Several nutritional disorders involving selective deficiency or excess of one or more essential dietary ingredients may have neurological implications in dogs and cats. In most instances, these essential dietary ingredients involve vitamins. Complications may arise in precise diagnosis in some cases due to possible multiple deficiencies co-existing in patients in association with conditions such as malnutrition and malabsorption disorders.

The following nutritional disorders involving the CNS will be discussed:

- Cobalamin Deficiency
- Hypervitaminosis A
- Nutritional Secondary Hyperparathyroidism
- Thiamine Deficiency
- Vitamin E Deficiency

**Cobalamin Deficiency**

Cobalamin (vitamin B12) is an essential cofactor for two enzyme systems (a) folate-dependent methionine synthetase activity, which is required for nucleic acid synthesis and for normal development, growth, and hematopoiesis. This cytosolic enzyme catalyzes the conversion of homocysteine and methyltetrahydrofolate to produce methionine and tetrahydrofolate; methionine is further metabolized to S-adenosylmethionine, a substrate necessary for methylation of myelin sheath proteins and phospholipids. (b) Methylmalonyl CoA mutase, which uses adenosylcobalamin for the degradation of propionate through methylmalonyl CoA to succinate in mitochondria [1,2]. Selective cobalamin malabsorption associated with chronic inappetance, lethargy, cachexia, and failure to thrive has been reported in Giant Schnauzer puppies and is inherited as an autosomal recessive trait [3,4]. This disorder is characterized by methylmalonic aciduria, homocysteinemia, and low serum levels of cobalamin, and due to a selective defect of cobalamin absorption at the level of the ileal enterocyte [4]. The spontaneous disorder is believed to be analogous to Imerslund-Grasbeck syndrome in humans [4]. Hereditary cobalamin deficiency has also been reported in Border Collie puppies [5]. Acquired cobalamin deficiency may occur in older dogs and cats in association with malnutrition, malabsorption, exocrine pancreatic insufficiency, or bacterial overgrowth of the small intestine [6-13]. A condition similar to the inherited disorder has been recently described in a 6 month old beagle presented with a three-month history of failure to gain weight, lethargy, intermittent vomiting, and seizures [14]. Laboratory test results of low serum cobalamin concentrations, anemia, leucopenia, and methylmalonic aciduria while the dog was receiving a balanced commercial canine diet were suggestive of a congenital selective malabsorption of cobalamin. Treatment with repeated injections of parenteral cyanocobalamin at 50 µg/kg every two weeks corrected the cobalamin-deficient state and reversed all the clinical abnormalities. The pathogenesis of the neurological dysfunction in this dog remains unclear, although cobalamin is converted to adenosyl or methyl coenzymes that are necessary for normal neural metabolism [15].

A progressive encephalomyelopathy has been reported in a 12 week old Labrador Retriever with a variety of signs including stiffness and ataxia that progressed to tetraparesis, persistent turning of the neck/body to the right, changing nystagmus, decreased menace response, anisocoria, decreased oculocephalic reflex, ventrolateral strabismus, diminished gag reflex, and apparent dysphonia [69]. Gross changes revealed enlargement of the lateral, third, and fourth ventricles of the brain and white and grey matter atrophy. Syringomyelia and hydromyelia of the central canal into the dorsal funiculus of the spinal cord extended from the cervical intumescence to the lumbar intumescence. Significant biochemical abnormalities included methylmalonic and malonic aciduria, mild lactic and pyruvic aciduria. Disordered cobalamin metabolism was suspected, although serum cobalamin levels were normal. Neither ketoacidosis nor hyperammonemia were present. The condition was considered to represent an inborn error of metabolism resulting in abnormal organic acid accumulation (accumulation of...
citric acid cycle intermediates including succinic, aconitic, and fumaric acids, and evidence of abnormal fatty acid oxidation, were also noted), with similarities to methylmalonic acidemia in neonatal humans, an autosomal recessive disorder caused by defective activity of methylmalonyl CoA mutase or by defective intramitochondrial processing of vitamin B12 [70]. Many of the human patients respond to large doses of vitamin B12. Interestingly, an 8 week course of L-carnitine (1000 mg/day), vitamin B12 (0.5 mg/day), and a protein restricted diet resulted in marked improvement in the organic acid values of this dog, but no clinical improvement.

