organic osmolytes as serum becomes hypertonic relative to the CNS [203]. This sudden new osmotic gradient can lead to cellular dehydration, including possible

axonal shrinkage away from myelin sheaths and other events leading to subsequent demyelination [203]. Results of an experimental study indicated that following rapid correction of chronic hyponatremia, a topographic correlation occurred between demyelination lesions and delayed accumulation of organic osmolytes [204]. There have been a few reports of a similar pathophysiological event occurring in dogs following rapid correction of naturally occurring hyponatremia using 0.9% saline (the rate of correction in two dogs ranged from 16 to 22 mEq/L/day, while in the third dog, the rate was 17mEq/L in 9 hours) [205,206]. Interestingly, the cause of the hyponatremia was heavy whipworm (*Trichuris vulpis*) infestation in all cases. Neurological signs were seen several days after saline infusion and included ataxia, weakness, hypermetria, visual deficits, depressed menace responses with normal pupillary light reflexes, deficient postural reactions, trismus, exaggerated licking movements, episodic myoclonus, episodic whole-body spasms, obtundation and tetraparesis. In experimentally induced hyponatremia in dogs, several were stuporous or comatose [197]. Cerebrospinal fluid evaluation in two clinically-affected dogs tested was normal. T2-weighted magnetic resonance imaging in two clinically-affected dogs revealed symmetrically increased signal intensity in the area of the central thalamic nuclei, which in one dog progressed to a marked increase in signal intensity with ring-like effects [205]. In one dog necropsied, macroscopic tan-colored foci were seen in the central lateral thalamus bilaterally (the more prominent being approximately 4x5x3 mm in size). Microscopic lesions were found in the thalamus as well as in the rostral commissures. Lesions were characterized by myelin loss, apparent decrease in numbers of oligodendrocytes and increased numbers of astrocytes, and degenerating oligodendrocytes, some of which appeared to have pyknotic nuclei and vacuolated cytoplasm. Axons and nerve cell bodies appeared normal. Myelin splitting was observed intrastructurally, and cells considered to be oligodendrocytes had electron-lucent cytoplasm containing numerous, dilated membrane-bound vacuoles. The authors stated that the myelin loss appeared to be secondary to acute degeneration and probable loss of oligodendrocytes and other glia [205]. In experimental studies using dogs in which hyponatremia was rapidly corrected using 3% saline (at a correction rate of 15 mEq/L/day), symmetrical lesions primarily involving myelin and oligodendrocytes were seen in the thalamus and other areas including the central pons, lateral aspects of the thalamus and adjacent internal capsules, caudate nucleus, putamen, red nuclei, deep layers of cerebral cortex and subjacent white matter, and cerebellum [197]. The histological lesions were almost identical to the naturally occurring lesions, although some loss of axons and neurons were found at the center of the lesions. Also, Purkinje cells loss was noted in areas of severe white matter involvement, and fibrillary gliosis was present in chronic lesions [197]. The cause(s) of this regional vulnerability in animals and people remains undetermined. The prognosis of dogs with hyponatremia-related myelinolysis is guarded to favorable. While one affected dog was euthanized, two others slowly recovered completely without medication over the ensuing 4 - 7 weeks [205,206].

In summary, in order to avoid rapid normalization of severe, sustained hyponatremia, recommended rates of correction for animals with chronic hyponatremia are 10 - 12 mEq/L per day or approximately 0.5 mEq/L per hour [205,206].

Hypothyroidism

Hypothyroidism results from decreased production of thyroxine (T4) and triiodothyronine (T3) by the thyroid gland. Thyroid hormones have myriad functions, for example, they increase metabolic rate and oxygen consumption of most tissues, have positive inotropic and chronotropic cardiac effects, increase the number/affinity of beta-adrenergic receptors, enhance response to catecholamines, have catabolic effects on muscle and adipose tissue, stimulate erythropoiesis, regulate cholesterol synthesis/degradation, and are essential for normal development of nervous and skeletal systems [207]. Hypothryoidism 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 [208,209]. An association between hypothyroidism and acquired myasthenia gravis has been suggested in dogs [239]. A recent study of a closed colony of Beagles showed that dogs with hypothyroidism associated with lymphocytic thyroiditis had an increased risk for thyroid follicular epithelial neoplasia [210]. Hypothyroidism is more common in certain breeds, such as Doberman Pinscher and Golden Retrievers, especially in neutered animals [211]. Common clinical findings include obesity, seborrhea, alopecia, weakness, lethargy, bradycardia, and pyoderma [211]. Impaired ventricular function, along with decreased amplitude of the P and R waves, has been shown in echocardiographic and electrocardiographic studies [212]. Clinicopathologic abnormalities may include hypercholesterolemia, non-regenerative anemia, high serum alkaline phosphatase activity, and high serum creatine kinase activity [207,211].

