

Myopathic Disorders (4-Feb-2003)

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Myotonic Myopathy

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Adult-onset Myotonic Myopathy

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Polyglucosan Myopathy

Toxic Myopathy

Vitamin E / Selenium-responsive Myopathy

* I have included a review of myasthenia gravis in this chapter. While this condition represents a junctionopathy, its inclusion here seems appropriate due to its clinical similarities with some myopathic disorders.

Abbreviations -

ADH (adrenal-dependent hyperadrenocorticism); ALT (SGPT) alanine aminotransferase; AST (SGOT) aspartate aminotransferase; ATPase (myofibrillar adenosine triphosphatase); CK (creatin kinase); CSF (cerebrospinal fluid); CT (computed tomography); EMG (electromyography); HAC (hyperadrenocorticism); MRI (magnetic resonance imaging); NADH-TR (reduced nicotinamide adenine dinucleotide tetrazolium reductase); NCV (nerve conduction velocity); PAS (periodic acid-Schiff); PDH (pituitary-dependent hyperadrenocorticism).

Bouvier des Flandres Myopathy

A degenerative myopathy has been reported in two female Bouvier des Flandres dogs [1]. Clinical signs were observed when dogs were about 2 years of age. Signs included regurgitation, exercise intolerance, generalized muscle atrophy, weakness, and a peculiar paddling gait characterized by overextension of the paws when walking. Cranial nerve function, postural reaction testing, and segmental spinal reflexes were normal. Contrast studies reveal megaesophagus. Serum creatine kinase (CK) levels were markedly elevated. Other hematological and blood chemistry values were normal. Electrodiagnostic testing demonstrated bizarre, high-frequency discharges in skeletal muscles. Motor nerve conduction velocities were normal. Muscle changes were characterized by moderate to pronounced fiber size variation associated with atrophic and hypertrophic fibers of both histochemical types (types 1 and 2), occasional giant-sized fibers with a whorled internal architecture and clefts, numerous internalized nuclei, multifocal necrosis, variable phagocytosis, basophilia, and marked increase in perimysial and endomysial fibrosis. These changes were seen in both limb and

esophageal muscle samples. Peripheral and intramuscular nerves were normal. Muscle biopsy samples taken from two clinically normal related dogs showed similar but less severe histopathological changes.

Prognosis is guarded to poor since the disease appears to progress rapidly. Corticosteroids given to one dog had no clinical effect. The clinical signs, elevated CK levels, and muscle pathology are similar to those seen in some dogs with muscular dystrophy.

A familial dysphagia, associated with megaesophagus, has been reported in Bouviers [2,3] mainly adults (age range: 6 months to 9 years), with histopathological findings in pharyngeal and/or esophageal muscle very similar to those described above, but without clinical signs of generalized weakness or exercise intolerance. In some Bouviers with megaesophagus, similar lesions were also observed in the masseter and temporalis muscles and in the intrinsic laryngeal muscles [2]. The EMG showed myopathic changes in oral/ pharyngeal/esophageal muscles. In 13 of 24 dogs, CK levels were elevated. This condition was considered to have similarities to oculopharyngeal muscular dystrophy in people, an autosomal dominant disorder characterized by progressive ptosis and dysphagia [4].

Central Core Myopathy

A myopathy has been recognized in young Great Danes beginning around 6 months of age. Clinical signs of generalized weakness exacerbated by moderate exercise [5,6]. In one report, exercise or excitement associated with feeding would induce an episode of general body tremor and collapse into sternal recumbency, with rapid recovery after a few minutes rest [6]. Clinical weakness progressed in affected dogs, so that around 15 to 18 months of age, exercise intolerance was severe, with one dog unable to walk more than a few feet before collapsing. Elevated serum levels of CK, aspartate aminotransferase, and alanine aminotransferase have been reported. The condition is unresponsive to intravenous edrophonium chloride (Tensilon). EMG abnormalities include presence of positive sharp waves and fibrillation potentials in all muscles examined, including proximal and distal limb and trunk muscles. At necropsy, moderate atrophy of proximal limb and paraspinal muscles were noted in one dog [5]. Approximately 50% of muscle fibers contained a central core that occupied from 20 to 80% of the fiber. The cores appeared dark staining with hematoxylin and eosin stains, lacked cross-striations, and some contained vacuoles and nuclei. The cores were found in both type 1 and type 2 fibers. In longitudinal sections, the cores sometimes extended from 50 to 150 μm along the fibers. The core structure varied from homogenous to finely granular or fibrillar. In Gomori trichrome stains, scattered rod-shaped bodies were seen. Scattered necrotic and regenerating (characterized by small basophilic fibers with subsarcolemmal nuclear chains) fibers were also observed. Ultrastructurally, the cores consisted of numerous mitochondria, glycogen granules and disarrayed, irregular filament bundles attached to thickened Z-lines. No abnormalities were seen in spinal cord, peripheral nerves, or intramuscular nerve branches. The condition has some similarities to certain congenital myopathies in people, including central core disease, an autosomal dominantly inherited disorder, although in humans there is an absence of oxidative enzyme activity in the cores, which consistently affect type 1 fibers [7]. Note that the cores resemble target fibers seen in denervating muscle [8], however unlike targets, cores extend along the length of the fiber [9]. In one dog, some clinical improvement occurred following oral prednisolone therapy, although signs quickly returned upon cessation of treatment [5]. Prognosis appears to be guarded to poor. The etiology of this myopathy is uncertain, although a possible genetic disorder involved with oxidative metabolism has been suggested [6].

Devon Rex Cat Hereditary Myopathy

A degenerative, congenital myopathy, often called "spasticity" (albeit, erroneously), occurs in Devon rex cats and is believed to be inherited as an autosomal recessive trait [10-13]. Male and female cats are susceptible and signs may be seen in young cats around 4 to 7 weeks of age but may be delayed until 12 to 14 weeks. The most consistent clinical feature is passive ventroflexion of the head and neck, which is especially noticeable during locomotion, urination or defecation [12]. In severe cases, the chin is tucked into the sternum. Affected cats show a high-stepping forelimb gait, head bobbing, and with shoulder blades held high and the neck arched downwards. There is exercise intolerance often accompanied by progressive shortening of the stride and tremor. A "dog-begging" position is commonly observed. Some affected cats appear to have difficulty prehending and swallowing food, which may lead to upper airway obstruction. Regurgitation may be observed. Some cats have partial trismus. Clinical signs may be accentuated by concurrent illness, stress, or cold ambient temperature [12]. Apart from variable muscle atrophy seen in some cats, neurological testing is normal. Routine hematology and blood chemistries are normal, including serum CK levels. Radiographic and imaging studies reveal presence of megaesophagus and esophageal hypomotility, sometimes with gastroesophageal reflux [12]. EMG changes are mild and include variable presence of fibrillation potentials and positive sharp waves in muscles, particularly in triceps brachii and dorsal cervical muscles. No gross changes are seen in skeletal muscles. Microscopic changes in muscle include fiber size variation associated with hypertrophic and round/angular atrophic fibers, occasional fiber degeneration/regeneration, and variable presence of internal nuclei. In muscle samples from young cats, the muscle lesions tend to be mild and variable, but become more prominent with age and/or clinical severity [12]. There is no evidence of myositis or fiber type grouping. Dystrophin staining is normal. No abnormalities are seen in peripheral nerves, spinal cord, or brain. Mitochondrial enzyme assays in muscle are normal. The condition seems to stabilize around 9 months of age and affected cats may learn to cope with eating and drinking over time (feeding from a raised platform may be beneficial). Contractures do not occur. With adequate care, cats can thrive, although they may continue to tire

easily [10]. In some cats, prognosis may be guarded due to propensity to asphyxiation and laryngospasms associated with obstruction of the larynx/pharynx with food.

Exertional Myopathy

Exertional myopathy, or exertional rhabdomyolysis (ER), is a disease that affects many animal species, including man [14]. It is an important complication commonly arising in newly captured wild animals and, in domestic animals, is most frequently encountered in horses, in whom the condition has been variously termed azoturia and paralytic myoglobinuria. The condition appears to be rare in cats. In dogs, exertional myopathy probably occurs most frequently in racing Greyhounds [15-18], although it is also common in sled dogs [19,20]. It has also been reported sporadically in dogs as a complication of prolonged convulsive seizures (and extreme muscle exertion) [21,533], babesiosis [22], malignant hyperthermia [23], and monensin-contaminated diets [24]. Rhabdomyolysis has been reported in dogs following experimental potassium and magnesium deficiency [25,26]. Rhabdomyolysis is occasionally seen in humans with lipid storage myopathies and defects of fatty acid oxidation [7]. The pathogenesis of ER is poorly understood since intensity and duration of muscle contraction are not the entire explanation [27]. Humidity and temperature may be factors in Greyhounds in Australia, and highly strung dogs that bark excessively and are overexcited at the track appear to be susceptible to developing rhabdomyolysis [15]. Results of a study performed during the 1998 Iditarod sled race showed no association between pre-race plasma vitamin E or total antioxidant status levels and risk of development of ER [19]. It has been suggested that mechanisms other than oxidative damage to muscles, such as repetitive trauma during eccentric exercise (e.g., running downhill), may be involved in initiating muscle damage and subsequent development of ER in sled dogs [19]. Energy for muscle metabolism is derived from blood glucose, muscle glycogen, and fatty acids (plasma free fatty acids, esterified fatty acids, and ketone bodies), while contributions from branched chain fatty acids and amino acids may increase with prolonged exercise [28]. Intense muscle exertion requires an adequate supply of glycogen (via glycolysis) and once depleted, the adenosinetriphosphate of muscle decreases leading to muscle cramps and muscle fiber necrosis. Sufficient muscle injury will lead to release of myoglobin (the red pigment responsible for the color of muscle) into the circulation and filtration through the renal glomerulus resulting in red-brown urine pigmentation and possibly, acute renal failure [29]. In racing greyhounds, severe lactic acidosis leading to muscle cell swelling, local ischemia, muscle cell necrosis and myoglobinuria with nephropathy has been proposed as a likely sequence of events in the pathogenesis of ER [15-17]. The nephropathy is considered to result from a mechanical obstruction of tubules by precipitated myoglobin [27]. Some Greyhounds have relapsing rhabdomyolysis without secondary renal involvement [18]. Clinical signs may occur during or within 24 - 48 hours of a race or trial and are characterized by extreme distress, hyperpnea, and generalized muscle pain, especially over the back and hindquarters, which may appear swollen and firm. Limbs may be rigidly tonic and affected dogs may have a "hunch-back" appearance and refuse to walk [15,17]. Myoglobinuria and death within 48 hours are common in severe, acute cases. There may be increased serum activities CK, aspartate aminotransferase (formerly SGOT), alanine aminotransferase (formerly SGPT), and lactate dehydrogenase; all of which may remain elevated for more than a week following an attack [15,17]. In one report on racing Greyhounds, presence of increased serum CK activities suggested possible subclinical muscle injury [30]. In the Iditarod study, blood CK activity was used to identify dogs withdrawn with exertional rhabdomyolysis (reference CK levels above which dogs were identified as having ER were > 10,000 IU/L, although some dogs had values > 400,000 IU/L) [19]. Interestingly, sled dogs prone to ER seem to develop the disorder early in the Iditarod race (e.g., within the first 500 miles) [19,20] and electrolyte disorders, such as hyponatremia (perhaps related to the high renal solute load associated with large energy intake) have been noted [19,20]. Hyponatremia (possibly from renal damage) and hyperkalemia have been reported in a Greyhound with ER [17]. Pathological findings in muscle include multifocal hemorrhage and myonecrosis that may involve 50 - 70% of muscle fibers [21]. Older lesions (several days) may show mineralization of necrotic muscle fibers, inflammatory infiltration by neutrophils, and sarcolemmal cell proliferation [14].

Prognosis depends on the severity of clinical signs. Dogs with hyperacute signs usually die within 48 hours from renal failure. Mortality rate is low in less severe cases that are treated with intravenous fluids, bicarbonate, anabolic steroids, antibiotics, body cooling, and rest [31]. Note that exertional rhabdomyolysis has certain features in common with stress-related malignant hyperthermia.

Fibrotic Myopathy

This acquired, non-painful disorder associated with a fibrous band within a muscle has been reported sporadically in dogs - most commonly in German Shepherds, usually male, with an age range from 8 months to 9 years [32-38]. Other breeds include Doberman Pinscher, Rottweiler, Bobtail, St. Bernard, Boxer, and Old English Sheepdog. Fibrotic myopathy has recently been called gracilis or semitendinosus myopathy [37]. The etiopathogenesis of this condition is unclear. In humans, fibrotic myopathy may be congenital, although intramuscular injections have been implicated in some patients [39-41]. Active dogs seem to be susceptible to this disorder [32], and recent studies in dogs suggest that fibrotic myopathy may be related to muscle injury from excessive activity, including jumping and sprinting that can lead to muscle strain [38], with a suggested sequence of inflammation, edema, localized hemorrhage, and eventually fibrosis. Increased angulation (flexion) at the stifle in normal German Shepherds may predispose these dogs to increased

hamstring stress during physical activity [38]. While onset in some dogs is acute (compatible with grade 2 or 3 muscle injury), the lameness appears to be insidious in most dogs (compatible with chronic or grade 1 muscle strain) [38]. Apart from semitendinosus and gracilis muscles, fibrous bands may occur in quadriceps muscles, biceps femoris, and semimembranosus in hind limbs [32,38], as well as in supraspinatus and infraspinatus muscles in dogs [33,34]. A palpable band has also been found in the teres minor muscle (see below). Duration of signs may range from weeks or several years [38].

Fibrotic myopathy of the semitendinosus muscle is associated with a palpable thickened fibrous band that may extend from the tuber ischii to the tibia within the belly of the semitendinosus muscle. Tight fibrous cords are also palpable in affected gracilis muscles extending from the midline of the pelvis to the caudomedial aspect of the stifle. In dogs with gracilis and/or semitendinosus muscle involvement, the hind-limb gait is characterized by a shortened stride with a rapid, elastic medial rotation of the paw, external rotation of the hock, and internal rotation of the stifle during the mid-to-late swing phase of the stride [35,37]. Kinematic analysis indicate that the range of motion of the stifle is reduced [42]. The gait anomaly results from restricted abduction of the coxofemoral joint and reduced extension of the stifle and hock. Note that the lameness is best appreciated at the trot. Bilateral involvement (of the gracilis or semitendinosus muscle) is commonly encountered, with reports varying from 39% to 61% of affected dogs [37,38], while both muscles may be involved ipsilaterally or contralaterally [35,36]. Histologically, the band consists of an abundance of dense collagenous connective tissue, with a distinct interface between connective tissue and muscle bundles. Morphological studies in our laboratory or in others have not identified primary muscle or peripheral nerve disease, although variable myofiber degeneration around the periphery of the fibrotic band has been seen occasionally, sometimes associated with mild mononuclear cell inflammation and focal hemorrhage [37]. The replacement of muscle fibers with dense collagenous connective tissue results in a mechanical lameness resulting from failure to fully extend the limb. Neurological examination is usually normal; however, pressure applied to the affected muscle, abduction of the coxofemoral joints of affected limbs, and extension of stifle/talocrural joints in affected limbs may elicit pain [37]. Serum CK levels may be normal or moderately elevated in some animals [35,43]. Absence of myoelectrical activity in the band during EMG evaluation is consistent with total replacement of muscle fibers by dense connective tissue [35,43]; however, spontaneous EMG activity in the vicinity of the band suggests recent muscle damage [38]. In occasional dogs, fibrillation potentials and rare myotonic discharges have been recorded [35,36]. Imaging techniques have been used to identify the intramuscular fibrous cords in people [44]. Soft-tissue swellings associated with the myotendinous areas of affected muscles may be detected on radiographs, and two-dimensional ultrasonography in one dog revealed increased size and reduced homogeneity of the gracilis muscle, with an enlarged tendon of insertion compared to the normal muscle [37]. Prognosis is guarded to poor since the condition in dogs tends to recur within several months following surgical resection of the fibrous band, or transection, partial excision, or complete resection of the affected muscle [37]. Non-surgical treatment (e.g., corticosteroids, non-steroidal inflammatory drugs, acupuncture) is usually ineffective. Non-surgical rehabilitation, including therapeutic ultrasound and cross-fiber friction massage, resulted in mild improvement in several dogs (slight increase in range of motion of the stifle and less crossing over of pelvic limbs) [38]. If fibrotic myopathy is causally related to muscle strain, appropriate preventive measures might include stretching, warm up exercises, and gradual build up to more intensive activities [38]. Inability to maintain the affected leg in extension during healing might contribute to recurrences [38]. The suggestion that oxygen-free radicals cause pericytic necrosis and fibroblastic proliferation in some forms of human fibrotic disorders may offer therapeutic possibilities [45].