Malonic aciduria without elevated methylmalonic acid has been reported in a family of Maltese dogs with signs of episodic seizures and stupor (the dog described was 3 years of age), along with hypoglycemia, acidosis and ketonuria [71]. Treatment with frequent feedings of a low-fat diet high in medium-chain triglycerides successfully reversed signs and resolved the malonic aciduria.

In people, vitamin B12 deficiency results in spongy demyelination of the posterior (dorsal) columns and corticospinal tracts (once termed "subacute combined degeneration of the spinal cord"), and white matter of the cerebral hemispheres [16]. Peripheral neuropathy has also been reported that is usually axonal in nature [17], or less often, demyelinating [18]. Results of experimental studies suggest the pathogenesis of the myelopathy associated with vitamin B12 deficiency is related to interference with the methylation reactions in the central nervous system (CNS) that are processed by S-adenosylmethionine, which is controlled by its product, S-adenosylhomocysteine [19,20]. As a consequence, there may be inhibition of methyltransferases involved in the synthesis of myelin. Neuropathological studies on vitamin B12 deficiency are sparse in small animals. However, a degenerative spinal myelinopathy with similarities to subacute combined degeneration of the spinal cord in people has been reported in dogs fed a diet composed mainly of ruminant stomachs (see hound ataxia) [21]. The disorder was associated with methionine deficiency and altered methionine synthetase activity. Peripheral nerves appeared normal. The condition disappeared when the diet was changed to one containing a high proportion of meat. A possible relationship between degenerative myelopathy (especially in German Shepherds) and vitamin B12 deficiency has been studied but no consistent abnormalities in serum cobalamin levels could be shown [22]. Furthermore, parenteral cobalamin was ineffective in preventing progression of the neurological signs (see [23]).

Hypervitaminosis A

Hypervitaminosis A or deforming cervical spondylosis is a crippling degenerative and proliferative bony disorder typically affecting the vertebral column and various long bones in cats fed whole liver (usually beef or sheep, but also pig and chicken) diets [24-29]. The disorder is caused by excessive intake of vitamin A in the liver. Excessive intake of vitamin A supplements can also produce the disease. In serum, vitamin A is transported in a retinol binding protein and as retinylesters (retinylpalmitate, -stearate) in very-low and low-density lipoproteins [30]. Chronic hypervitaminosis A in cats is characterized by new bone formation or exostoses, principally involving cervical vertebrae, and in the region of tendon, ligament, and joint capsule attachments [26]. Early changes involve periarticular cartilaginous and osseous hyperplasia of cervical vertebrae, especially the first three diarthrodial joints, without changes in the articular hyaline cartilage or other signs of inflammation [26]. These lesions tend to coalesce, overgrow joints, and cause complete bony ankylosis [25,31]. Cartilaginous epiphyseal growth plates are seriously disrupted in kittens [32]. In chronic cases, all cervical and cranial thoracic vertebrae may become involved, as well as sternebrae, periarticular regions of long bones and ribs. Nerve roots are often damaged secondary to exostoses encroaching on intervertebral foramina. Histopathological changes include subperiosteal proliferation of new woven bone around joints of affected vertebrae and proliferation of cartilage from the margins of the articular hyaline cartilage. There is erosion of adjacent cortical and cancellous bone and fibrous replacement of the myeloid marrow [25,31]. Poroosteo proliferation may involve the tendinous insertions of muscle on the vertebrae and extend into surrounding muscle causing replacement and atrophy of the muscle fibers. In a study using back-scattered scanning electron microscopy [33], the more recently formed areas of bony proliferation were composed mainly of chondroid tissue surrounded by different degrees of woven bone. As the bony reaction continued, trabecular remodeling occurred leading to progressive substitution of chondroid tissue by woven bone surrounded by apposition of lamellar bone. In this study, there was no evidence of calcified cartilage present. In animals with extensive involvement of the spinal nerve roots, the spinal cord may show atrophy with disappearance of neurons and fibers, especially in the dorsal horns of the gray matter [25].