Myxedema coma is an extremely rare form of decompensated hypothyroidism [213] in which patients may manifest bradycardia, hypothermia, and stupor/coma, along with hypoventilation, hypoxia, and hypotension [214-216]. The hypothermia in affected dogs tends to be characterized by absence of shivering [214,217]. The pathogenesis of the coma remains enigmatic [1], although it has been stated that the hypothyroidism is often profound and associated with an inciting event such as respiratory depressant drugs, infectious diseases (especially respiratory), heart failure, decreased blood volume (e.g., diuretics), or other stressors such as exposure to cold environment or surgery [1,217,218]. In affected dogs, the more classical signs of hypothyroidism (see above) will also be present [217].

Diagnosis of hypothyroidism is suggested by low resting free T4 levels and confirmed by performing a thyroid stimulating hormone (TSH) response test. A diagnosis is likely if both the pre- and post-TSH serum total T4 levels < 1.5 µg/dl [207]. Treatment involves administration of synthetic L-thyroxine at 0.02 mg/kg PO, bid for several weeks , according to results of therapeutic monitoring. Maintenance dosage is at 0.02 mg/kg PO daily, once clinical signs have resolved and total T4 levels are normalized [207]. Recommended dosage of L-thyroxine for animals in myxedema coma is 5 µg/kg every 12 hours, intravenously, along with fluid therapy, warming and ventilatory support [207]. Administration of glucocorticosteroids and broad-spectrum antibiotics has also been suggested [217]. If possible, the diagnosis of myxedema coma should be suspected based on the clinical presentation, and treatment should not be delayed while awaiting confirmatory laboratory data [217]. Prognosis is guarded for animals with myxedema coma. In a recent report involving a 7 year old male English Coonhound with suspected myxedema coma (the dog was comatose and cold to the touch, had bilateral rotary nystagmus, bradycardia and irregular cardiac rhythm, a non-detectable peripheral pulse, and showed bilaterally symmetrical alopecia of the base of the ears and caudal aspects of the thighs) [216], successful treatment involved a combination of active external and core rewarming techniques (e.g., recirculating water heating pads placed over and under the dog), intravenous (1.0 µg/kg, q 12h) and oral (4.0 µg/kg, q 12h) administration of L-thyroxine, supplemental oxygen, and administration of warmed fluids (Lactated Ringer's solution and 0.9% saline at 20 ml/kg).

Signs of CNS disease may also occur in dogs with hypothyroidism and atherosclerosis (see infarction), while secondary hypothyroidism can be caused by pituitary tumors (see neoplasia). Signs of peripheral nerve disease are commonly encountered in animals with hypothyroid neuropathy.