Post-traumatic fibrotic myopathy has also been reported in an 18 month old female Dalmatian together with myositis ossificans [46]. Clinically, there was markedly reduced range of motion of hip extension and stifle flexion, and a firm mass beneath the sartorius muscle in the region of the rectus femoris muscle. Surgical studies revealed replacement of the rectus femoris muscle by a white fibrous band that was histologically characterized by dense fibroblastic connective tissue. A firm calcified mass was found on the iliac shaft. Immediately upon resection of the fibrous band, the coxofemoral and stifle joints were returned to a normal range of motion. No recurrence of lameness was seen after 6 months.

More recently, teres minor myopathy causing sudden onset left forelimb lameness of 8 month's duration was reported in a 5 year old working Labrador Retriever [47]. Minimal circumduction was present in the left forelimb and the left suprascapular muscles were atrophied. A painful palpable band-like structure was found in the region of the teres minor muscle. Ultrasonography revealed an area of increased echogenicity within this band. EMG studies were normal. Exploratory surgery identified the band to be the teres minor muscle, which was adhered to the joint capsule and infraspinatus/deltoid muscles. Histological examination revealed focal areas of inflammation with mononuclear cells, floccular degeneration of contractile elements, patchy regeneration, but surprisingly, without significant fibrosis. Following excision of the teres minor muscle, there was complete resolution of the lameness with no apparent adverse effects on joint function. The etiology of this condition was not determined although trauma was suspected to be the initiating factor. A comparable condition involving the semitendinosus muscle was reported in a mature castrated male Himalayan cat [43] in which the lameness was characterized by marked flexion of the hip, stifle, and hock as the limb was advanced. Since the limb could not be fully extended, the paw was placed abruptly, sometimes with knuckling. A single injection of methylprednisolone acetate (10 mg, IM) had no discernible effect. Surgical exploration indicated that the semitendinosus muscle was firm, white, and cord-like. Tenorrhaphy produced a favorable long-term response (1 year after surgery, the cat's gait remained abnormal but had little effect on ambulation).

Glycogenesis

Several glycogen storage diseases may result in weakness and muscle changes, including type II, III, IV, and VII glycogenoses (see glycogenesis).

Hepatozoon Myositis

This disease is caused by *Hepatozoon canis*, a protozoan organism that infects dogs [48-51], and rarely, cats [52]. It is transmitted primarily by the tick *Rhipicephalus sanguineus*. The disease has a world-wide distribution [53-56], although the North American strain of *H. canis*, seems clinically distinct from those in other parts of the world in which signs tend to be subclinical [57,58]. Indeed, the North American strain has recently been identified as *Hepatozoon americanum*, a species of the apicomplexan protozoan parasite [59,532]. The definitive host for *H. americanum* is believed to be the tick *Amblyomma maculatum* [60,61]. In the U.S., most cases are reported from the Gulf Coast region of Texas and Louisiana, and Oklahoma, but recent reports extend the range to Georgia and Alabama [62]. Infection occurs by ingestion of an infected tick [58]. Sporozoites are released in the intestine of the dog, penetrate the intestine and spread via the blood or lymph to various tissues where they undergo schizogony. Merozoites are released from schizonts. Merozoites that enter leukocytes become gametocytes. Infection of blood-sucking ticks occurs by ingestion of infected leukocytes. Vertical transmission has been reported in puppies [63].

Commonly reported clinical signs of *H. americanum* include fever (unresponsive to antibiotics), lethargy, weight loss, anorexia, depression, muscular hyperesthesia (especially over paraspinal areas), paraparesis or paralysis, bloody diarrhea, mild anemia and purulent ocular and nasal discharges. Glossitis, pharyngitis, and skin lesions have also been reported. Hyperesthetic animals may be reluctant to move and often assume a sitting posture with rigidity of the trunk and neck ("master's voice" posture) [58]. Temporal muscle atrophy may be present. Concurrent infection or immunosuppression may facilitate infection and accelerate development of clinical signs. Young dogs (< 6 months of age) appear most susceptible to infection. The clinical course may be prolonged with spontaneous remissions and intermittent periods of fever and pain.

Laboratory findings include neutrophilic leukocytosis (ranging from 20,000 to more than 200,000 cells/ μ l), occasional eosinophilia and basophilia, mild regenerative anemia, low serum glucose (probably an artifact associated with the extreme neutrophilia [58]) and albumin levels, increased serum alkaline phosphatase and increased inorganic phosphorus concentrations [62]. Analysis of CSF from affected dogs may reveal neutrophilic pleocytosis (e.g., > 300 WBCs/ μ l) and increased protein levels (e.g., > 100 mg/dl) [64]. Radiography may demonstrate pronounced periosteal bone proliferation and/or smooth laminar thickening of the periosteum affecting any bone except the skull, although the diaphysis of the more proximal long bones of the limbs is commonly involved [65]. EMG studies reveal abnormal spontaneous potentials.

Muscle biopsy is often useful in establishing a diagnosis [50,62,66] - changes include myositis and pyogranulomas composed of macrophages, neutrophils, and occasionally eosinophils, sometimes adjacent to large, thin-walled cysts (schizonts) approximately 250 - 500 μ m in diameter (pain, fever, and periosteal bone proliferation may be a consequence of the polymyositis). The nuclei of the cysts are surrounded by host-derived bluish, mucinous mucopolysaccharide material associated with fine lamellar membranes [66,67]. Some cysts contain numerous small, round, basophilic bodies considered to be micromerozoites. Tissue stages of *H. americanum* may be identified in tissue sections using immunohistochemical techniques [68]. Organisms can be seen within neutrophils and monocytes in Romanovsky-stained peripheral blood smears [49,57,58]. At necropsy, gross visible pyogranulomas may be seen in cardiac and skeletal muscles (including extraocular muscles), smooth muscle, liver, skin, lymph nodes, lung, and kidney [57]. Glomerulonephritis, amyloidosis, and the nephrotic syndrome are commonly found [57]. An indirect enzyme-linked immunosorbent assay (ELISA) has recently been reported to be a reliable tool for diagnosing American canine hepatozoonosis [69].

Until recently, no antiprotozoal agents consistently caused long-term remission of signs, and most infected dogs could be expected to die within 2 years of clinical diagnosis [58]. Temporary remission of signs for several months had been achieved by administering trimethoprim sulfadiazine (15 mg/kg PO bid), clindamycin (10 mg/kg PO tid), and pyrimethamine (0.25 mg/kg PO sid) (TCP) for 2 weeks [62]. Aspirin given at 5 mg/kg PO bid for several days was helpful in reducing the fever. Temporary remissions had also been achieved using toltrazuril at 5 mg/kg PO bid for 5 days [62], a drug no longer available for clinical use in the United States. The initial favorable response to TCP is typically followed by periodic relapses that subsequently result in chronic debilitation leading to renal failure, death, or euthanasia. Corticosteroids frequently exacerbate clinical signs or induce a recurrence of signs. However, in a recent study, treatment of affected dogs with TCP for 2 weeks followed by long-term administration of decoquinate, a quinoline anticoccidial agent at 10 to 20 mg/kg, every 12 hours mixed in food (the drug is available from feed stores in 50-lb bags, and the dosage is 0.5 to 1.0 teaspoon/10 kg, mixed in food, twice daily) has increased survival time (> 33 months) without any deleterious side-effects [70]. Continuous treatment with decoquinate for 2 years is being recommended. Note that decoquinate is ineffective in dogs with advanced disease/glomerulonephropathy at the time treatment is begun. Control of ticks by routine dipping of dogs from infected areas will help to limit spread of the disease and reinfestation of susceptible hosts [51]. Hepatozoonosis does not appear to be an important public health concern.

Hyperadrenocortical (Cushing's) Myopathy

An acquired degenerative myopathy has been reported in dogs in association with hyperadrenocorticism (Cushing's disease) [71-75]. Several forms of hyperadrenocorticism (HAC) exist and are listed below, all of which are characterized by chronic high serum cortisol (glucocorticoid) concentrations [76]:

1. Pituitary-dependent HAC (PDH) - Often accompanied by tumors of the adenohypophysis that produce ACTH or a similar acting hormone. Eighty percent or more of cases of pituitary Cushing's disease are reportedly associated with a pituitary tumor. These tumors may stem from the pars distalis (80%) or the pars intermedia (20%), since both regions contain cells that are capable of producing adrenocorticotrophic hormone (ACTH). This form of HAC is most frequently associated with bilateral adrenocortical hyperplasia. If the hypothalamus is disrupted by the tumor, signs of a hypothalamic syndrome may accompany signs of HAC (see pituitary tumor). Approximately 75% of dogs with PDH weigh < 20 kg and Poodles, Beagles, German Shepherds, Dachshunds, and Terrier breeds appear overrepresented [76,77].
2. Adrenal-dependent HAC (ADH) - Usually associated with primary adrenocortical neoplasia (adenoma or carcinoma) with contralateral adrenocortical atrophy, and which occurs in approximately 10 to 20% of dogs with HAC [77]. Occasionally, tumors may involve both adrenal glands. Poodles, German Shepherds, Dachshunds, Terrier breeds, and Labrador Retrievers appear overrepresented in dogs with adrenal tumors and approximately 50% of dogs weigh > 20 kg [76,77].
3. Iatrogenic HAC - Associated with excessive/prolonged corticosteroid administration, especially fluorinated agents such as triamcinolone, betamethasone, and dexamethasone [78]. It is usually associated with bilateral adrenocortical atrophy. Interestingly, a presumed glucocorticoid-induced myopathy was reported in a dog receiving ophthalmic corticosteroid therapy that was associated with adrenal suppression [79].

Clinical signs of HAC include panting, polydipsia, polyuria (due to a reversible form of central diabetes insipidus), bilaterally symmetrical alopecia, pendulous abdomen, hyperpigmentation, comedones, and hepatomegaly [76]. Myopathic signs may include gradual development of a stiff, stilted gait, weakness, stumbling, and generalized muscle atrophy that is often marked in epaxial, temporal, and masseter muscles [71-75]. Proximal limb muscles may appear enlarged and bulging in some dogs [72]. Pelvic limb rigidity, especially in middle-aged and older dogs, especially Poodles, is not unusual. Some hyperadrenocorticoid dogs have a form of myotonia with signs of muscle dimpling and myotonic-like discharges seen on EMG (see below), generalized increase in muscle tone, rigid epaxial muscles, arching of the back, ears drawn back, and tongue protrusion [71,72,75]. Feldman states that myotonic-like stiffness occurred in only 5 of 800 dogs with Cushing's syndrome in his practice [80]. Tendon reflexes are usually normal. Gastrocnemius muscle rupture, believed to be associated with the underlying myopathy, was reported in a 6 year old spayed female Shetland Sheepdog with iatrogenic HAC [81]. Note that one potential complication of HAC is thromboembolism, possibly related to coagulation protein loss in urine [76], and signs of pelvic limb weakness, pain and collapse as a result of occlusion of the distal aorta and/or the iliac arteries [82]. Electromyographic studies of proximal and distal limb muscles and paraspinal muscles may reveal evidence of bizarre high frequency discharges, often producing a "dive-bomber" sound. The discharges may wax and wane in amplitude and frequency suggesting they represent myotonic potentials [75], although in most dogs with hyperadrenocorticoid myopathy, the discharges do not wax and wane and are termed pseudomyotonic potentials (See Electrodiagnostics). It has been suggested that pseudomyotonia in French Poodles is not a simple consequence of HAC but a separate, possibly genetic, disease [524]. In one recent study of 30 dogs with HAC, complex-repetitive discharges were recorded that were more prominent in proximal appendicular muscles while fibrillation potentials and positive sharp waves were found in 60% of affected dogs and localized in the distal limb muscles [525]. Myotonic discharges were not found in this study. Nerve conduction studies may be normal or slowed (see hyperadrenocortical neuropathy).

Diagnosis of hyperadrenocortical myopathy is based on laboratory data, signalment (mature, female Poodles may be predisposed to the myopathy), clinical and electrodiagnostic findings, and muscle biopsy. Laboratory findings include "stress" blood count (lymphopenia, eosinopenia, neutrophilia, and monocytosis), increased serum alkaline phosphatase (in dogs), hyperglycemia (usually lower than renal threshold in dogs), hypercholesterolemia and lipemia from the glucocorticoid-induced lipolysis, and reversible (usually) hypertension in dogs [76,83]. Serum CK activity may be elevated [72,75]. Histological findings include mild degenerative changes associated with fiber size variation, presence of subsarcolemmal masses, focal necrosis and fiber splitting, target fibres or fibres with "central areas", and fiber atrophy, especially of type 2 fibers [71,73]. Fiber grouping may be present, and in some dogs, we have seen demyelination/remyelination in peripheral nerves (see hyperadrenocortical neuropathy). Ultrastructural changes in muscle include splitting and disorientation of myofibrils, disruption of mitochondrial cristae, subsarcolemal and intermyofibrillar aggregates of mitochondria, presence of large bizarre-shaped mitochondria, increased numbers of intermyofibrillar vacuoles, small increase in sarcoplasmic glycogen deposition, and variable dilatation of the sarcotubular system [73,84].

The pathophysiologic basis for hyperadrenocortical myopathy is unknown, although the changes probably result from excessive circulating glucocorticoids and muscle protein catabolism, since identical muscle changes are observed in dogs

and cats receiving corticosteroids [72,73,84,85]. Muscle weakness and atrophy are believed to be mediated by the glucocorticoid induction of the enzyme glutamine synthetase [86,87], and the increased glutamine synthetase activity may be reduced by growth hormone or insulin-like growth factor [87]. It was proposed that selective muscle atrophy (i.e. type 2 fibers) may result from differences in myofiber glucocorticoid sensitivity [88], although density of glucocorticoid receptors appears to be comparable in different muscle fiber types [89]. In people with Cushing's disease, ACTH excess may also be directly myopathic [90]. Specific findings for the different forms of HAC are as follows [77,91].

1. Pituitary-dependent HAC (PDH) - Normal or high baseline plasma cortisol and ACTH levels; exaggerated cortisol response to ACTH stimulation; and suppression of plasma cortisol with high-dose (but not low-dose) dexamethasone. Approximately 20 - 30% of dogs with this form of HAC are resistant to dexamethasone suppression.
2. Adrenal-dependent HAC (ADH) - Normal or high baseline plasma cortisol; normal or exaggerated cortisol response to ACTH stimulation; failure to suppress plasma cortisol with any dose of dexamethasone; and undetectable plasma ACTH concentration.
3. Iatrogenic HAC - Normal or low baseline plasma cortisol; little or no cortisol response to exogenous ACTH; and undetectable plasma ACTH concentration [76,92].

In one review, the most sensitive tests in distinguishing dogs with pituitary-dependent HAC from dogs with adrenocortical tumors were the plasma endogenous ACTH concentrations, abdominal radiography, and abdominal ultrasonography, although none of the tests alone were completely reliable [77]. Recently, however, a single determination of endogenous plasma ACTH levels and adrenal ultrasonography were considered to be discriminatory in a prospective study to differentiate between PDH and ADH and more accurate than dexamethasone suppression testing [93]. Ultrasonography appears to be a reliable test for functional adrenocortical tumors [94]. The number of PDH dogs with macroadenomas is probably higher than the literature suggests [95]; however, on the basis of endocrine test results, dogs with PDH and large pituitary tumors cannot be adequately distinguished from dogs with PDH and microscopic pituitary tumors prior to onset of clinical signs [95]. Nevertheless, it has been suggested that inadequate serum cortisol suppression during high-dose dexamethasone suppression testing in dogs with PDH, may be a prognostic indicator for subsequent development of an invasive pituitary tumor [96]. It should be noted that pituitary and adrenal tumors can coexist in dogs with HAC, leading to a confusion of test results and complicating diagnosis and treatment [97]. Note also that diabetes mellitus can be a complication of HAC, especially in cats, and that dogs with a reduced beta cell mass prior to development of HAC are more likely to develop concurrent diabetes or to develop diabetes with glucocorticoid administration (Dr. Richard Nelson, University of California-Davis, personal communications, 2002).

Myopathic signs may abate following surgical or medical management of the hyperadrenocorticism [76,98-101]. Several treatments used in the medical management of PDH and ADH in dogs include mitotane (a potent adrenocorticolytic drug that causes necrosis of the zona fasciculata and reticularis, and thus effects "medical adrenalectomy"), and ketoconazole (a drug that inhibits steroid biosynthesis and suppresses cortisol secretion with minimal effects on mineralocorticoid production) [101]. L- deprenyl (Anipryl) thought to control Cushing's by downregulating ACTH via enhanced brain dopamine levels [76], is not recommended as the sole treatment for canine PDH [102]. Other clinicians do not recommend it at all [76]. Another potentially useful drug for treating dogs with PDH or ADH is trilostane, which interferes with adrenal steroid biosynthesis [103].

Note that withdrawing or reducing the dose of the glucocorticoid is the primary method of treating steroid myopathy, or using non-fluorinated steroids since steroid myopathy is most often associated with fluorinated steroids (e.g., triamcinalone, betamethasone, and dexamethasone) [104,105].