The underlying pathophysiologic mechanisms are not fully understood, but vitamin A toxicosis does appear to induce bone lesions via a direct effect on skeletal tissue. In young animals, toxicosis results in suppression of both chondrocytic and osteoblastic activity, leading to growth retardation and thinning of cortices. A high intake of vitamin A is necessary for several months or years before cervical exostoses develop, although experimental studies in kittens indicate that radiographic changes in the cervical spine can be detected as early as 15 weeks after beginning a diet rich in vitamin A [26]. After 24 weeks on the diet, the cervical spine from the occiput to C6 became completely rigid. Trauma may be a contributing factor in the pathogenesis due to constant movement of the neck in coat cleaning [26]. It seems that an individual predisposition to disturbances of vitamin A metabolism may be an important factor in the pathogenesis of the disease [34]. There are reports of
some cats having no symptoms while others in the household develop typical lesions [35]. Clinical signs usually occur in adult cats (e.g., 2 to 10 years of age) of either sex and in any breed [31,35-37]. Affected animals may be depressed, walk with pelvic limbs flexed, and may show lameness of one or both thoracic limbs associated with periarticular exostoses around the elbow joints, which, in chronic cases, are typically fixed in a flexed position. There may be ankylosis of the shoulder and carpal joints. Palpable exostoses of the forelimb distal to the elbow or of other regions of the skeleton are relatively uncommon [25]. Cats frequently assume a characteristic rabbit or kangaroo-like sitting posture. The head may be held in a ventroflexed position and there may be scoliosis of the cervical spine, which is frequently palpably rigid. The atlantoaxial joint is often fused, thus preventing any head-neck movement. Manipulation of the neck may be painful. Neurogenic muscle atrophy and signs of cervical hyperesthesia can result from spinal nerves compressed by the bony proliferation. Cutaneous hyperesthesia may be present over the shoulder and neck regions. Affected cats often have an unkempt coat because of inability to groom themselves. Affected cats typically have a fixed stare, presumably associated with reduced movement of the eyeballs caused by the head-neck rigidity [25]. Some animals have a voice change, probably related to proliferative exostoses that compress laryngeal structures (e.g., larynx, laryngeal muscles, and nerves). Some cats may show aggressiveness when handled [31,35]. Cats with advanced disease tend to become emaciated. In 6 to 8 week-old kittens fed raw sheep liver, severe retardation of skeletal growth was accompanied by delayed eruption, retention, and displacement of the incisor teeth with diffuse hypercementosis of the roots [38].

Radioactive studies reveal extensive new bone formation and variable autolysis of cervical and rostral thoracic, and sometimes, lumbar vertebrae [25,39]. In some cats, the skull and the cervical and first few thoracic vertebrae can be rigidly fused [25,40]. Periosteal exostoses can be seen involving multiple long bone articulations, especially in elbow and shoulder joints, and also ribs (in the region of vertebral articulation), sternebrae (showing irregular bony overgrowth, replacement and deformation of sternebrae with ankylosis of sternebral articulations), pelvic girdle, and hip joints. Curiously, there have been a few instances in which exostoses involving the pelvic girdle and hip joint were the major skeletal changes, without involvement of the cervical spine or forelimbs [25,33]. Rarely, affected cats showing typical clinical signs have no radiographic abnormalities in the cervical spine [40]. Vitamin A serum levels are elevated, but other hematologic and blood chemistries are usually normal, including alkaline phosphatase activity, serum calcium, and blood inorganic phosphate levels [25,29,37]. Vitamin A concentration is very high in liver and kidney [31,32] and there is extensive lipid infiltration of the spleen [26], and fatty changes in the liver have been observed occasionally [29].

Prognosis of chronically affected cats is guarded to poor. Change in diet may halt further new bone formation and exostoses; however resolution of radiographic changes and clinical signs is unlikely, although some remodeling of bone may occur over a long period. Epiphyseal damage is irreversible. Nevertheless, encouraging improvement in signs has been noted in some cats following removal of liver from the diet [35,41] (along with use of analgesic drugs, e.g., phenylbutazone, 13 mg PO, bid [37]. Cats have been treated with higher doses of phenylbutazone (12 - 16 mg/kg PO bid) for over a year without any toxic side-effects noted [25]. Rarely, temporary or permanent recovery may occur spontaneously [34]. Note that liver is highly palatable to cats and a change to another diet may be met with resistance [41].

The particular susceptibility of cats to hypervitaminosis A is difficult to explain. Spontaneous hypervitaminosis is rare in dogs but it has been experimentally induced in mixed Labrador Retriever pups [42]. Clinical signs were loss of body weight, dullness, emaciation, roughened coat, pain in limb joints, and retarded growth. Radiographic findings included reduced length and thickness of long bones, with osteophyte formation, periosteal reactions, and premature closure of epiphyses. No vertebral involvement was reported.