Uremic Encephalopathy
Uremic encephalopathy (UE) is an ill-defined condition that has been infrequently reported in young and old dogs with renal failure [40,219,220]. Clinical signs include depression or stupor, generalized seizures, muscle fasciculations (especially in facial muscles), myoclonic head bobbing movements, and weakness. In one retrospective report involving 29 dogs, dementia was more common in dogs with chronic renal disease, while seizures were more commonly associated with acute renal failure [220]. Laboratory studies reveal increased levels of blood urea nitrogen and creatinine. Renal lesions that have been reported include nephrosclerosis, nephrocalcinosis, peritubular fibrosis, tubular degeneration, pyelonephritis, and hydronephrosis [219]. In this report, parathyroid hyperplasia was present in one dog, while no gross or microscopic lesions were seen in the brain of 2 dogs euthanized [219]. The cause of uremic encephalopathy is presently unknown. Suggested mechanisms include depressed cerebral oxygen consumption, cerebral hypoxia, increased brain calcium levels, and increased blood levels of parathyroid hormone (PTH). In experimental uremia in dogs, increased brain calcium levels have been associated with an increase in the serum PTH levels, while administration of PTH to normal dogs produced EEG changes similar to those seen in uremic animals [221]. The EEG abnormalities, as well as the increased brain calcium , could be prevented by performing a parathyroidectomy before the induction of uremia. Serum calcitriol levels (1,25-dihydroxyvitamin D) are reduced in animals with renal failure [222]. The accumulation of toxic organic acids as a possible mechanism of UE is not supported by findings of normal acid-base balance in the CSF, blood, brain, and skeletal muscle of uremic dogs [223]. Water, osmolality, and electrolyte abnormalities do not appear to play a role in the development of UE in people [1]. Furthermore, clinical signs in dogs are probably not related to hypocalcemia and hypocalcemic tetany due to renal failure, since the metabolic acidosis of uremia tends to maintain the ionized calcium fraction at normal or increased levels [219] (see Hypocalcemia). A recent study suggests that several guanidine compounds (GCs) may play an important role in the etiology of uremic encephalopathy in people, including creatinine, guanidine, guanidinosuccinic acid, and methylguanidine [224]. The excitatory effects of uremic GCs on the central nervous system may be explained by the activation of N-methyl-D-aspartate (NMDA) receptors and concomitant inhibition of GABA-A receptors, and other depolarizing effects. Prognosis for animals in renal failure would appear to be guarded, although earlier research studies indicate that calcitriol, at 1.5 to 3.4 ng/kg/day PO, lowers serum levels of PTH, reverses neurological depression in dogs and cats with chronic uremia, and has a salutary effects on the dog's or cat's sense of well being, appetite, activity, strength, and lifespan [225,226]. Low doses of calcitriol are most effective when started early in uremia before the advanced stages of renal secondary hyperparathyroidism. Serum phosphate levels must be normalized before initiating calcitriol therapy because hyperphosphatemia enhances the tendency for calcitriol to promote renal mineralization and injury [222]. Other treatments should be aimed at the causes of the acute or chronic renal failure, such as correction of hypercalcemia, administration of antibiotics/antimycotics to eliminate bacterial/mycotic infections, removal of lesions (e.g., tumors, uroliths) causing obstructive uropathy, and correction of abnormal renal perfusion that has caused ischemic renal lesions [222]. Hemodialysis, peritoneal dialysis, and renal transplantation are also available treatment strategies. Note that rapid hemodialysis of uremic animals may induce a syndrome characterized by increased CSF pressure, grand mal seizures, and EEG abnormalities [223]. There is a fall in pH and bicarbonate concentration in CSF, and brain osmolality exceeds that of plasma, resulting in a net movement of water into the brain (cerebral edema). This syndrome has been called experimental dialysis disequilibrium syndrome.

Miscellaneous Metabolic Disorders

Acidosis - Acidosis secondary to respiratory or metabolic disorders may lead to cerebral vasodilation, increased cerebral blood flow, and sometimes increased intracranial pressure. Neurological signs of CSF acidosis including altered mentation, delirium, and coma [12], and usually result from increased blood levels of CO_2, which readily crosses the blood-brain-barrier leading to CO_2 narcosis, rather than from metabolic acidosis [1]. In patients with metabolic acidosis, CSF pH decreases slowly and usually does not reach blood pH levels [227]. Treatment should be directed at the underlying cause of the acidosis. A transient paradoxical CSF acidosis may follow administration of bicarbonate [16,227].

Alkalosis - Hyperventilation can lead to hypocapnea, respiratory alkalosis, cerebral vasoconstriction, decreased cerebral blood flow, reduced availability of oxygen, a reduction in ionized serum calcium levels, and hypophosphatemia [1,227]. Signs may include confusion and disorientation [12]. Metabolic alkalosis commonly accompanies hypokalemia as a result of translocation of hydrogen ions: as intracellular potassium moves out of cells down the concentration gradient, hydrogen ions (and sodium) shift into cells, causing extracellular alkalosis.

Hyperthyroidism - Hypothyroidism in cats may be associated with hyperactivity (hyperkinesis) characterized by pacing, circling, or restlessness, and variable personality changes including anxiety, confusion, and aggression [228-231]. Focal and generalized seizures may also be seen [230]. Neuromuscular signs attributable to hyperthyroidism include weakness, neck ventroflexion, decreased ability to jump, fatigue after physical activity, muscle tremors, nonspecific gait disturbances, and collapse [230]. Some or all of these neuromuscular signs might be related to hypokalemia [232](see hypokalemic myopathy). The pathophysiology of these manifestations is presently unknown, although perturbations in central and peripheral beta adrenergic tone may play a role [1].