Prognosis is guarded in dogs with HAC if contractures and severe muscle atrophy are present in pelvic limbs. Myotonic signs may progress despite effective mitotane therapy, in which case procainamide administration (e.g., at 12.5 mg/kg PO bid) may reduce the myotonic stiffness [75]. Exercise programs and physical therapy may assist recovery and probably should be encouraged in any animals receiving glucocorticoids.

Hyperkalemic Myopathy

Increased serum potassium values may occur in association with adrenocortical insufficiency, diabetes mellitus, acute renal failure, or severe acidosis (see feline muscular dystrophy). In conjunction with the characteristic signs of these diseases, animals may manifest episodic weakness, loss of strength and tendon reflexes due to increased intracellular positivity (with hyperkalemia, the chemical gradient for potassium efflux is decreased) to the point that resting membrane potential falls below the threshold potential with subsequent minimal depolarization and less excitable membranes [106,107]. Muscle weakness with hyperkalemia typically occurs with serum potassium levels > 8 mEq/l [535]. Diagnostic aids include serum potassium and sodium, plasma cortisol, ACTH response testing, blood glucose, blood urea nitrogen, urinalysis, creatinine, and blood pH values.

Hyperkalemic periodic paralysis (HPP) is a rare disorder in dogs that is characterized by episodic weakness, limp neck, protruding tongue, collapse and paralysis and may be precipitated by exercise and/or excitement [108]. Attacks lasted 10

to 15 seconds after which the animal appeared drowsy but quickly resume normal behavior. Attacks were also precipitated by oral potassium administration. No changes in serum glucose or lactate levels were found. In humans, the pathogenesis of this disorder is associated with a sodium channelopathy, an inherited disorder resulting in reduced inactivation of the sodium channel, leading to increased muscle cell permeability to sodium and muscle membrane hypoexcitability, and episodic weakness [109,110]. The sodium current, through noninactivating channels, may cause the skeletal muscle weakness in HPP by depolarizing the cell, thereby inactivating normal sodium channels, which are then unable to generate an action potential. In addition, myotonic potentials may occur as a result of a small depolarization and repetitive excitation (see also, myotonic myopathy) [110]. Thus, the hyperkalemia appears to be the consequence rather than the cause of the periodic paralysis [9]. A very similar condition occurs in horses as an autosomal codominant genetic disease [111]. Attacks are usually associated with increased plasma potassium levels. Focal necrosis and variable vacuolar changes may be seen in skeletal muscle fibers. EMG abnormalities may be detected, including prolonged insertional activity, complex repetitive discharges, spontaneous activity and myotonic discharges [112]. Treatment with acetazolamide, 2 mg/kg, bid, PO, was beneficial in treating the 7 month old Pit Bull with HPP [108]. Acetazolamide is a thiazide derivative and carbonic anhydrase inhibitor that promotes renal loss of sodium and potassium. In humans with HPP, thiazide diuretics are effective [9].

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) [113]. 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 ventroflexion 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 eunatraemia, secretion of pituitary hormones became normal. It was suggested that hypothalamic dysfunction, possibly related to hydrocephalus, induced both hypodipsia and transient hypopituitarism [113].

Hypokalemic Myopathy

Hypokalemic myopathy is a metabolic disorder of older cats that has been linked with chronic renal disease and excessive urinary potassium loss [114-116], although a similar, if not identical disease, was reported in 1984 [117]. Synonyms are feline kaliopenic polymyopathy-nephropathy syndrome, and sporadic feline hypokalemic polymyopathy. Low dietary potassium intake secondary to inadequate potassium levels in certain commercial rations has been associated with episodic hypokalemic myopathy [114,118]. Additionally, potassium urinary loss may be exacerbated by some diets that are acidified to reduce development of crystalluria and urolithiasis. It has been suggested that increased potassium loss induced by renal dysfunction may represent a phenomenon peculiar to cats [115]. Furthermore, chronic potassium depletion (e.g., from deficient rations) may lead to progressive renal disease (associated with renal ischemia, increased renal ammoniogenesis, activation of the alternate complement pathway, and tubulointerstitial injury) as well as sudden changes in muscle membrane sodium permeability [114]. Decreased extracellular potassium levels will produce an increase in resting membrane potential, resulting in a greater difference between resting and threshold potential necessary for muscle contraction [119]. This lessened state of electrical excitability underlies the muscle weakness [107]. Additionally, hypokalemia may negatively affect insulin release and end-organ sensitivity to insulin [106]. Other causes of hypokalemia include gastrointestinal loss of potassium, post-obstructive diuresis following relief of urethral obstruction in cats, administration of loop or thiazide diuretics, and rarely, mineralocorticoid excess [535]. Clinical signs are characterized by acute onset of a stiff-stilted gait, reluctance to walk, exercise intolerance, ventroflexion of the neck (especially in cats), and muscle pain. Spinal reflexes may be depressed. Serum CK levels are moderately to markedly elevated, while serum potassium values are low (e.g., < 4.0 mEq/L). Serum creatinine levels may be markedly increased. In the hypokalemic cats fed a high protein vegetarian diet, plasma taurine concentrations decreased and glutamic acid increased markedly [118]. Mild, diffuse electromyographic changes (e.g., presence of positive sharp waves) have been recorded in various skeletal muscles. Light microscopic evaluation of muscle samples is usually normal, although myofiber vacuolation and mild myonecrosis may occasionally be observed. Ultrastructural changes in people indicate that the vacuoles are membrane-bound and reveal the frequent presence of tubular aggregates that selectively involve type 2 fibers [120]. Rhabdomyolysis in severe hypokalemia might be related to osmotic

expansion of cells due to increased intracellular sodium and chloride levels or reflect ischemic myonecrosis due to decreased muscle blood flow associated with impaired potassium metabolism during muscle contraction/exercise [106,114].

Prognosis is guarded to favorable and may depend upon the severity of the underlying renal disease, if present. Most cats reportedly show significant improvement in muscle strength within 2 to 3 days of initiation of treatment. Oral potassium supplementation (e.g., potassium gluconate - Tumul-K[™], Daniels Pharmaceuticals), at 5 to 10 mEq/ cat /day, divided bid, is recommended for severely hypokalemic cats. For less severely affected animals, 2 to 4 mEq/day is usually adequate. Permanent daily supplementation with regular re-evaluation of serum potassium, serum creatinine, and urinary potassium loss is recommended, since cats that are not supplemented have a tendency to become hypokalemic again.

Severe hypokalemia and generalized flaccid paralysis has been reported in a 6 year old female Miniature Poodle after furosemide administration for suspected congestive heart failure [121]. In this case, hypokalemia presumably resulted from an increased flow rate in the distal tubules and increased secretion of aldosterone secondary to volume depletion caused by the thiazide diuretic. Muscle biopsies showed severe myonecrosis, phagocytosis, fiber splitting, internalized nuclei, and atrophy/hypertrophy. Peripheral nerve biopsy was normal. After treatment of the hypokalemia (intravenous fluids and potassium supplementation), the dog was clinically normal within 16 days of complete paralysis, while muscle biopsies were normal within 30 days.

Note that hypokalemia may also result from various metabolic and endocrine disorders [122]. In one report, hypokalemic myopathy occurred in 9 cats as a result of severe diabetic ketoacidosis and its therapy (e.g., hypokalemia may result from the attendant osmotic diuresis, correction of the acidosis, or insulin-mediated cell uptake) [123]. In this study, normokalemia and the myopathy resolved within a few days of potassium supplementation. Acute onset of muscular weakness and ventroflexion of the neck have been reported in several hyperthyroid cats in association with hypokalemia, the cause of which was not determined [13,119,124]. Cats responded quickly to potassium supplementation or following resolution of the hyperthyroidism. In humans, nonfamilial hypokalemic thyrotoxic periodic paralysis is commonly seen among Asians [125,126]. It has been reported that sudden paralysis occurring while at rest after a large carbohydrate meal or strenuous exercise is a common presentation and that intracellular shifts of potassium triggered or facilitated by hyperthyroidism and hyperinsulinemia are the biochemical features [126,127]. Correction of the hyperthyroidism is the definitive treatment in people. A periodic myopathy characterized by muscle stiffness, weakness, and pain secondary to persistent hypokalemia and metabolic alkalosis has been reported in a German Shepherd with an hepatic neuroendocrine carcinoma, thought to be a primary hepatic carcinoid [128]. Ectopic adrenocorticotrophin hormone secretion was suspected as the cause of hypercortisolism and hypokalemia (possibly associated with cortisol inactivation overload). Note that in most dogs with hyperadrenocorticism, hypokalemia is either not seen or is mild and clinically insignificant [76]. Hypokalemia secondary to an aldosterone producing tumor of the adrenal gland (Conn's syndrome) has been observed in cats [13]. Aldosterone normally regulates electrolyte/fluid balance by facilitating sodium retention and potassium excretion. Clinical signs included intermittent muscle weakness and collapse that became progressively more severe. Blood biochemical studies revealed elevated aldosterone levels and high serum creatine kinase levels. Temporary improvement resulted from administration of spironolactone at 10 - 100 mg PO daily.

A second type of hypokalemic myopathy has been reported in young Burmese kittens, 2 to 6 months of age [129-131], although the disorder has also been reported in a 2 year old Burmese cat [132]. This condition is considered to be a homozygote recessive hereditary disease and is characterized by periodic muscle weakness and ventroflexion of the neck associated with intermittent hypokalemia (e.g., < 3.0 mEq/L) and increased serum creatine kinase values, sometimes reaching very high values, e.g., > 50,000 - 90,000 IU/L [129,131]. The condition has also been termed periodic hypokalemic myopathy [132]. Attacks occur suddenly and are transient and may be precipitated by stress or vigorous exercise. The variable clinical course is characterized by improvement followed by relapse, and there may be weeks between episodes. A head tremor is seen in some cats. Cats are reluctant to walk and tire easily, have a stiff, stilted gait with thoracic limb hypermetria, and a wide-based stance in the hind limbs. Carpal knuckling can be a distinctive clinical feature and some cats sink on their hocks [129]. There are only minor electromyographic and histopathologic changes seen in muscle. Neither decreased potassium intake nor increased renal potassium loss have been found in affected Burmese cats. Continued dietary supplementation of oral potassium usually produces a favorable response (e.g., potassium gluconate solution at 2 to 4 mEq or mmol/cat PO daily, until serum potassium levels are stable) [133]. Some kittens improve without treatment. The periodic hypokalemic attacks in these cats are similar to those seen in humans with hypokalemic periodic paralysis, an inherited calcium channelopathy disorder associated with abnormal muscle membrane excitability and influx of potassium into the muscle fiber that causes muscle fiber depolarization and inexcitability [9]. Patients have an increased sensitivity to insulin moving potassium into cells.

Hypothyroid Myopathy

Myopathies have been reported infrequently in mature dogs with primary hypothyroidism [134]. Clinical signs of bilaterally symmetrical flank alopecia and obesity are often associated with the hypothyroidism. Presence of lethargy, weakness, and reduced exercise tolerance in some dogs with chronic hypothyroidism may reflect the underlying myopathy [135]. A polymyopathy has been seen in several dogs with megaesophagus and myasthenia gravis [136]. We have seen myotonic-like discharges in muscles of some hypothyroid dogs on EMG studies [137]. In people, skeletal

muscle changes may precede clinical and laboratory evidence of hypothyroidism [138]. The etiopathogenesis of this endocrine myopathy is unknown. A disturbance in carbohydrate metabolism has been proposed to explain the preferential type 2 fiber atrophy which occurs in human and canine muscle [139]. In hypothyroid people, phosphorus magnetic resonance spectroscopy studies suggested a defect of the high energy phosphate metabolism (lower phosphocreatine recovery rate) reflecting probable mitochondrial metabolism impairment [140]. Muscle glycogenolysis is impaired that may result in fasting hypoglycemia in human patients, and there is net protein catabolism [105]. Atrophic type II fibers are oval or angular in outline and are distributed throughout all muscle fascicles. A deficiency of type II fibers has also been noted in some dogs. Variable fiber hypertrophy may be present and nemaline rod inclusions may be observed in some muscle fibers, especially in type I fibers. No cellular response or myodegeneration is seen and intramuscular and peripheral nerves are normal. In people, internal nuclei may be increased, along with glycogen and mitochondrial aggregates, dilated sarcoplasmic reticulum, proliferating T-system profiles, and focal myofibrillar loss [120]. More recently, muscle fiber cores have been found in needle biopsies in people [141]. Reversal of the myopathy may follow thyroid hormone replacement, although animals with severe neuromuscular signs may have slow or incomplete resolution of signs [142]. The few cases I have seen appear to have been primary myopathies, with no qualitative or quantitative (morphometric) evidence of peripheral nerve changes [134]. This is interesting given the fact that hypothyroid neuropathies comprise a significant proportion of cases seen in my peripheral nerve laboratory (see hypothyroid neuropathy). Some reports of dogs with hypothyroidism and unilateral forelimb lameness along with widespread electrodiagnostic changes in muscles (positive sharp waves, fibrillation potentials) that are not reflected clinically, may be examples of hypothyroid myopathy [143].

Hypotrophic Myopathy

A subclinical myopathy has been reported in pectineus muscles of German Shepherd dogs that is characterized by a retardation in muscle fiber growth particularly of type 2 fibers [144]. It has been suggested that hypotrophy of the pectineus muscle may potentially influence the development of the coxofemoral joint; however, the relationship between pectineal myopathy and subsequent development of hip dysplasia has not been substantiated. Indeed, hip dysplasia can still develop in dogs in which the pectineus muscle has been exercised.

Immobilization Myopathy

A syndrome characterized by pelvic limb hyperextension, generalized muscle atrophy in the affected limb, abducted gait, and a limited range of stifle joint range of motion has been reported in five dogs, four of which were immature [145]. Distal femoral fractures, of traumatic origin, were found in all dogs; four dogs were subjected to limb immobilization in extension for three to seven weeks. Lesions in muscle biopsies included fiber size variability associated with multifocal/diffuse presence of small atrophic fibers, increased prominence of subsarcolemmal nuclei, increased perimysial fibrosis and focal necrosis. These changes were most severe in the vastus lateralis, with less severe changes seen in the biceps femoris and gastrocnemius muscles. Histochemical and morphometric studies demonstrated a significant type 1 fiber atrophy and loss in the vastus lateralis muscles in the limbs with femoral fractures treated by hyperextension. The shortest time period between onset of fracture and the presence of type I fiber atrophy was seven weeks (there was no correlation between the extent of type 1 fiber atrophy and duration of limb immobilization). The pathogenesis of this condition, termed "stiff-stifle syndrome", is not well understood, although immobilization of muscle induces muscle atrophy and this change is especially influenced by the degree of stretch in which the muscle is held. In animals with limb immobilization in extension, the quadriceps muscle group, held in a shortened state, undergoes selective and progressive atrophy. Additionally, joint stiffness may be exacerbated by fibrous adhesions in and around the stifle joint while it is maintained in an extended position. A similar condition occurs in people [146-148]. Experimental studies indicate an increase in numbers of glucocorticoid receptors in immobilized muscles [88]. Prognosis is guarded, as all dogs in our study failed to show clinical improvement after removal of the immobilization device. Breakdown and removal of adhesions by surgical management may result in a return of function of the femorotibial joint. In experimental studies in dogs, a reversible type I fiber atrophy occurred in most restricted muscles and early type II fiber atrophy was seen in a few muscles after trauma and splinting [149]. Multifocal fiber necrosis was the only irreversible change seen after 3 weeks of splinting with or without concurrent muscle trauma. Relative fiber percentages did not change appreciably during splinting or recovery. In this study, the limited joint motion appeared to be related to shortening of the extensor mechanism of the femorotibial joint. Clinical signs similar to the stiff-stifle syndrome are seen in dogs with congenital limb contractures [150]. Interestingly, we did not observe muscle lesions in a dog with a proximal tibial fracture followed by a 3 week period of immobilization.

Ischemic Neuromyopathy

This is a disorder that occurs not infrequently in cats caused by thromboemboli usually associated with cardiomyopathy [151]. While hypertrophic cardiomyopathy has now become the most important cardiac disorder in cats following the discovery of the role of taurine deficiency in dilated cardiomyopathy [152-155], in one review aortic thromboembolism reportedly occurred in approximately 50% of cats with hypertrophic cardiomyopathy, 25% of cats with dilated cardiomyopathy, and 25% of cats with restrictive cardiomyopathy [151]. It has also been seen in a small percentage of

cats with cardiomyopathy associated with excessive moderator bands [156]. In one report on 100 cats with distal aortic thromboembolism [157], the average age was 7.7 years, with the neutered male being overrepresented. Evidence of preexisting cardiac disease was found in 11% of the cases, with murmur or arrhythmia noted in > 50 % of the cases on presentation, and the most frequent underlying disease was hypertrophic feline cardiomyopathy. Cardiovascular disease (cardiomyopathy and thromboembolism) associated with taurine depletion was an unexpected finding in 3 of 6 healthy adult cats during a potassium - depletion study [158].