**Nutritional Secondary Hyperparathyroidism**

Once this condition was relatively common in small animals but is now infrequent with the advent of commercially available balanced pet foods. The cause of nutritional secondary hyperparathyroidism (NSH) is chronic dietary calcium deficiency which leads to increased serum levels of parathormone, and accelerated bone resorption. Neurological signs most often relate to spinal fractures associated with severe osteopenia (decreased calcification or density of bone) associated with increased mobilization of calcium from bone. In a recent report of NSH in cats, seizures were a common reason for presentation [43]. Additional information on NSH is found in the section on hypocalcemia.

**Thiamine Deficiency**

Thiamine or vitamin B1 deficiency (also called Chastek paralysis) occurs sporadically in dogs and cats if their commercial rations are naturally low in thiamine [44-47], or if their food (e.g., liver-beef diets in cats and mutton or mutton-beef in dogs) is overcooked prior to feeding or in processing of canned foods [44,48]. Sufficient quantities of thiamine to meet the requirements of dogs and cats are usually found in fresh meat [49]. Thiamine and thiamine pyrophosphate are thermolabile and destruction by heat (e.g. temperatures over 100°C) increases from a slight amount at pH 3.0 to a considerable degree at pH 7.0 [48,50]. In cats especially, thiamine deficiency may occur with an all-fish diet, since viscera of many freshwater and saltwater fish contain thiaminase [50]. Storage may have an effect on thiamin levels [47]. Thiamine in food, especially
processed meats, is also destroyed by sulfites or sulfur dioxide used as a preservative [49,51]. Experimentally-induced thiamine deficiency has also been studied in dogs and cats [44,50,52,53]. The metabolically active form of thiamine is thiamine pyrophosphate that plays an essential role in the intermediary metabolism of carbohydrate, and is especially involved in three enzyme systems [2]:

a. Pyruvate dehydrogenase (converts pyruvate to acetyl coenzyme A);
b. Alpha ketoglutarate dehydrogenase (catalyzes the conversion of alpha ketoglutarate to succinate in the Krebs cycle);
and
c. Transketolase (catalyzes the pentose monophosphate shunt).

Thiamine is thus essential for complete oxidation of glucose through the Krebs cycle (citric acid cycle or tricarboxylic acid cycle). As a consequence of thiamine deficiency, serum levels of pyruvate and lactate are increased, along with reduced red blood cell transketolase activity. Tissues dependent on glucose or lactate-pyruvate for energy, such as the brain and heart, are particularly compromised in thiamine deficiency. It still remains uncertain how thiamine deficiency leads to the phenomenon of selective vulnerability of neuronal cell death [2,52]. Impaired vascular perfusion might play a role in this disorder; results of experimental studies suggest that hemorrhages could be related to hemodynamic changes resulting from thiamine deficiency-induced vascular dysfunction [54]. In addition, events such as blood-brain barrier breakdown, N-methyl-D-aspartic acid receptor-mediated excitotoxicity, and increased reactive oxygen species have been implicated [55,56].

Clinical signs in dogs include anorexia, emesis, depression, wide-based hind limb stance, kyphosis, sensory ataxia, progressive spastic paraparesis, crouching hind limb gait, torticollis, head ventroflexion, circling, exophthalmos, generalized tonic-clonic seizures, profound muscular weakness, recumbency, opisthotonus, coma and death [48,53]. Patella reflexes are usually exaggerated, and there may be proprioceptive and menace deficits, tremors, and occasionally, nystagmus. Some dogs show signs of hysteria [53]. In cats, vestibular signs, head tremor, ataxia-dysmetria, transient seizures often precipitated by handling, depression, ventroflexion of the head with the chin almost touching the sternum (especially when the cat is suspended by the hind limbs), lying in a tight semicircular posture, dilated, poorly-responsive pupils, and absent menace response may be observed [50,57]. Cats with severe lesions may manifest semicoma, persistent crying, opisthotonus and limb spasticity, followed by death. Electrocardiographic abnormalities have been cited in dogs and cats, including bradycardia, tachycardia, sinus arrhythmias, QRS prolongation, P waves with notched peaks, elevation of the ST segment, and T-waves flattening or inversion [53]. Whole blood thiamine content is reduced in affected dogs [48].