Hypophosphatemia - Severe hypophosphatemia (i.e., serum inorganic phosphate concentration < 1 mg/dl) occurs infrequently in animals [17,233,234]. It is most often associated with diabetic ketoacidosis (DKA) (see above) in small animals, especially in cats [16]. Hypophosphatemia results from urinary loss of phosphate associated with the osmotic diuresis and replacement fluid therapy in animals with DKA and from insulin-induced movement of phosphate into cells (note that phosphate shifts between the intracellular and extracellular compartments in a similar manner as potassium)[5]. In addition, phosphate depletion may be caused by decreased intake from anorexia and vomiting, and translocation following alkali administration [16]. Other conditions associated with hypophosphatemia in small animals include hyperadrenocorticism, hyperparathyroidism (primary and pseudo), and hypothermia [233]. Respiratory alkalosis associated with hyperventilation will also cause phosphate to move into the intracellular space resulting in hypophosphatemia [233]. Phosphate is necessary for the production of 2,3 diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP); both are important for normal cellular metabolism. When serum inorganic phosphate levels fall below 1 mg/dl, high energy demanding body cells such as red blood cells, muscle cells (skeletal muscle and cardiac), and brain cells may be preferentially affected with subsequent development of hemolytic anemia, seizures, altered mentation, cardiomyopathy, and skeletal muscle weakness/rhabdomyolysis [16,233]. Note that severe hypophosphatemia may be clinically silent [3]. Treatment in most cases usually involves correction of the underlying cause of the hypophosphatemia; however, in severe cases (e.g. when serum inorganic phosphate levels < 1 mg/dl), parenteral phosphate therapy (e.g., sodium or potassium phosphate solutions) is recommended at a dosage of 0.01 to 0.03 mmol phosphate/kg/h for six hours, before rechecking serum inorganic phosphate levels [5]. A caveat of phosphate therapy is potential risk of deposition of insoluble calcium phosphate into soft tissues and hypocalcemia [5,16,234].

Hypercalcemia - Hypercalcemia occurs when serum calcium (from bone resorption or from gastrointestinal absorption) exceeds calciuresis [1]. Physiological hypercalcemia refers to ionized calcium levels increased above their normal range (e.g., > 5mg/dL). Myriad clinical signs associated with hypercalcemia include heart failure, unexplained shock, gastrointestinal disturbances (e.g., vomiting, constipation), renal failure, abdominal pain, tachypnea, restlessness, weakness, hyporelexia , listlessness, depression, obtundation, and coma [227,235]. Causes of hypercalcemia include primary hyperparathyroidism, hypercalcemia of malignancy, neoplastic bony metastases, vitamin D toxicity, hypoadrenocorticism, and renal failure (acute or chronic) [236]. Paraneoplastic hypercalcemia has been seen with a variety of tumors including lymphosarcoma, lymphocytic leukemia, myeloproliferative diseases, and myeloma, as well as solid tumors with metastasis to bone (e.g., nasal, pancreatic, pulmonary carcinomas) and without bony metastases (anal sac apocrine gland adenocarcinoma, squamous cell carcinoma, thyroid adenocarcinoma, pulmonary carcinoma, pancreatic adenocarcinoma, and fibrosarcoma [236]. Treatment should be aimed at the underlying cause of the hypercalcemia. Calciuresis is promoted with intravenous fluid therapy (e.g., using 0.9% saline at 10 ml/kg bolus over 15 minutes) and furosemide (1 mg/kg/hour) [227,235,236]. Lowering serum ionized calcium using sodium bicarbonate or sodium phosphate should be avoided due to calcium precipitation into soft tissue and potentially compromising major organs [235].

Potassium Disorders - Hypokalemia and hyperkalemia in animals and people are usually not associated with metabolic encephalopathies [1,12]. These disorders are more typically associated with neuromuscular disorders (see hyperkalemic myopathy and hypokalemic myopathy). The major complication of hyperkalemic (usually with serum levels > 7 mEq/L) is cardiac toxicity with irregularities in the EKG, arrhythmias, and/or cardiac arrest [237].

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