The cause of the disease and emboli formation in the heart are uncertain, although recent studies suggest a possible role for vitamin B12 and arginine in cardiomyopathy and arterial thromboembolism [159]. Predisposing factors to thrombus formation may include exposed vascular subendothelial tissue, abnormal circulation patterns and heightened platelet activity, and increased blood coagulability [151]. The origin of the embolus is a thrombus, an aggregate of fibrin and platelets attached to an endocardial surface, usually within the left atrium. An embolus breaks loose from the cardiac thrombus and occludes one or more branches of the aorta. The emboli may be carried to any site within the arterial circulation. The most common site of occlusion is the aortic trifurcation. Embolic occlusion at this site obstructs internal and external iliac arteries and the median sacral artery. Emboli which extend into the iliac arteries have been termed "saddle thrombi". A less common embolic site is the brachial artery [160]. Vasoactive substances released from embolic platelet products, such as serotonin, thromboxane A₂, prostaglandins and 5-hydroxytryptamine may impair collateral circulation [161]. Cats of the Persian breed may be at risk for ischemic neuromyopathy [162], although this has been disputed [163].

Clinical signs are acute in onset and usually include pelvic limb pain during the first 24 hours, plantigrade stance, and paraparesis or paralysis. Signs may be unilateral or bilateral. Femoral pulse may be weak or absent, the cranial tibial and gastrocnemius muscles are firm and often painful, and the limb(s) are cool. Distal limb muscles below the stifle are particularly affected. Flexion and extension of both hip and stifle joints and the patellar reflex are usually present, although initially, limb(s) may be held rigidly extended because of ischemic muscle contracture [151]. Pain sensation to noxious stimuli is typically absent in the distal limbs. The nail bed of pelvic limbs is cyanotic. Left forelimb paralysis is seen with brachial artery embolization.

Electrodiagnostic studies reveal an absence of or markedly reduced evoked potentials from interosseous and cranial tibial muscles. Nerve conduction velocities are frequently reduced. Chest radiography may indicate cardiopulmonary disease (pulmonary edema, biventricular failure), and electrocardiographic/echocardiographic abnormalities are common (e.g., increased septal and/or left ventricular free wall thickness) [157,163]. Diagnosis of occlusive vascular disease can be confirmed from an aortogram. Pathologically, changes occur in skeletal muscle and peripheral nerve [164]. Lesions in peripheral nerves begin in the mid-thigh region, with the central fibers in a fascicle being more susceptible than peripheral fibers. The majority of fibers show changes of axonal degeneration, while others have evidence of paranodal/segmental demyelination. In skeletal muscle, ischemic myopathy characterized by focal necrosis, myophagia, internalized nuclei, and occasional mononuclear cell infiltrates, contributes to the clinical signs.

Improvement in nerve conduction velocities and evoked potentials correlates well with return of limb function. Femoral pulses frequently return within 1 to 2 weeks. At present there are no results that show that any treatment of the aortic thromboembolism produces a significantly better recovery than no therapy. Surgical embolectomy does not appear to be warranted; besides, cats with unstabilized cardiomyopathy are definite surgical risks. Use of thrombolytic agents to dissolve the emboli awaits clinical trials. For animals that are in pain, movement should be restricted. Morphine sulfate, at 0.1 mg/kg, subcutaneously, will produce analgesia (without excitement) for 4 hours [151]. This can be repeated every 4 to 6 hours for 2 days. In an attempt to prevent future episodes, affected cats should receive aspirin, at 25 mg/kg PO, every third day, for life. Aspirin inhibits platelet aggregation and preserves collateral circulation. While aspirin might prevent recurrences, it will have little effect on the underlying cardiomyopathy. It has been reported that there is no difference in survival time or rate of recurrence with warfarin vs. aspirin, and that low-dose aspirin (5 mg PO q3d) is an inexpensive option for thromboprophylaxis that seems to be as effective as high-dose aspirin (40 - 162 mg PO q 2 - 4 d) and warfarin [517]. Supportive care for initial cardiac decompensation includes administration of oxygen, diuretics, fluid therapy, glucocorticoids, and external heat [151].

Although the collateral circulation does return in the majority of cases with return of function to varying degrees (some cats with extensive limb necrosis do not recover; others retain dropped hocks) within 6 weeks to 6 months (an increase in nerve conduction studies and evoked potentials may correlate with return of limb function [164]), the long-term prognosis is guarded to poor because of the potential of further thromboembolism. Other potential complications are associated with reperfusion of ischemic tissues and include release of toxic factors such as lactic acid, potassium, and myocardial depressant factor [151]. Thus, the severity of the cardiac disease usually determines prognosis. Limb complications may include necrosis requiring amputation or wound management, and limb contracture [517]. In one retrospective study of idiopathic feline hypertrophic cardiomyopathy, analysis of survival revealed that all cats with thromboembolism were dead 6 months after diagnosis [163]. In another study involving cats with distal aortic thromboembolism, the average, long-term survival in the 37% of cases that survived the initial thromboembolic episode was approximately 12 months, while the remaining cases either died (28%) or were euthanized (35%) [157]. Long-term survival time is reportedly significantly shorter in cats with congestive heart failure during the initial episode [517]. Hypothermia has been associated with poor outcome [517].

Ischemic neuromyopathy secondary to aortic foreign body obstruction have occasionally been reported in cats [165,166].

In one case, in addition to muscle and nerve damage similar to that described above in thromboembolic disease, spinal cord infarction was present in lumbosacral spinal cord gray matter resulting in clinical signs of a lumbosacral syndrome (absent anal tone, bladder incontinence, megacolon, pelvic limb paresis, and flaccid analgesic tail) [165]. Removal of the foreign body by aortotomy was successful in another cat that recovered almost completely within one year after the surgery (external coaptation splints facilitated return of function of the pelvic limbs)[166]. Post-surgical therapy included heparin (100 U/kg IV q4h for 3 days), aspirin (25 mg/kg PO every 3 days for a total of 4 treatments), cefazolin (20 mg/kg IV q6h for 4 days), and methylprednisolone sodium succinate (20 mg/kg IV immediately after surgery and again 6 hours later).

Thromboembolic disease is not common in dogs but may be seen associated with hypercoagulable states, bacterial endocarditis, dirofilariasis, hyperadrenocorticism, neoplasia, cardiac disease (although thromboembolism secondary to cardiomyopathy has not been reported in dogs) [82,151,167-169]. Yet curiously, aortic thromboembolism in dogs has been reported infrequently [82,170-172]. In one report of 36 dogs with aortic thromboembolism, 4 had severe atherosclerosis associated with thyroid disease [170]. Thrombotic occlusion of the distal aorta and/or the iliac arteries in dogs results in signs of pelvic limb weakness, pain and collapse. Diagnosis is based on clinical signs, angiography and ultrasonography. In one report, dogs that survived the acute episode received aspirin in an attempt to prevent recurrence of thrombosis and all regained pelvic limb function [82]. For dogs that survived longer than one month after the acute episode, repeat thrombosis was uncommon. Aortic thromboembolism in dogs carries a more favorable prognosis than feline aortic thromboembolism.

A possible genetic predisposition to femoral artery occlusion occurs in Cavalier King Charles Spaniels [173]. The condition is usually subclinical due to sufficient collateral circulation (femoral pulse may be undetectable unilaterally or bilaterally).

Labrador Retriever Hereditary Myopathy

A degenerative myopathy that is inherited as an autosomal recessive trait has been reported in Labrador Retriever dogs in the United States and United Kingdom, and has been seen in Continental Europe and Australia [174-180,520]. The condition has been called Labrador Retriever hereditary myopathy (LRHM), Labrador Retriever myopathy, type 2 muscle fiber deficiency and muscular dystrophy. The disorder affects male and female dogs and has been seen in animals with both black and yellow coat color. The age at onset and the severity of clinical signs may be variable. Some puppies have clinical signs at 6 to 8 weeks of age. In others, a later onset at 6 to 7 months has been observed. Cases of both early (8 weeks) and late (6 months) onset have been observed within the same litter. In typical cases, clinical signs become obvious at 3 to 4 months of age and include muscle weakness, abnormalities of gait and posture, and decreased exercise tolerance. Severely affected puppies may have a low head posture, with ventroflexion of the neck. The back is arched, and the gait is characterized by short, stilted strides in which the hind legs are often advanced simultaneously in a synchronous, bunny hopping fashion. Clinical signs become more accentuated as the animal tires, and, if encouraged to continue, the puppy may collapse forward with the head and neck to one side. There is no loss of consciousness or cyanosis. Exercise tolerance may be reduced to 20 yards in severely affected animals. Severe tetraparesis, inability to walk, hyporeflexia, and elevated serum CK levels have been seen in two 4 month old littermates [178]. However, mildly affected dogs may be presented because they seem to be "slow" puppies that are less playful than their littermates and less willing to exercise. These dogs may not collapse unless forcibly exercised, at speed, for several minutes. Rest results in some improvement, but the clinical signs rapidly recur on resumption of exercise. Joint posture is often abnormal, with affected dogs having carpal overextension, carpal valgus, splaying of the digits, and a "cow-hocked" stance. As the condition progresses, generalized atrophy of skeletal muscles develops. The proximal muscles of the limbs and the muscles of the head are particularly affected, but in milder cases, the atrophy may not be dramatic. Signs may be exacerbated by excitement or stress and particularly by exposure to cold weather. After exposure to cold, an affected dog may be unable to stand or to lift its head. Moving the animal to a warm kennel usually results in improvement within a few hours. A less common complication observed in adult dogs (some of whom have been pregnant) is the development of a transient megaesophagus. Other sporadic complications that have been observed include the presence of a luxating patella and clinical and radiographic evidence of degenerative joint disease in the hip of one affected dog that was obese. Affected dogs are bright and alert, although often poorly muscled when compared with their normal littermates. Temporal muscle atrophy is often a feature, but cranial nerve functions are otherwise normal. Muscle tone may be normal or reduced. There is no muscle pain on palpation nor dimpling on percussion. Severely affected puppies are obviously weak and may have difficulty wheelbarrowing or hopping, although in less affected puppies, postural testing may indicate no abnormalities. Proprioceptive function is normal, and no sensory deficits have been observed. Tendon reflexes are generally reduced or absent, even in mildly affected dogs with little muscle atrophy. There is no impairment of bladder function and no signs of autonomic nervous system dysfunction.

Serum CK levels may be within normal limits or moderately elevated. Levels may increase following exacerbation of signs after exposure to cold weather but do not reach the levels reported in other degenerative muscle diseases, such as the inherited muscular dystrophy described in Golden Retrievers (see muscular dystrophy). Other routine hematological and blood biochemical parameters are within normal limits. Motor nerve conduction velocities are within the normal

range in affected dogs, and there is no decremental response to repetitive nerve stimulation. On EMG examination, there frequently is spontaneous activity, particularly in the proximal limb muscles, musculature of the head, and the thoracolumbar paraspinal muscles. The most commonly recorded abnormalities are fibrillation potentials, positive sharp waves, and bizarre high-frequency discharges [181]. Myotonic-like discharges and fasciculation potentials are recorded infrequently. EMG changes may be less pronounced in mildly affected dogs and may be difficult to detect in very young dogs. Results of electrocardiographic examination of affected adults and puppies have indicated no cardiac involvement. Despite the abnormal joint posture seen in many affected dogs, there have been no abnormalities on radiography of hocks, carpi, and the vertebral column. In some cases, however, changes consistent with hip dysplasia have been present. A wide range of morphological features may be observed in muscle biopsies from affected dogs. The changes reported include small and large group atrophy, small fibers of both fiber types that tend to have a round rather than angular appearance, occasional fiber type grouping, large numbers of internal nuclei, disturbances in myofiber architecture, necrosis, regeneration, and replacement of muscle fibers with fat and fibrous tissue. Alterations in fiber type percentages are a common finding. In most muscles there is a reduction in the proportion of type 2 fibers (except for the cranial tibial muscle in which an increase in the percentage of type 2 fibers has been noted) [182]. These changes in fiber type proportions appear to become more accentuated as the disease progresses. No abnormalities have been found in brain, spinal cord, or peripheral nerves. Note that similar histological findings have been observed in clinically normal Labrador Retrievers closely related to those with LRHM [520]. It has been suggested that an additional gene or an environmental factor is responsible for expression of the subclinical form of the disease [520].

The underlying pathophysiological mechanisms involved in this disease are still unclear, although the myopathy has genetic, clinical, pathological, and histochemical similarities to the limb-girdle form of muscular dystrophy in people [183]. Myofiber dystrophin staining is normal. However, immunocytochemical and Western blot studies reveal that sarcoglycans, alpha-actinin, dysferlin, and calpain 3 are present in affected dogs [184]. These sarcolemmal and Z-disc (alpha-actinin) proteins have been incriminated in various limb-girdle muscular dystrophies in people [185-187]. Muscle biochemical studies indicate significantly elevated concentrations of sodium, calcium, zinc, copper, and chloride and reduced levels of potassium and magnesium in muscles from affected adult Labrador Retrievers [182]. There is a significant increase in the intracellular water and sodium levels and a concomitant reduction of intracellular potassium content [188]. In addition, a significant decrease in muscle-specific proteins has been identified in the biceps femoris muscle of affected dogs [189]. Also, lipid fluidity of erythrocyte membranes is significantly different in affected Labrador Retrievers [190]. Results of other studies have not supported the hypothesis of a possible vascular defect [191]. Diagnosis is based on signalment, clinical signs, and muscle biopsy data. Prognosis is generally favorable for longevity. In most cases, the clinical signs stabilize between 6 months and 1 year of age. There may be some improvement in ability to exercise, particularly in those dogs with the mildest signs. The atrophy of skeletal muscles persists, however, and although affected dogs may be acceptable house pets, they are not suitable for work. Owners of affected dogs should be warned that stress, including exposure to low temperatures, can result in a dramatic worsening of clinical signs, even in clinically stable adults. The life span of affected dogs does not appear to be directly affected by the condition, although the prognosis for dogs with megaesophagus should be more guarded because of the risk of developing inhalation pneumonia.

There is no definitive treatment for this condition, although various forms of medication have been used. Diazepam, given orally at a dose of 10 mg twice daily, may have some ameliorating effect. Diphenylhydantoin has little effect, and edrophonium chloride may worsen clinical signs. Anabolic steroids have apparently been beneficial in some cases; however, the evidence for this is anecdotal. Low muscle carnitine levels have been found in a few dogs tested suggesting that administration of L-carnitine (at 50 mg/kg PO bid) might be beneficial [192]. Because there is no way of detecting heterozygous carriers at this time, breeders should be advised against breeding from parents or siblings of affected puppies. Molecular studies are currently being undertaken at the Scott-Ritchey research Center, Auburn University College of Veterinary Medicine. There has been a recent preliminary report of a condition termed "canine centronuclear-like myopathy" in Labrador Retrievers in which onset, clinical signs, pathology (including centrally-placed myofiber nuclei) and histochemistry are virtually identical to those seen in LRHM [521]. The authors report that the gene for this condition (CNM gene) is localized on canine chromosome CFA2 and suggest that the disorder is a homologue of the human autosomal centronuclear myopathy. The relationship of this disorder to LRHM, if any, remains to be seen.

Limber Tail

A condition colloquially referred to as "limber tail", "limp tail", and "cold tail" is familiar to people working with hunting dogs, primarily Pointers and Labrador Retrievers [193-198]. The typical case consists of an adult dog that suddenly develops a flaccid tail. The tail either hangs down from the tail base or is held out horizontally for several inches from the tail base and then hangs straight down or at some degree below horizontal. Initially, the hair on the dorsal aspect of the proximal tail may be raised and dogs may resent palpation of the area 3 - 4 inches from the tail base. Affected Pointers almost always have a history of prolonged cage transport, a hard workout the previous day, or exposure to cold or wet weather. Pain may be noted in acute stages of the condition. In cases where people are not familiar with this disease, other conditions such as a fracture, spinal cord disease, impacted anal glands, or prostatic disease have been incorrectly diagnosed. Results of a recent study [193] in 4 affected Pointers showed evidence of coccygeal muscle

damage, which included mild serum elevation of CK early after onset of clinical signs, needle electromyographic examination showing abnormal spontaneous discharges (e.g., positive sharp waves and/or fibrillation potentials) restricted to the coccygeal muscles several days after onset, and histopathologic evidence of muscle fiber damage (fiber size variation associated with multifocal fiber hypertrophy and scattered round/angular fibers many of which were basophilic, internal nuclei, fiber splitting, and mild fat infiltration, and in some instances, diffuse fiber atrophy). Specific muscle groups, namely the laterally positioned intertransversarius ventralis caudalis muscles, were affected most severely. Intramuscular nerves appeared normal. Infrared thermography revealed increased temperatures of the sacrococcygeal area and the entire tail in acute cases, indicative of reduced blood flow possibly associated with local edema, swelling and vascular stasis. Radionuclide perfusion imaging indicated uniform vascular perfusion over the lumbosacral area and tail of one affected dog, however, an area of increased radioactivity (indicative of increased vascularity or perfusion) was seen in the proximal tail caudal to the anus in another dog. No significant abnormalities were seen in the lumbosacral or coccygeal regions using imaging techniques (MRI, CT). The authors suggested the condition may be related to acute compartment syndrome (a condition in people associated with muscle ischemia, pain, pallor, pulselessness, paresthesia, and paralysis [199,200]) caused by tail injury, perhaps from damage associated with eccentric muscle contractions from tails being whipped from side to side. Treatment strategies include rest to allow healing of the muscle damage and short-term administration of anti-inflammatory drugs during the acute stages (anecdotal reports suggest that anti-inflammatory drugs administered within 24 hours of onset hasten recovery) [38]. Prevention is aimed at minimizing predisposing factors, including instituting regular training programs so as to avoid overexertion in unconditioned dogs, and regular stops with exercise when travelling long distances [38]. Prognosis is usually favorable with most dogs recovering spontaneously within a few days to weeks. Less than one half of affected dogs experience a recurrence.