Pathological findings in dogs and cats with experimental or spontaneous thiamine deficiency are similar and are characterized by polioencephalomalacia with bilaterally symmetrical spongiosis, necrosis, and hemorrhage of upper brainstem nuclei, primarily in periventricular gray matter [50,52,58]. The caudal colliculi are consistently involved and hemorrhagic or yellow-tan or brown malacic lesions may be seen macroscopically [48,50]. Gross lesions have also been noted occasionally in ventromedial and dorsomedial occipital cortex, dorsomedial parietal cortex, hippocampal gyrus, medial vestibular nuclei and cerebellar nodulus in dogs with experimentally-induced thiamine deficiency [52]. Microscopically, lesions involving the caudal colliculi consist of severe/total parenchymal necrosis with intense reactive changes associated with hypertrophy and hyperplasia of endothelial and adventitial cells, edema, gitter cell formation and intense microgliosis [48]. Spongy changes may be present in ventromedial and dorsomedial occipital cortex and dorsomedial parietal cortex, basal nuclei, red nucleus, oculomotor nucleus, vestibular nuclei, rostral olives, cerebellar peduncles, cerebellar nodulus and/or lingula, and cerebellar roof nuclei. Other findings include microvascular proliferation and occasional mild, lymphocytic perivascular cuffing. Spongiosis is due to hydromic vacuolation of the neuropil and myelin sheaths. This constellation of pathology varies with the stage of the disease: early, intermediate, and advanced lesions have been described in experimentally-induced thiamine deficiency in dogs [52]. Ultrastructurally, there is hydropic swelling of astrocytic processes and intramyelinic edema. In advanced stages, there is lysis of the neuropil, marked demyelination, accumulation of lipid macrophages, and variable axonal degeneration. White matter lesions are reportedly minimal and limited to the corona radiata adjacent to areas of cerebrocortical necrosis, and to medullary cores of folia within totally affected cerebellar cortex [52]. No spinal cord or peripheral nerve lesions have been observed in dogs or cats [48,50,52]. Myocardial degeneration has also been reported in hearts of affected dogs and cats [52,59]. In humans, thiamine deficiency may also lead to peripheral nerve axonal degeneration [60]. Prompt administration of thiamine hydrochloride, even in severely affected animals, can result in complete remission of clinical signs, e.g., 25 to 50 mg/day IM in dogs, and 10 to 20 mg/day IM, in cats, over several days; although learning deficits have been reported in cats that recovered from experimentally-induced thiamine deficiency [61].

**Vitamin E Deficiency**

Vitamin E is a fat-soluble vitamin of plant origin. Alpha-tocopherol is the most active form of vitamin E and it appears to be
taken up preferentially by the CNS [62]. Alpha-tocopherol is incorporated into chylomicrons in the small intestine prior to absorption, and in the liver it is bound and recycled by alpha-tocopherol transfer protein and incorporated into low-density and very-low density lipoproteins. It is delivered to cells where alpha-tocopherol functions as an antioxidant and helps prevent free radical peroxidation and injury to cell membranes [2]. Deficiency can occur at any level of tocopherol metabolism. In humans, vitamin E deficiency is associated with axonal membrane injury leading to axonal degeneration of peripheral nerves, dorsal root ganglia and posterior (dorsal) columns. In dogs and cats, vitamin E deficiency appears to be rarely involved with pathology of the nervous system. At one time, degenerative myelopathy (especially in German Shepherds) was considered to be possibly related to vitamin E deficiency [23]; however Averill failed to find evidence for vitamin E deficiency in his group of dogs [63] and recent studies suggest that this association is unlikely (in fact serum alpha-tocopherol concentration was significantly higher in German Shepherd dogs with the condition) [64]. Additionally, vitamin E supplementation had no effect on clinical signs. Statistical studies in this report indicated that the concentration varied more widely in individual affected dogs than in unaffected dogs, irrespective of breed. Vitamin E deficiency has been reported in visually impaired Walker Hounds and Beagles that were fed a diet of table scraps [65]. Sensory retinal degeneration was found in all dogs, and severity of changes varied with age of the dog. Plasma, serum, and tissue concentrations of vitamin E were low in affected dogs. Lipofuscin accumulation was found in retinal pigment epithelium and neurons of the CNS. Findings were consistent with nutritional vitamin E deficiency and oxidative injury to photoreceptors of the retina. Changes in these dogs were similar to those described for central progressive retinal atrophy and equine lower motor neuron disease. Vitamin E deficiency has occasionally been associated with reports of myopathies in dogs and cats (see vitamin E-selenium-responsive myopathy). Serum vitamin E concentrations are reportedly lower in adult and immature Brittany Spaniels with hereditary canine spinal muscular atrophy [66]. Vitamin E deficiency has been implicated in distemper vaccination failures [67] and generalized lipofuscinosis in dogs [68].

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