Malignant Hyperthermia

Malignant hyperthermia (MH) is a life-threatening hypermetabolic and contractile condition that is triggered in humans, pigs, dogs and cats by certain anesthetic agents (e.g., halothane and succinylcholine). The underlying defect in calcium (Ca) homeostasis occurs at the level of the skeletal muscle sarcoplasmic reticulum where there is hypersensitive and heightened ligand-gating of the Ca-release channel [201]. The Ca channel is readily opened by certain drugs, such as caffeine and halothane. Caffeine- or halothane-induced muscle contracture develops as a result of sustained increase in cytoplasmic Ca levels and subsequent activation of the actin-myosin contractile proteins. In addition, calcium uptake is reduced. The continuous contraction results in depletion of glycogen stores, hypoxemia, and accumulation of heat, hyperkalemia, lactic acid, and metabolic and respiratory acidosis. In people, as a consequence of severe muscle necrosis, CK levels may rise 100-fold and myoglobinuria and disseminated intravascular coagulation may occasionally occur, which may lead to renal failure [9]. Recent reports indicate that canine malignant hyperthermia is caused by a mutation in the gene encoding the skeletal muscle calcium release channel (RYR1) [23], similar to that found in pigs and humans. Malignant hyperthermia has been reported in various breeds of immature and mature dogs: St. Bernard, Border Collie, Labrador Retriever, Pointer, Spaniel, Greyhound and animals crossbred with Doberman Pinscher [202-207]. MH in some colony-bred dogs is inherited as an autosomal dominant trait [23,204]. Dogs susceptible to MH may be nervous and difficult to handle. Their muscles may be hypertrophic with greater than normal muscle tone and strength. Resting body temperature may be high normal or slightly above and serum CK and aspartate transaminase levels may be mildly elevated. While Greyhounds are often reported with MH, some studies indicate they may not be specifically MH susceptible [208]. MH has been reported only sporadically in cats [209].

Reports of MH in dogs and cats are most often associated with halothane anesthesia. It should be noted that this disorder does not always occur during the first exposure to halothane anesthesia. Clinical signs can include hyperthermia, tachycardia, tachypnea, severe limb rigidity, and trismus, followed by respiratory and cardiac arrest. In some animals, extreme trismus and generalized muscle rigidity occur immediately after death. Succinylcholine and enflurane, but not methoxyflurane, have also been implicated as triggers of MH in the dog. A MH-like episode was reported in a 5 year old Greyhound anesthetized with thiamylal sodium and also given lidocaine for premature ventricular contractions [210]. In another adult Greyhound, two episodes of malignant hyperthermia occurred at 20 and 44 hours post-surgery following anesthesia with fentanyl-droperidol and sodium pentobarbital [206].

Histopathologic features in skeletal muscle tend to be fairly non-specific and include fiber size variation, fiber hypertrophy, and increased numbers of internal nuclei in muscle cells [203]. Occasional perivascular infiltrates of lymphocytes with infrequent perimysial and epimysial neutrophils have also been noted [209]. In some patients, muscle biopsies are normal. Ultrastructurally, there may be loss of mitochondria, presence of moth-eaten fibers, cores, and Z-line streaming. Cardiac histomorphometric parameters are normal in MH-susceptible dogs [211].

Diagnosis of fulminating MH can be suggested by historical data relating to breed or colony susceptibility, and by development of characteristic clinical signs while under or following (see above) anesthesia. Signs may occur after 30 to 300 minutes of halothane exposure.

Prognosis is guarded. Removal of triggering agents and symptomatic treatment (total body cooling, corticosteroids, sodium bicarbonate, intravenous fluids) usually are ineffectual in reversing MH episodes, although hyperventilation with 100% oxygen, stomach lavage with iced water, body surface cooling, and IV administration of cold isotonic saline

solution was successful in one report [202]. Dantrolene is the drug of choice for treating affected animals [212]. It can prevent a malignant hyperthermia crisis or reverse anesthetic-induced MH if given early in the development of the syndrome [213]. A recommended intravenous dosage is 3 to 5 mg/kg. Injectable dantrolene may also be prepared from an oral preparation [214].

In instances where MH is suspected, susceptible animals can safely undergo anesthesia if triggering agents are avoided. Screening tests for animals susceptible to MH include caffeine/halothane-contraction tests (CCT), erythrocyte osmotic fragility test (EOFT), lymphocyte Ca test, and biochemical tests for defective Ca-transport in sarcoplasmic reticulum isolated from skeletal muscle [203,215,216]. Several reports have noted that the initial sign of a MH episode was a rapid increase in end tidal partial pressure of carbon dioxide before any increase in rectal temperature or muscle tone [204,213].

It is now established that the Ca channel may also be triggered by stressors such as excitement, fighting for dominance, and sudden increase in ambient temperature in pigs, and by exercise, in dogs. This exercise-induced hyperthermia has been termed "canine stress syndrome" [203,217] and has been reported in several breeds including an English Springer Spaniel and a Greyhound [218,219]. In susceptible dogs, the stress of moderate exercise can cause a reversible MH-like syndrome characterized by hyperthermia (e.g., 42°C), muscle cramping, dyspnea (labored stertorous breathing), panting (e.g., respiratory rate > 200 breaths/minute), hemoconcentration, hyperlactemia, respiratory alkalosis, and raised levels of muscle enzymes. Similar findings have been reported in Labrador Retrievers following strenuous exercise [220]. Dogs with the exercise-induced hyperthermia are clinically normal but reportedly have a hyperactive temperament [218,219]. Absence of myoglobinuria rules out a diagnosis of exertional rhabdomyolysis. Hypercontracted myofibers have been observed in muscle biopsies [219]. Recovery can be relatively rapid (e.g., within 30 minutes of rest) and this condition may represent "mild aborted malignant hyperthermia" [219]. A suggested diagnostic protocol for animals with canine-stress syndrome includes exercise/challenge testing, EOFT, and serum CK levels [219]. In susceptible animals, CCT and EOFT are not always positive [218]. The halothane-challenge test is likely risk prohibitive. Note that in dogs with exercise-induced hyperthermia, administration of dantrolene prior to exercise may not prevent the stress syndrome occurring [219].

Megaesophagus

This condition refers to esophageal dilatation with absence of effective esophageal peristalsis. Megaesophagus has been termed esophageal achalasia, esophageal dilatation, esophageal hypomotility, and esophageal neuromuscular disease. Both congenital idiopathic (CIM) and acquired forms of megaesophagus occur. Congenital megaesophagus has been reported in Great Danes, German Shepherds, Irish Setters, Newfoundlands, Shar Peis, and Greyhounds. The condition occurs as an inherited disease in Wire-Haired Fox Terriers (autosomal recessive) and Miniature Schnauzers (autosomal dominant or 60% penetrance autosomal recessive). A suspected hereditary form has been reported in Bouvier des Flandres dogs (see Bouvier des Flandres myopathy) [2]. Idiopathic megaesophagus is also reported in cats [221-223], with a predisposition noted in Siamese and Siamese-related breeds [222]. The congenital form is usually apparent in animals around the time of weaning. Less commonly, adult-onset idiopathic megaesophagus may be detected [224]. Readers should refer to other texts for more information on megaesophagus associated with obstructive esophageal disease such as neoplasia, granulomas, vascular rings, strictures, periesophageal masses, and foreign bodies.

Acquired megaesophagus may occur in dogs or cats at any age, although in one study, older (mean = 8 years), heavier dogs were at risk, including German Shepherds, Golden Retrievers and Irish Setters [225]. In many cases, the cause is unknown; however, the condition has been observed in association with certain systemic neuromuscular disorders such as myasthenia gravis, botulism, hypoadrenocorticism (associated with glucocorticoid deficiency with or without concurrent mineralocorticoid deficiency), polymyositis, dermatomyositis, myotonic myopathy, nemaline myopathy, polyradiculoneuritis, distemper, giant axonal neuropathy (German Shepherds), tick paralysis, lead toxicosis, thallium toxicosis, canine and feline muscular dystrophies and dystrophy-like conditions, laryngeal paralysis-polyneuropathy complex, dysautonomia, glycogen storage disorders, feline mannosidosis, sensory ganglioradiculitis, and spinal muscular atrophy [136,225-231]. In acquired myasthenia gravis in dogs, megaesophagus may be the only clinical sign. It has also been reported sporadically in canine pituitary dwarfs, dogs with tetanus, and Labrador Retriever puppies with familial reflex myoclonus [227]. In one report, megaesophagus was noted in English Springer Spaniels with a polysystemic disorder comprising dyserythropoiesis, polymyopathy, and cardiac disease [232]. Megaesophagus may also occur with bilateral vagal nerve damage due to surgery, trauma, or neoplasia as well as with various brainstem lesions - neoplasia, distemper encephalitis, granulomatous meningitis/meningoencephalomyelitis, trauma, and infarction [233]. It has also been observed in dogs secondary to tiger snake envenomation [536]. It has been stated that the relationship between hypothyroidism and megaesophagus has yet to be established [225,539]. In one report, megaesophagus was found in 5 dogs with hypothyroidism and myasthenia gravis [136].

The pathogenesis remains elusive. Megaesophagus may result from lesions involving the esophageal muscle, or afferent/efferent pathways controlling esophageal motility [226,234]. Afferent pathways include esophageal sensory

receptors, afferent fibers in the vagus nerve and its branches (e.g., cranial laryngeal nerve), and the solitary tract/nucleus complex. The efferent limb of the reflex comprises the vagus nerves (including special visceral efferent axons from the nucleus ambiguus and general visceral efferent fibers from the parasympathetic vagal nucleus), neuromuscular junction, and esophageal muscle (primarily skeletal, with less involvement of smooth muscle) [234,235]. Electrolytic lesions of the nucleus ambiguus in dogs and of the parasympathetic nucleus of the vagus in cats produce esophageal dysfunction similar to the clinical syndrome [236]. A reduction of the normal number of neuronal cell bodies in the nucleus ambiguus has been recorded in clinically affected dogs, but not in affected cats [237,238]. These neuroanatomical differences between dogs and cats with megaesophagus probably relate to differences in proportion of striated and smooth esophageal muscle between the two species [226,235]. In one study in 12 week old Chinese Shar Peis with CIM, no histological lesions were found in the nucleus ambiguus or parasympathetic nucleus of the vagus, or in ganglion cells of the myenteric plexus [239]. CIM appears to be associated with loss of peristaltic function in the esophagus due to developmental immaturity of innervation and/or musculature [240]. Based upon studies of upper and lower esophageal responses to intraesophageal balloon distension, CIM was considered to be at least partly due to a faulty afferent component of the reflex neural pathway that controls swallowing [241]. Seemingly consistent with this finding, more recent studies on dogs with CIM showed no electrophysiological evidence for segmental demyelination or axonal degeneration in cervical vagal motor fibres innervating striated muscle of the thoracic esophagus portion and no EMG abnormalities indicative of esophageal muscle denervation or primary myopathy [242]. Additionally, demonstration of a normal Hering-Breuer lung inflation reflex is consistent with an organ specific, selective vagal afferent dysfunction in dogs with CIM [538]. Note that few cases of megaesophagus appear to be related to disturbances of gastroesophageal sphincter function [226]. In one study, resting caudal esophageal sphincter pressure was similar in clinically normal dogs and in dogs with congenital or acquired idiopathic megaesophagus [243].

Clinically, megaesophagus is characterized by postprandial regurgitation of undigested food, with radiographic evidence of megaesophagus, usually to the level of the diaphragm. Abnormal esophageal motility may be demonstrated by contrast radiography/fluoroscopy. In some dogs, respiratory signs such as cough, dyspnea and/or abnormal secretions may be the only signs observed.

Prognosis of congenital megaesophagus in young dogs is guarded. Some animals appear normal by the time they mature, based on radiographic, manometric, and clinical examination, while others show no clinical improvement with time.

Acquired, idiopathic megaesophagus generally has a poor prognosis for recovery [226], although transient megaesophagus followed by spontaneous recovery has been reported occasionally in dogs [178,224]. The prognosis for secondary megaesophagus varies with the underlying cause, for example, cats with megaesophagus and dysautonomia have a poor prognosis, while clinical improvement has been noted in dogs following treatment of the primary disease process, e.g., myasthenia gravis, hypoadrenocorticism, hypothyroidism, botulism, tetanus, and lead poisoning [226,231,244-246,537]. Cachexia becomes an important complication and death is a common consequence of inhalation pneumonia. Recommended management includes elevated feeding and/or gastrostomy tube feeding of high caloric diets [227,240]. Surgical treatment remains controversial. Pharmacological management, using drugs that relax the gastroesophageal sphincter or increase strength of esophageal contractions, has been disappointing [226], although sildenafil, a phosphodiesterase-5 inhibitor, is reported to have profound effects on esophageal motility in cats by modifying propagation and amplitude of esophageal contractions [247]. Nifedipine, a calcium channel blocker, resulted in temporary clinical improvement (2 months) in an adult German Shepherd with megaesophagus [248].

Mitochondrial Myopathies

A myopathy has been reported in young Clumber and Sussex Spaniel puppies (male and female) in which clinical signs are usually seen with the introduction of lead training - about 3 months of age [249-253]. Animals tire easily, pull back on the leash, and collapse in sternal recumbency. Animals attempt to rise only after 10 to 15 minutes. During this time, excessive panting and tachycardia are noted. Animals appear thirsty and remain depressed for about an hour after each episode. Tensilon testing for myasthenia gravis is normal. Serum CK levels, along with EMG studies and nerve conduction velocities are normal [253]. Blood biochemical studies reveal a metabolic acidosis (nonhypoxic) in arterial blood samples due to elevated levels in lactate and pyruvate (resting levels are higher than normal and both increase dramatically above the levels expected following exercise), presumably leading to clinical weakness and muscle cramping. This metabolic disorder is believed to be associated with abnormal mitochondrial function. Biochemical studies showed that muscle mitochondria were unable to oxidize pyruvate (via the tricarboxylic acid cycle/Krebs cycle) due to a deficiency of pyruvate dehydrogenase (PDH) [249,251]. Recent studies have confirmed PDH deficiency in cultured fibroblasts from one affected Clumber Spaniel [253]. In this report, lactic acidemia with a lactate to pyruvate ratio < 10 was considered diagnostic for PDH deficiency. The etiology remains unknown, although the condition appears to be inherited (note that interbreeding between Clumber and Sussex Spaniels has occurred in the past). Treatment should be aimed at reversing the acidosis. More recently, a suggested treatment protocol includes a high fat and low carbohydrate dietary regimen, in conjunction with L-carnitine (50 mg/kg PO bid) and thiamine (100 mg daily) may improve exercise tolerance [253]. Prognosis appears guarded as dogs may die suddenly following exercise from cardiac arrest (presumably related to the metabolic acidosis).

A similar condition has been reported in two male Old English Sheepdog littermates (presented at 1 year of age and 2.5 -

years of age, respectively) with a history of clumsiness since 3 months of age [254]. Other signs included reluctance to play rigorously, and progressive exercise intolerance. Muscle biopsy data revealed scattered myonecrosis, ragged red fibers characterized by reddish-purple subsarcolemmal stain using modified Gomori's staining and dark blue subsarcolemmal deposits using the oxidative stain NADH-TR, empty sarcolemmal tubes, fibrosis, vacuolated fibers, and marked increase in numbers of internalized nuclei. Ultrastructural findings included scattered myofibrillar disruption, increased numbers of mitochondria, and increased myofibrillar glycogen. Electromyographic studies revealed increased insertional activity and complex repetitive discharges. Nerve conduction velocities were normal. Arterial blood analysis immediately after exercise showed a high anion gap metabolic acidosis associated with lactic acidosis and increased pyruvate levels, elevated lactate/pyruvate ratio, along with dramatic increase in serum CK, alanine aminotransferase, and aspartate aminotransferase activity. A subsequent biochemical study using fibroblasts and skeletal muscle from one of the affected dogs demonstrated a partial deficiency in cytochrome oxidase [255], suggesting that the exercise intolerance and elevated lactic acidosis resulted from impaired mitochondrial oxidative phosphorylation and reduced pyruvate usage. In skeletal muscle from the affected dog, reduced activity of two additional mitochondrial inner membrane enzymes (i.e., ATPase and NADH-ferricyanide reductase) was also found. Empirical treatment with vitamin C (at 10 mg/kg, daily), a drug considered to be useful in people with mitochondrial myopathy caused by complex III deficiency, had little effect in either dog.

More recently, similar clinical and pathological findings were reported in a 4 month old Jack Russell Terrier [256]. In this dog, exercise intolerance was progressive so that by 10 months of age, it could walk for only about 30 meters before collapsing. The dog was able to resume walking after a short rest (30 seconds). The muscle changes were worse at 10 months of age (increased numbers of ragged red fibers and increased fiber size variation associated with marked muscle fiber atrophy). While serum CK values were slightly increased, serum biochemical studies revealed a lactic acidosis before and after feeding, along with increased fasting level of pyruvate and a marked increase in the post-feeding lactate/pyruvate ratio (the pyruvate levels decreased to normal range after feeding). While mitochondria in this dog appear to be structurally normal, the authors regarded the blood biochemical findings to be consistent with a defect in the electron transport involved in oxidative phosphorylation, or in the enzyme pyruvate decarboxylase. Electrophysiological studies (nerve conduction velocities, EMG) in this dog were normal.

Exercise intolerance leading to ataxia and collapse within 15 minutes of strenuous activities is encountered in some working young-adult Labrador Retrievers [257] suggesting possible abnormal muscle oxidative metabolism. In a controlled study using healthy Labrador Retrievers, only brief periods of strenuous exercise were required to produce a marked increase in rectal temperatures, significant increase in arterial blood pH and oxygen partial pressure, significant decrease in arterial blood bicarbonate levels and carbon dioxide partial pressure, and marked increase in plasma lactate and pyruvate levels (the lactate/pyruvate ratio, however, remained normal) [220]. In this study, the metabolic acidosis were unassociated with clinical weakness or collapse. Similar metabolic changes have been noted in healthy racing Greyhounds [258-260]. The condition in the Labradors may be another example of exercise-induced hyperthermia (see Canine Stress Syndrome).

A lipid storage myopathy characterized by abnormal accumulations of lipid droplets (using lipid stains such as oil red O or Sudan black), localized predominantly in type 1 fibers, have been reported in male and female dogs of various breeds and ages with signs of myalgia, weakness, and muscle atrophy [261,262]. The occurrence of lactic acidemia, hyperalaninemia, lactic and pyruvic aciduria, variably increased urinary excretion of carnitine esters, and muscle carnitine deficiency suggested a metabolic block in mitochondrial oxidative metabolism. Recommended treatment for affected dogs includes L-carnitine (50 mg/kg, PO bid), coenzyme Q (100 mg PO daily), and riboflavin (100 mg PO daily) [262].

Note that mitochondrial dysfunction is considered to play a role in other myopathies, including hypothyroid myopathy and hyperadrenocortical (Cushing's) myopathy. Mitochondrial abnormalities (ultrastructural and abnormal biochemical respiration characteristics) were found in Irish Terrier puppies with possible X-linked inherited myopathy characterized by stiff gait, lumbar kyphosis, and dysphagia [263] and in older Golden Retrievers with muscular dystrophy [264] (see muscular dystrophy). Abnormal mitochondria within neuronal perikarya and axons are a feature of mitochondrial encephalomyelopathy in dogs [265]. In people, mitochondrial myopathies are a complex and heterogeneous group seen in most diseases of oxidative phosphorylation [266]. The mitochondrial abnormalities are due to defects in the respiratory chain enzymes associated with mitochondrial DNA deletions [7]. Ultrastructural abnormalities in mitochondria may involve the number, size, or shape of mitochondria, and there may be changes in the patterns of the cristae and/or presence of crystalline or osmiophilic inclusions [120].

Muscular Dystrophy

The muscular dystrophies are hereditary, degenerative dystrophinopathies and disorders of dystrophin-associated proteins. Dystrophinopathies are those muscular dystrophies in which there is a defect in the dystrophin gene (the cause of Duchene muscular dystrophy) [4]. Dystrophin binds to a complex of proteins and glycoproteins called dystrophin-associated proteins and dystrophin-associated glycoproteins. Muscle dystrophin occurs on the plasma membrane surface in skeletal muscle fibers, on plasma membrane and transverse tubule surfaces of cardiac muscles, and on smooth muscle

membranes. This membrane-associated protein is thought to help maintain membrane integrity. Dystrophin is a member of the spectrin superfamily of proteins. Dystrophin itself is closely related to three proteins that constitute a family of dystrophin-related proteins (DRP): utrophin, DRP2, and dystrobrevin [267]. There are several subcomplexes that form the glycoprotein complex involved with dystrophin [4,268]:

- a. The dystroglycan complex that consists of α - and β - dystroglycans and forms the dystrophin-axis. The basal membrane of each muscle fiber contains several components including laminin, a subunit of which, merosin (also called laminin α 2), is bound to α - dystroglycan, which binds to the cysteine-rich and carboxyl-terminus domains of dystrophin. Merosin is also found in the basement membrane of Schwann cells of peripheral nerves (see congenital muscular dystrophy, below). The N-terminus domain of dystrophin is bound to actin filaments forming the cytoskeleton of the subsarcolemma. The dystrophin homologue, utrophin, is believed to bind to actin and the dystroglycan complex.
- b. The sarcoglycan complex that appears to be fixed to dystrophin axis in skeletal and cardiac muscles. There are four of these transmembrane glycoproteins: α -sarcoglycan (also called 50DAG, A2, and adhalin), β -sarcoglycan (43DAG, A3b), γ -sarcoglycan (35DAG, A4), and δ -sarcoglycan.
- c. The syntrophin complex α , β 1, and β 2 that binds to the distal part of the carboxy-terminal domain of dystrophin.

Perturbations in these proteins and glycoproteins result in several types of muscular dystrophy in people, as well as in dogs and cats.

Canine Muscular Dystrophy -

Dystrophinopathies as exemplified by Golden Retriever muscular dystrophy have received considerable comparative interest because of their similarities to Duchenne muscular dystrophy (DMD) in people [269-272]. Molecular biology studies have shown that the Golden Retriever canine model is genetically homologous to DMD and its molecular basis has been described [273]. This degenerative myopathy in dogs, which has received the most attention of the canine "models" of human disease so far, has an X-linked inheritance (in which the disease is expressed in males and carried by females) and has been termed canine X-linked muscular dystrophy (CXMD). The genetic symbol *xmd* was proposed for this canine mutation [272]. Mutations in the DMD gene lead to disturbances in dystrophin expression, and this protein also is lacking in skeletal and cardiac muscle of affected dogs. Dystrophic muscle has also been shown to exhibit abnormal sarcolemmal expression of utrophin [274], but not of laminin [275]. Histopathological studies of skeletal muscle from affected Golden Retrievers reveal pronounced fiber size variation associated with atrophy and hypertrophy, endomysial and perimysial fibrosis, internalization of nuclei, marked hypercontraction, and segmental necrosis of muscle fibers with phagocytosis and regeneration (basophilic fibers), and increased levels of intracytoplasmic calcium [264,271]. Fibrosis may be mediated by fibrogenic cytokines, particularly transforming growth factor-beta1 [528]. Differential skeletal muscle involvement has been noted [276,277] while studies of postnatal muscle changes have shown that muscle damage occurs before completion of muscle maturation in dystrophic dogs, that necrosis and hypercontraction appear stable in adults but fiber regeneration declines, and that muscle fibrosis does not increase with age [278,527]. In CXMD dogs, there is a selective loss of fibers expressing fast myosin and persistence of immature developmental fibers [279]. Histochemical studies indicate a predominance of type I fibers in many muscles, and occasional fiber type grouping [264]. Ultrastructurally, there is dilatation of the sarcoplasmic reticulum, focal subsarcolemmal areas of degeneration, Z-band streaming and duplication, mitochondrial accumulation, and presence of nemaline rods (especially in older dogs) [264]. No abnormalities have been found in the central or peripheral nervous systems [276].

Clinical signs are first observed in affected male dogs from 6 to 9 weeks of age. These include stunting, weakness and gait abnormalities (e.g., stiff, stilted shuffling gait with abduction of elbows and bunny hopping in pelvic limbs), exercise intolerance, marked muscle atrophy of temporal, truncal, and limb muscles, fibrosis, and contractures by 6 months of age (semimembranosus and semitendinosus muscles may be hypertrophied). Other signs may include plantigrade stance, inability to fully open the jaw, progressive enlargement of the base of the tongue, signs of pharyngeal and esophageal dysfunction and excessive salivation, and weak bark. Skeletal deformities including variable lumbar kyphosis that may develop into lordosis by 1 year of age and curvature of the costal arch may also be seen, along with various muscle/limb conjectures [280,281]. Spinal reflexes may be diminished later in the disease. Clinical signs slowly progress during the first 6 months of life and then tend to stabilize [280]. Signs of inhalation pneumonia and congestive heart failure have been noted in older dogs and a lethal neonatal form has been recognized in some puppies [280].

Serum CK levels are markedly elevated and affected puppies can be identified by 1 week of age. CK levels reportedly peak at 6 to 8 weeks of age, just before onset of overt clinical signs [280]. After this time, CK levels plateau at approximately 100 times normal values. Serum CK levels do not show a clear correlation with clinical severity. Serum levels of muscle enzymes (CK and aspartate aminotransferase), as well as alanine aminotransferase activity, are increased after exercise [282], suggesting that in the absence of dystrophin, exercise-induced muscle injury may play a role in the dystrophic process [283]. Electrodiagnostic testing reveals pseudomyotonic discharges, especially in dogs over 10 weeks of age. Myotonic discharges may also be present but are less frequent. Positive sharp waves and

fibrillation potentials are not commonly noted. Flash electroretinographic abnormalities have been recently detected [284,529] that suggest a dysfunction in the rod signaling pathway. Prognosis is guarded to poor. At present, there is no effective treatment; however, potential strategies for gene therapy (including chimeraplast-mediated gene repair for dystrophin mutations) and bone marrow transplantation are being pursued at several institutions with variable success [267,285-288,526,530]. Treatment by nitric oxide donors (argenine and molsidomine) failed to modify the evolution of the disease in one study [523]. Molecular testing now provides rapid, accurate diagnosis of carrier and affected Golden Retrievers [289,290].

Females with the X-linked muscular dystrophy (produced from carrier female x dystrophic male breedings) manifest milder clinical signs compared to the males, but with similar CK levels and comparable histological lesions [264,281]. Results of breeding studies indicate that obligate female carriers of CXMD usually have no clinical evidence of disease although CK levels may be mildly elevated [280]. In skeletal muscle of carrier animals, dystrophin is expressed in a mosaic pattern with normal dystrophin-staining fibers muscle interspersed with severely affected fascicles and negatively-staining fibers, but as animals mature, dystrophin staining becomes more homogeneous and the number of negative-staining fibers declines [291]. In a recent developmental study, calcium- and albumin- positive fibers observed in carrier dogs, always expressed dystrophin abnormally [278], while utrophin was absent from muscle fiber surfaces in 2 day old animals, present between 15 and 30 days, and disappeared by 60 days [279]. Variable loss of dystrophin, dystrophin-associated proteins, or laminin $\alpha 2$ deficiency has also been identified in female purebred and mixed-breed dogs in whom variable clinical signs were seen (including generalized weakness, exercise intolerance, muscle hypertrophy/atrophy, and limb deformities) along with variable CK levels (ranging from normal to high values) [292]. Histological changes included fiber size variability, degeneration/regeneration, and fibrosis.

Similar muscular dystrophies/dystrophinopathies have been reported in several canine breeds, including Rottweiler [293], German Shorthaired Pointer [294], Irish Terrier [295], Belgian Groenendaeler Shepherds [296], Samoyed [297], Miniature Schnauzer [298], Brittany Spaniel [299], Rat Terrier [300], and Labrador Retrievers [301,522]. We have seen similar pathological findings in a 4.5 month old, male, Welsh Corgi presented with stiffness, apparent muscle enlargement, and extremely high CK levels. Electromyography revealed diffuse, pseudomyotonic, bizarre high-frequency discharges in skeletal muscles. Prominent muscle changes were characterized by moderate/pronounced fiber size variation associated with atrophic (round, some angular) and hypertrophic fibers, scattered as well as in groups, multifocal necrosis, macrophage infiltration (positive acid phosphatase staining), multifocal fibers with internal nuclei, multifocal mineralization, fiber splitting, basophilia, and fibrosis. Histochemical staining showed involvement of both type 1 and type 2 fibers, although there appeared to be a type 2 fiber loss in some fascicles. There was also fiber type grouping. Immunocytochemical staining revealed an absence of dystrophin staining in myofiber sarcolemmal membranes. Spectrin staining was normal. An attenuated form of canine dystrophinopathy has also been reported in Japanese Spitz dogs in which staining was absent against the rod domain of dystrophin but not against the carboxy terminus, suggesting possible similarities to Becker's muscular dystrophy in people [302]. Labrador Retriever Hereditary Myopathy has genetic, clinical, pathological, and histochemical similarities to the limb-girdle form of muscular dystrophy in people, although a recent study [184] demonstrated that the canine disease was not due to a deficiency of alpha-actinin (a Z-disc protein that may be implicated in some forms of autosomal dominant limb-girdle muscular dystrophy in people), or any of the known autosomal recessive limb-girdle muscular dystrophy proteins identified in people, namely the sarcoglycans, dysferlin and calpain 3 [187]. A muscular dystrophic-like condition has also been reported in Bouvier des Flandres (see Familial Dysphagia) and in three related young English Springer Spaniel dogs with regurgitation from an early age [232] associated with slowly progressive temporal muscle atrophy with partial trismus, and generalized skeletal muscle atrophy. All dogs exhibited moderate dyserythropoietic anemia, polymyopathy (histological evidence of muscle fiber size variation and internalized nuclei without regeneration/inflammation) with megaesophagus, and varying degrees of cardiomegaly. The cause of this condition was not determined. In the English Springer Spaniels, EMG changes (fibrillation potentials) were patchy and there was no increase in serum CK levels.

Distal myopathies are a form of muscular dystrophy that occur rarely in people and are characterized by progressive muscular weakness and atrophy that starts in the hands or feet. Several types have been identified: late adult onset type 1 (autosomal dominant); late adult onset type 2 (autosomal dominant); early adult onset type 1 (autosomal recessive); early adult onset type 2 (autosomal recessive); and early adult onset type 3 [303]. Dysferlin, a sarcolemmal-associated protein, is absent in the early adult onset type 2 form (Miyoshi myopathy) although dystrophin and other dystrophin-associated proteins are normal in these patients [304]. Serum CK levels may be very high while nerve conductions are normal. A distal myopathy (termed juvenile-onset distal myopathy) has recently been reported in young Rottweilers (male and female) from three different litters in California (2 of the puppies were littermates) presented for decreased activity and various postural abnormalities, including plantigrade and palmigrade stance and splayed forepaw digits [305]. These clinical signs were seen in some puppies as early as 3 weeks of age. Neurological examination was normal. EMG studies revealed rare fibrillation potentials and positive sharp waves. While motor nerve conduction velocities were normal, compound muscle action potentials from the interosseous muscles were decreased. Serum CK levels were normal or

mildly increased. Histopathologic changes (more prominent in distal muscles) included myofiber atrophy with mild myonecrosis, endomysial fibrosis and replacement of muscle with fatty tissue. While plasma and muscle carnitine concentrations (total and free) were low in most puppies, the significance of this finding is uncertain but may be related to the degenerative process (metabolic testing did not reveal abnormalities in any intermediary metabolites). Dystrophin immunocytochemistry was normal. The condition in these dogs is considered to be inherited.

Feline Muscular Dystrophy -

Muscular dystrophy-like disorders in cats have been reported in the Netherlands, Germany, and the US [306-309]. To date, all cats have been male, suggesting an X-linked inheritance. Clinical signs may be first seen in cats about 5 to 6 months of age and include generalized skeletal muscle hypertrophy, excessive salivation, reduced exercise tolerance, stiff gait and bunny-hopping when running, difficulty in jumping, adducted hocks, cervical rigidity, vomiting/regurgitation, and partial protrusion of the tongue. Multifocal lingual calcification (submucosal), hepatosplenomegaly, and megaesophagus have been noted in some cats [308]. Based on the clinical features, including the extensive muscle hypertrophy, the term "hypertrophic feline muscular dystrophy" has been proposed for this condition [308]. Serum CK levels may be markedly increased, often accompanied by variably elevated levels of aspartate aminotransferase and alanine aminotransferase. Atrial and ventricular dilatation, left ventricular wall thickening, and papillary muscle hypertrophy have been detected in echocardiographic studies. Notching of R waves has been noted with electrocardiographic testing. Electromyographic studies of skeletal muscles reveal bizarre high frequency discharges (also called complex repetitive discharges), sometimes interspersed with positive sharp waves [309,310]. Motor nerve conduction velocities are normal. Necropsy examination has shown severe hypertrophy of the diaphragmatic musculature, and enlargement of muscles of the tongue and larynx. Pathological findings are similar to those described for dystrophic dogs and include muscle fiber hypertrophy (involving both type 1 and type 2 fibers), fiber splitting, accumulation of calcium deposits within muscle, myonecrosis and phagocytosis (mononuclear cell infiltrates may be seen), hypercontracted fibers, numerous internalized nuclei, and occasional fiber type grouping. Aging studies have shown a significant decrease in the number of type 2A myofibers and increase in numbers of type 2X fibers in younger dystrophin-deficient cats [311], with an apparent loss of type 1 fibers in older cats [312]. Endomysial or perimysial fibrosis is not a feature in axial or appendicular muscles. Immunoblotting and immunofluorescent studies have shown marked dystrophin deficiency in skeletal muscles [307-309], although, a small percentage of fibers may stain positive [311]. Molecular studies have demonstrated deletion of the dystrophin muscle promoter in affected cats [313]. No histological lesions are seen in carrier females despite presence of a mosaic staining pattern for dystrophin in skeletal muscle (irregular staining in most myofibers or absent staining in rare fibers) [311]. Mineralization, fibrosis, and myodegeneration have been seen in cardiac muscle of some affected cats. Ultrastructural changes in skeletal muscle include distention of the sarcoplasmic reticulum and the T system, swollen mitochondria, and Z-band streaming. Prognosis is guarded in cats because of the development of diaphragmatic and lingual hypertrophy which potentially leads to megaesophagus, insufficient water intake, dehydration, hyperosmolar syndrome (see hypernatremia), and acute renal failure [308]. Another potential complication is rhabdomyolysis, possibly associated with increased sensitivity of the dystrophin-deficient sarcolemmal membrane to volatile anaesthetic agents, stress, or intense muscular activity. In one report, 3 dystrophin-deficient cats developed peracute, lethal rhabdomyolysis following either isoflurane anesthesia or manual restraint for a procedure) [312]. Serum chemistries revealed severe hyperkalemia, hyperphosphatemia, hypocalcemia, massive increases in CK, aspartate aminotransferase, and alanine aminotransferase concentrations, and high ion gap metabolic acidosis. Skeletal muscle changes included severe acute hyaline necrosis and endomysial edema without infiltration of inflammatory cells.

Congenital Muscular Dystrophy - A novel muscular dystrophy has recently been reported in cats associated with deficiency of merosin (laminin α 2) [314]. Laminins are large glycoproteins found in the basement membrane of a variety of tissues, including skeletal muscle fibers and Schwann cells of peripheral nerves. Clinical signs in the cats beginning around 6 months of age included progressive muscle weakness, muscle atrophy, and extraordinary muscle contractures resulting in rigidity and extension of the pelvic limbs in one cat. The second cat was non-ambulatory and hypotonic/hyporeflexive in all limbs. Serum CK levels were markedly elevated. Histological muscle changes were characterized by marked endomysial fibrosis, myofiber necrosis, variability of fiber size, and perimysial lipid accumulation. In both cats, immunohistochemical labeling showed complete absence or marked reduction in staining against laminin α 2. However, staining for dystrophin and all the components of the dystrophin-associated glycoprotein complex were present and normal. In one cat studied, motor nerve conduction velocity was decreased, and demyelination and vacuolar Schwann cell degeneration were observed in peripheral nerves. No abnormalities were seen in the CNS and there was no evidence of cardiomyopathy. The disease was considered similar to primary or secondary merosin (laminin α 2)-deficient congenital muscular dystrophy in people.

Myositis

The incidence of myositis appears to be increasing in dogs and cats. Although several forms of myositis have been described in animals, a precise classification has not been established at this time. In this section, the different types of

myositis are listed, based upon anatomical and/or etiological factors. Some forms of myositis have been shown to be immune-mediated, some are suspected of being immune-mediated, others are infectious, and some remain idiopathic [315-317]. These myopathies share common histological features including presence of inflammatory cell infiltrates (the hallmark of myositis/polymyositis) and various degenerative changes in the muscle fibers. Note that inflammatory cells are also sometimes seen in muscles of animals with muscular dystrophy. Also note the caveat that "... absence of any inflammatory infiltrates in a biopsy does not exclude an inflammatory myopathy" [120].

Masticatory Myositis -

This inflammatory myopathy (synonym is eosinophilic myositis) is one of the most common forms of myositis in dogs and is particularly common in adult, larger-breed dogs [318-322]. Results of one retrospective study indicated that most dogs were under 4 years of age with no gender or breed predilection [321]. This disease is characterized by recurrent inflammation of muscles, especially those of mastication (masseteric, temporalis, and pterygoid muscles), sometimes in association with peripheral blood eosinophilia. In most instances, the condition is restricted to muscles of mastication. This is an autoimmune disease in which B-lymphocyte-mediated antibodies are directed against type 2 M fibers in masticatory muscles. Type 2 M fibers are the dominant fiber type in masticatory muscles [323,324]. Biochemical studies have shown that masticatory muscles contain a unique myosin isoform, unique myosin light chains, and unique myosin heavy chains [325]. In one study of dogs with masticatory myositis, 86% of cases had autoantibodies fixed to type 2 M fibers of the temporalis muscle [326]. Incubation of normal muscle with sera from affected dogs resulted in labeling of 82% of type II M fibers. Immunocytochemical studies suggest that transforming growth factor-beta (TGF-beta) and latent transforming growth factor-beta binding protein (LTBP) may play a role in muscle tissue repair, inflammation and fibrogenesis in masticatory myositis [327].

Lesions consist of myonecrosis, hemorrhage, edema and multifocal or diffuse cellular infiltrates including macrophages, lymphocytes, plasma cells, occasional neutrophils, and rarely, eosinophils. Skeletal muscle fiber atrophy involving all fiber types may be pronounced, sometimes with foci of small round fibers comprising entire muscle bundles [321]. Fiber hypertrophy is usually not a feature. Perimysial and endomysial fibrosis is usually marked. Regeneration of muscle fibers, characterized by vesicular nuclear changes and fiber basophilia is frequently found.

Clinical signs are characterized by acute onset of painful, swollen, masticatory muscles. The jaw is held partially open (pseudotrismus) and passive manipulation is painful. Unilateral or bilateral exophthalmos may also be present [319], which in some cases may cause optic nerve compression or stretching resulting in blindness [321]. Dogs are often febrile, and tonsils and mandibular lymph nodes may be swollen. The acute phase may last 2 to 3 weeks, with signs reaching a peak by 10 to 14 days. Serum CK levels are elevated early in the disease and gamma globulin levels may be increased. Diagnosis is based on signalment, clinical, and muscle biopsy data, although histological demonstration of antibodies against type 2M fibers is also a sensitive index (the antibody titer may be reduced if corticosteroids have been administered previously). Prognosis is usually favorable. In most cases, the acute disease responds to corticosteroids, e.g., prednisone 1.0 to 2.0 mg/kg PO bid. The dose is reduced after remission of signs, and gradually withdrawn using alternate day therapy. Note that the lowest alternate-day dosage may be required for up to 6 months [317]. Repeated clinical episodes are not uncommon, which usually result in muscle atrophy. In one study, better clinical responses were noted in dogs receiving prednisone early in the course of the disease, for at least one month, and with the dosage tapered gradually from the initial immunosuppressive dosage [321]. Other immunosuppressive drugs such as azathioprine (at 0.6 mg/kg PO every one to three days) may also be used in conjunction with prednisone, with a steroid-sparing effect, or alone, to maintain remission. There is no apparent correlation between response to treatment and the extent/severity of the muscle lesions. Note that manual manipulation of the jaw carries an inherent risk of mandibular luxations/fractures [321]. In some severely affected dogs, there may be a permanent inability to adequately open the jaw, necessitating blending of the food for intake/ingestion [317].

Recently, a masticatory myositis has been reported in dogs with leishmaniasis (*Leishmania infantum*) [328] (see infectious myositis).

I have observed masticatory myositis in several cats and an autoimmune process is suspected. Note that many tissue samples received in our laboratory from dogs with suspected masticatory myositis have evidence of neurogenic atrophy with little or no sign of inflammation. These cases probably represent idiopathic trigeminal neuritis.

Atrophic Masticatory Myopathy/myositis -

This is a chronic degenerative myopathy that is characterized by atrophy of muscles of mastication which can occur in dogs of any breed [329,330]. It has also been termed atrophic myositis and cranial myodegeneration. The pathogenesis of this condition is uncertain. It may be a stage of masticatory myositis or it might represent neurogenic atrophy secondary to idiopathic trigeminal neuritis associated with severe axonal degeneration. In some dogs with leishmaniasis, severe masticatory muscle atrophy may be present [331] (see infectious myositis). Atrophic masticatory myopathy may also be prominent in younger dogs with dermatomyositis. There is no peripheral or local eosinophilia present. The atrophy is accompanied by a state of trismus (lock-jaw) which may not be reduced, even under general anesthesia, and which may interfere with eating (although this is not a feature seen in dogs with leishmaniasis). Pathological studies reveal large numbers of atrophic fibers and increased perimysial connective tissue. Focal areas of lymphoplasmacytic infiltrates may

be seen occasionally in masticatory and other skeletal muscles.

Prognosis of this form may be guarded because of the severe trismus. However, in most dogs jaw function returns to normal. Some animals appear to respond to corticosteroids. Note that bilateral masticatory muscle atrophy may be seen in some cats with nemaline myopathy.

Polymyositis -

Polymyositis is a relatively common myopathic disorder in dogs, but less common in cats. It has been suggested that polymyositis, masticatory myositis and other clinical variations, such as pharyngeal-esophageal and focal appendicular myositis, may represent different clinical and pathological expressions of a single primary muscle inflammatory disease [332]. The cause of polymyositis in dogs is not always known, although the responsiveness of the disease to immunosuppressive therapy suggests that the pathogenesis is immune-mediated. In people with polymyositis, the pathogenesis appear to involve cell-mediated immune mechanisms, with the inflammatory cells being mainly CD8+ T cells [333]. Polymyositis has been reported in dogs with specific autoimmune diseases, including systemic lupus erythematosus [334], primary lymphocytic thyroiditis, and immune-mediated polyarthritis (see below). Furthermore, it has been seen as an autoimmune paraneoplastic complication of thymoma, usually accompanied by myasthenia gravis [335,336]. Polymyositis and myasthenia gravis have also been reported in a dog following fetal liver transplant (see myasthenia gravis) and immunological mechanisms were considered to be involved [337]. Polymyositis is also a feature of dermatomyositis in Collie dogs and Shelties, another suspected immunological disease (see dermatomyositis). Clinical signs are variable and are usually observed in larger breed, mature adults of either gender; however, there are reports in younger animals, including two 7 month old littermates [338]. Onset of signs may be acute or chronic. Signs may include acute vomiting and excessive salivation, weakness of gait with rapid fatigue, megaesophagus, dysphagia, shifting lameness and/or stiffness of gait, muscle swelling and/or pain, pyrexia, muscle atrophy, voice change and depression. Some dogs show signs of cervical ventroflexion [317]. Neurological examination is usually normal. Early in the disease, serum levels of CK, aspartate aminotransferase, alanine aminotransferase may be elevated but may not reflect the severity of clinical signs or the underlying muscle pathology (see below). Total serum protein may be elevated associated with increased β - and γ -globulin fractions. Some animals have positive antinuclear antibodies and circulating antimuscle antibodies. Electrodiagnostic changes include polyphasic motor unit potentials, positive sharp waves, and fibrillation potentials. Motor and sensory nerve conduction velocities are normal. Histopathological findings in skeletal muscle (appendicular and masticatory) are focal/multifocal or diffuse myonecrosis, phagocytosis and lymphoplasmacytic cellular infiltrates, endomysial/perimysial fibrosis, considerable fiber size variation, and areas of fiber regeneration. Rarely, eosinophilic cells may predominate [339]. Deposition of immunoglobulin G (but not C3 component) on sarcolemmal membranes has been demonstrated [340]. In dogs with polymyositis associated with leishmaniasis, IgG immune complexes are detected in muscle samples [328].

Diagnosis is based on clinical signs, increased serum levels of muscle enzymes, electromyographic abnormalities, and histopathological evidence of muscle necrosis and inflammatory cell infiltrates. Not all of these criteria may be found in any one animal. Diagnosis is definite if all criteria are present, probable if three are present, and possible if two are found [229]. Muscle enzyme activity is an unreliable index of polymyositis.

Prognosis is usually favorable for animals with polymyositis, provided inhalation pneumonia is not a complication, and severe damage has not occurred in esophageal and laryngeal muscles. The disease is usually responsive to corticosteroids, e.g., prednisolone at 1 to 3 mg/kg PO sid or bid. The dose is reduced after remission and gradually withdrawn using alternate day therapy. In some instances, long-term therapy for 12 months or longer may be required. Azathioprine may also be used in combination with corticosteroids and has a steroid-sparing effect [341]. Repeated clinical episodes are not uncommon. A fentanyl patch (25 - 50 μ g/h) for pain relief during the first 2 to 3 days has been recommended [317]. Prognosis is guarded in animals with thymoma because of the potential for malignancy and occurrence of other non-thymic tumors.

A connective tissue disorder characterized by non-erosive polyarthritis and polymyositis has been reported in 6 young adult dogs [518]. Clinical signs included stiffness, joint swelling, joint pain, muscle atrophy, muscle pain and contracture and the presence of chronic active inflammation (lymphocytes, neutrophils, macrophages, and plasma cells) in biopsies of muscle and synovium. There was no muscle fiber immunofluorescence. Systemic lupus erythematosus was excluded by the absence of circulating antinuclear antibody. 5 of the dogs were of Spaniel breeds. Prognosis was poor with only 2 dogs recovering after treatment with cyclophosphamide (2 mg/kg on 4 days each week) and prednisolone (1 mg/kg/day) for 2 months. In another report, however, 2 dogs with this condition (signs included lethargy, exophthalmos, muscle pain, and atrophy of masticatory/appendicular muscles) responded favorably to immunosuppressive corticosteroid therapy [519].

Polymyositis occurs sporadically in cats [342], sometimes in association with thymoma [343]. The inflammatory infiltrates are predominantly mononuclear, with small lymphocytes and macrophages. Neutrophils are seen infrequently. Eosinophils are rare. A polymyositis has also been observed in cats usually over 1 year of age, without breed or sex predisposition [117], and while the cause was not defined, many affected cats were hypokalemic (see hypokalemic myopathy). Pathological findings included myonecrosis, lymphocytic cellular infiltrates, internal nuclei and fiber

regeneration. Clinical signs were characterized by a persistent ventroflexion of the neck, appendicular weakness especially in the thoracic limbs, painful muscles and exercise intolerance. Serum levels of CK and aldolase were elevated. Electromyography revealed fibrillation potentials, positive sharp waves and bizarre high-frequency waves. Prognosis was guarded. Some cats recovered spontaneously while others appeared to respond to corticosteroids. Recurrences were observed.

We have seen suspected immune-mediated, mononuclear polymyositis in muscles of several cats, including samples from one cat with myasthenia gravis and thymoma. In muscle samples from another cat with myositis, numerous muscle fibers stained positively with staphylococcal protein A-horseradish peroxidase.

Extraocular Myositis -

This condition has been reported in dogs aged between 6 months and 3 years [344-346]. It appears to be more often reported in Golden Retrievers, but other breeds include Doberman Pinscher, German Shepherd and mixed-breed dogs. Male and female dogs may be affected. The dominant clinical sign is acute bilateral exophthalmos, although unilateral involvement has been noted. Extraocular muscle myositis and restrictive strabismus (unilateral or bilateral) has been reported in 11 dogs of different breeds [346,347]. Clinically, abnormalities are restricted to the extraocular muscles with sparing of the masticatory muscles and limb muscles. An immune mechanism directed against specific muscle fiber antigens in the extraocular muscles is suspected. Direct and indirect pupillary reflexes and fundic examination are normal. Visual impairment may be present and intraocular pressure may be elevated [344]. Swelling of extraocular (extrinsic) muscles may be detected using ultrasonography or computer tomography [346]. EMG studies reveal presence of fibrillation potentials and positive sharp waves. Fine needle aspirate biopsies can be diagnostic. In one study, macroscopic findings were confined to the extraocular muscles, the central zones of which appeared swollen and pallid, while microscopically, there was severe lymphocytic inflammation with variable, mild plasmacytic, neutrophilic and eosinophilic infiltrates, multifocal necrosis, phagocytosis, basophilia, internalized nuclei, slight fibrosis, and occasional foci of hemorrhage [344]. No abnormalities were seen in blood vessels or nerves.

Oral corticosteroid therapy for two weeks usually results in complete resolution of signs. Relapses may occur but usually respond well to a second treatment. No dogs exhibit clinical signs of hypothyroidism. Surgical correction may restore eye position and vision in dogs with restrictive strabismus [347].

Dermatomyositis -

Dermatomyositis or familial canine dermatomyositis is a well documented disease of Collie dogs, of all coat colors and both coat lengths. Dermatomyositis has also been reported in the Shetland Sheepdog (Sheltie), Beauceron Shepherd, Pembroke Welsh Corgi, Australian Cattle dog, Lakeland Terrier, Chow Chow, German Shepherd, and Kuvasz [348-355]. The condition is considered to be inherited as a dominant trait with variable expressivity in Collies and in Shetland Sheepdogs [355,356]. Cutaneous lesions involving the face, lips, ears, and skin over bony prominences of the limbs, feet, sternum, and tip of the tail are noted usually between 2 and 6 months of age. Male and females can be affected. Other clinical signs range from generalized weakness and exercise intolerance, to difficulty in lapping water, chewing and swallowing. Megaesophagus may lead to inhalation pneumonia. Generalized or localized muscle atrophy may be noted, especially of muscles of mastication and distal limbs. Cutaneous pain is often seen in Beucerons.

Dermatomyositis is an inflammatory disease of muscle and skin, and sometimes blood vessels. The cutaneous lesions consist of pustules, ulcers, and vesicles which may progress rapidly to crusted or alopecic areas. Myositis develops several months later and principally involves muscles of mastication and muscles of the extremities below the elbow and stifle. The muscle lesions appear to be correlated with the severity of the skin lesions. Muscle lesions consist of multifocal muscle fiber necrosis, internalization of muscle nuclei, atrophy, fibrosis, and regeneration, and mild to severe interstitial and perivascular inflammatory cell infiltrates (lymphocytes, neutrophils, plasma cells, and macrophages). Small intrafascicular nerves may be surrounded by inflammatory cells. Vasculitis is seen in skin, muscle, and occasionally in other tissues. Necrotizing vasculitis of small venules and arterioles is characterized by fibrinoid thickening of the vessel wall, pyknosis and karyorrhexis of endothelial cell nuclei, and neutrophilic inflammation [357]. In many cases, the lesions spontaneously regress by 6 to 8 months of age, although severely affected dogs may have dermatitis throughout their lives. Differential diagnosis of the skin lesions includes demodicosis, dermatophytosis, staphylococcal folliculitis, epidermolysis bullosa simplex, and discoid lupus erythematosus [355].

This condition is believed to be immune-mediated, although some clinicians favor an infectious etiology [358]. Others have suggested it is a subset of lupus erythematosus [359]. A type III hypersensitivity reaction may be involved in the pathogenesis [357]. Autoantibodies to muscle or skin have not been demonstrated, and antinuclear antibody titers and lupus erythematosus cell testing are negative. Coombs' test may be positive. There is a dramatic increase in serum concentrations of IgG and circulating immune complexes, which may be detected before clinical signs and which show a positive correlation with disease severity, and which decline as animals enter remission [357]. There is no deficiency of complement (C3, C2, C4, or CH50) [360]. In people with dermatomyositis, the capillary lining is thought to be the target of the circulating immune complexes, and perifascicular muscle atrophy may be a consequence of ischemic changes secondary to endomysial vasculopathy [333]. Non-regenerative anemia due to chronic inflammation may occur in severely affected dogs. CK levels are usually normal but may be increased. Cerebrospinal fluid analysis and nerve

conduction studies are normal. The presence of fibrillation potentials, positive sharp waves, and bizarre high frequency discharges has been demonstrated electromyographically.

The cyclic and self-limiting nature of this disease complicates treatment evaluation. Rarely, affected adult dogs may die from acute renal failure as a result of severe secondary amyloidosis [361]. Hypoallergenic shampoos are beneficial. Prognosis tends to be guarded, especially in severely affected dogs. Prednisolone, at 1 to 2 mg/kg PO bid, may be effective in some animals [355]. If improvement is seen, the dosage should be tapered to alternate day therapy. Vitamin E (200 - 800 U daily PO) or marine lipid supplements may be useful in refractory cases. Pentoxifylline may be included as a corticosteroid-sparing drug. (at 200 - 400 mg q24 - 48h). Dogs with disease remission by 1 year of age tend to have a good prognosis [357]. Note that muscle disease may progress as skin lesions regress leading to severe muscle atrophy in some older dogs, and with potential problems in eating and drinking due to masticatory muscle atrophy.

Myositis Ossificans -

Myositis ossificans or ossifying myopathy, perhaps a misnomer (see below), is an uncommon myopathic disorder of animals that is characterized by heterotopic ossification of skeletal muscle. Local and generalized forms of this disease have been reported in dogs and cats [46,362-364]. The etiopathogenesis is uncertain. Trauma may be associated with localized, ossifying myopathy [46,365], but it is not a prerequisite. Focal masses have been reported adjacent to the zygomatic arch and near the coxofemoral joint in dogs. The generalized form in people is suggested to be congenital or hereditary in nature.

Histopathological lesions of focal myositis ossificans in animals vary from mild interstitial fibrosis, to complete replacement of muscle by fibrous tissue and heterotopic bone. In one report, the mass was well circumscribed with fibrous tissue around the periphery, then cartilage, and cancellous bone with bone marrow/fibrous tissue centrally [366] (this may have been a case of heterotopic osteochondrofibromatosis). Focal masses need to be differentiated from extraskeletal osteosarcomas [367]. The generalized form is characterized by fibrosis, muscle fiber degeneration, mononuclear myositis, muscle atrophy, dystrophic calcification, and ossification [363]. Clinical signs of the focal form are usually associated with lameness. In one dog with a focal mass near the zygomatic arch, the jaw could not be opened more than 3 cm. In the generalized form, signs are variable and may include progressive weakness, swollen muscles, muscle pain, stiffness, and palpable firm enlargements in affected muscles. We have seen generalized myositis and calcification in muscle samples from a 4 year old female Domestic Shorthaired cat with a history of relapsing weakness. Muscles were firm, serum CK levels were very high, and myoglobinuria was noted. Electromyographic testing revealed diffuse abnormal potentials that were more severe in proximal muscles. Muscle lesions were characterized by diffuse mineralization (calcium deposits that stained positively with Alizarin Red), disseminated necrosis and phagocytosis, mononuclear cell infiltration, and fibrosis. At necropsy, multifocal white areas were observed in most skeletal muscles. The cause of this apparent generalized myositis ossificans was not determined.

Radiographic studies of myositis ossificans may reveal focal or multiple soft tissue radiopacities of irregular linear calcification, along with variable periosteal reactions [363,368]. Prognosis is guarded in animals with generalized myositis ossificans; however, surgical excision of focal masses has been performed successfully [366,368]. In some cases, focal lesions may regress. In people, the more generalized form of myositis ossificans may be seen as a complication of dermatomyositis in childhood [7].

As mentioned above, the term "myositis ossificans" may be too simple, or even incorrect, in some reported cases in animals. For example, another condition seen occasionally in cats, termed fibrodysplasia ossificans, differs from myositis ossificans in that it does not primarily involve muscle, is multicentric, often symmetrical, and unrelated to trauma [369-371], and Valentine and colleagues [372] have included the above-mentioned cases of generalized myositis ossificans, progressive ossifying myositis, and fibrodysplasia ossificans under the category of fibrodysplasia ossificans progressiva (FOP). Absence of muscle fiber lesions and lack of abnormal EMG findings in some animals are more commensurate with a primary connective tissue disorder associated with fibrovascular proliferation, chondroid and osseous metaplasia in epimysium, tendons/ligaments, or fasciae, than a primary defect of skeletal muscle (any muscle changes present may be secondary to the connective tissue disease) [372]. In people, FOP is an extremely rare hereditary disorder (autosomal dominant) of connective tissue characterized by progressive heterotopic ossification of the tendons, ligaments, fasciae, and striated muscles [373]. Other forms of heterotopic calcification in dogs occur with calcinosis circumscripta/tumoral calcinosis. Recently, bilateral cervical heterotopic ossification associated with a thoracic limb lameness, was reported in an adult German shepherd dog [374]. Hard, non-painful masses were palpable under the cranial border of the scapula in both forelimbs. Radiographs revealed two mineralized densities ventrolateral to the lateral processes of the 6th cervical vertebra. These lesions appeared to be adjacent to the tendons of insertion of the longissimus cervicis muscles that attach to the lateral processes of the 6th cervical vertebra. The lameness resolved following surgical removal of one of the masses. The lesion was classified morphologically as fibrodysplasia ossificans, and it was postulated that the heterotopic ossification resulted from the metaplastic change of calcinosis circumscripta lesions.

Laryngeal Myositis -

I have seen myositis in laryngeal muscles of several dogs (a 7 year old male Boykin Spaniel; a 10 year old male Malamute; and a 3 year old Bouvier des Flandres) presented with signs of chronic laryngeal paralysis and dysphagia.

Laryngeal muscle changes included multifocal myonecrosis, phagocytosis, mononuclear cell infiltrates, and variable fibrosis. Intramuscular nerve bundles appeared normal although there was mild evidence of neurogenic atrophy in laryngeal muscles of all three dogs. Electromyographic studies on laryngeal and/or esophageal muscles revealed fibrillation potentials, positive sharp waves, and high frequency, bizarre discharges. With the exception of mild, focal inflammation seen in temporalis muscle from one dog, pathological and electrodiagnostic changes were restricted to laryngeal / pharyngeal muscles. Laboratory tests were normal in all dogs. The etiopathogenesis, treatment and prognosis of this condition remain to be determined. Prognosis is guarded to favorable: one dog was euthanized because of respiratory distress, a castellated laryngoplasty was performed on one dog, and the third dog that was marginally hypothyroid, responded to thyroid hormone replacement and corticosteroids.

Infectious Myositis -

Infectious myositis is most commonly seen in dogs with several protozoan diseases, including hepatozoonosis and toxoplasmosis and neosporosis. Myositis also occurs with trypanosomiasis. More recently, myositis has been reported with leishmaniasis, an endemic protozoan disease in Mediterranean countries and Portugal that is caused by *Leishmania infantum* [328,331]. The disease usually occurs in older dogs (with a range from 1.5 to 10 years) and affects dogs of either gender and of various breeds. Clinical signs include skin lesions (e.g., exfoliative dermatitis and skin ulcerations) and atrophy of the masticatory muscles. In some dogs, there is also appendicular muscle atrophy. The masticatory atrophy tends to be insidious, slowly progressive, usually unassociated with trismus. Exercise intolerance, megaesophagus, or gait disturbances are not seen. In some dogs, the myositis is subclinical. Serum CK levels are often elevated, especially in those dogs with severe muscle atrophy. EMG studies reveal positive sharp waves, fibrillation potentials, and bizarre, high frequency discharges. Nerve conduction studies are normal. Histological changes in muscle include myofiber necrosis, degeneration, regeneration, with varying degrees of atrophy, along with fibrosis, interstitial and/or perivascular mononuclear cell infiltration (macrophages, lymphocytes, occasional plasma cells), and neutrophilic vasculitis, sometimes with mild to severe thrombosis. Leishmanial amastigotes are frequently seen within macrophages and skeletal muscle cells. IgG complexes are found within myofibers and also on the sarcolemma, and circulating antimuscle antibodies are found in serum. While the exact pathogenesis of the muscle lesions remains uncertain, the immunological findings suggest at least partial immune-mediated pathology. Other muscle changes might be related to ischemia secondary to vasculitis/thrombosis. The vasculitis is considered to be the result of a type III hypersensitivity reaction.

Prognosis is guarded. Note the zoonotic potential for leishmaniasis. Treatment is complicated due to resistance to therapy of *Leishmania* organisms; however, allopurinol (at 7 - 15 mg/kg PO bid for 26 weeks) has been recommended, although complete recovery is rarely achieved [375].

Bacterial myositis is reported sporadically in dogs and cats. Normal muscle in people is resistant to bacterial infection and suppurative myositis is rarely seen [376]. Polymyositis associated with *Leptospira australis* infection was documented in a 10 year old male greyhound [377]. Signs included fever, severe back pain, arched back and semiflexed limbs, and reluctance to stand. Neurological examination was normal. Electromyography revealed generalized abnormal spontaneous potentials. Serum CK levels were markedly elevated. Other findings included red colored urine (attributed to the presence of myoglobin), neutrophilia, and positive titer for *L. australis*. Clinical signs abated somewhat with non-steroidal inflammatory anti-inflammatory medication and amoxicillin. Polymyositis has also been seen with *Leptospira icterohaemorrhagiae* [378]. There are several reports of clostridial myositis (e.g., associated with *C. chauvoei* and *C. septicum* infection) in dogs and cats, often in association with muscle wounds/injuries, or surgical procedures [379-385]. Pain, swelling, and lameness may be seen with limb involvement. Grossly, crepitant swelling, subcutaneous edema and black, emphysematous muscles are often found. Histologically, hemorrhages, congested vessels, myofiber necrosis, and variable neutrophilic infiltration is seen in affected muscles [381].

Treatment usually requires radical surgical aeration, along with appropriate antibiotics, e.g., clavulanate potentiated amoxicillin at 22 mg/kg PO bid for 5 - 7 days, in combination with metronidazole, at 10 mg/kg PO bid or tid (dog) (or 62.5 mg, PO bid for cats) for 5 - 7 days, and allowing healing by secondary intention [379]. Less frequently, myositis may occur with migrating parasites and rickettsial disease (also see rickettsial meningoencephalitis) [386,387].

Trichinosis myositis associated with *Trichinella spiralis* has been observed in a 6 year old female Fox Terrier used for badger hunting with signs of acute onset weakness [388].

Viral myositis appears to be rare in dogs and cats; however, an inflammatory myopathy was experimentally-induced in adult cats using feline immunodeficiency virus [389]. The predominant histologic abnormalities consisted of perivascular and pericapillary lymphocytic infiltration (CD8+ lymphocytes), myofiber necrosis, phagocytosis, and regeneration.

Paraneoplastic Myositis -

Low-grade myositis is seen sporadically in dogs with malignant tumors, such as bronchogenic carcinoma, myeloid leukemia, and tonsillar carcinoma [378,390] and it is thought to represent a paraneoplastic complication (see paraneoplastic syndromes).

Drug-induced Myositis -

A polymyositis reportedly occurred in several Doberman Pinschers as part of a multisystem allergic drug reaction (type III hypersensitivity) following treatment with sulfadiazine [391]; although supporting evidence from electrodiagnostic studies or muscle biopsies were not provided.

Myotonic Myopathy

Myotonia refers to a state in which active contraction of a muscle persists after cessation of voluntary effort or mechanical/electrical stimulation. This condition is characterized by muscle spasm (stiffness) and by temporary inability to initiate movement. Myotonia may be clinically observed, noted during EMG studies, or both. Reduced muscle membrane chloride conductance leading to membrane hyperexcitability, after-depolarization and repetitive firing, is the underlying mechanism responsible for congenital myotonia in children (including both the autosomal dominant Thomsen's disease and autosomal recessive Becker's disease) [9,392]. A similar chloride channelopathy occurs in goats with Thomsen's disease [393,394]. Paramyotonia congenita (autosomal recessive) is one of several recently classified sodium channelopathies in people [395,396]. In contrast, dystrophic myotonia (myotonic dystrophy or Steinert's disease) is an adult-onset, non-channelopathy, autosomal dominant, multisystem degenerative disease occurring in people characterized by myotonia, progressive muscular weakness, gonadal atrophy, cataracts, and cardiac dysrhythmias [4]. Myotonia is also sometimes seen in human patients with hyperkalemic periodic paralysis (see hyperkalemic myopathy) associated with a sodium channelopathy [9]. Congenital and acquired forms of myotonia have been reported in dogs, and congenital myotonia has been seen in cats. Congenital myotonic myopathy (myotonia congenita) has been reported in male and female Chow Chows, Staffordshire Terriers, Great Danes, and Miniature Schnauzers [397-407]. These conditions are considered to be inherited (probable autosomal recessive in Chows and Staffordshire Terriers), although results of breeding trials await confirmation. Spontaneous mutations are likely in the sporadic cases reported. However, in the Miniature Schnauzer puppies, the myotonia congenita is autosomal recessive and caused by a mutation in the skeletal muscle voltage-dependent chloride channel, CIC-1 [407,408]. A multisystem membrane defect associated with low serum cholesterol was suggested in Chow Chows [400]. Congenital myotonia has also been reported in male and female kittens [409-411]. The condition in cats is thought to be inherited and the disease is currently being investigated. Clinical signs in puppies may be seen as early as 2 to 3 months of age. Signs include stiffness in the first movements after a period of rest, splaying of thoracic limbs, and a bunny hopping pelvic limb gait. Dogs will remain in rigid hyperextension in lateral recumbency for up to 30 seconds if they are suddenly rotated onto their sides. Affected dogs may not be able to climb stairs or mount raised platforms. Some dogs may manifest dysphagia and respiratory difficulty from stenosis of the glottis. Laryngeal paralysis was noted in the Miniature Schnauzers. Stiffness and weakness largely disappear with exercise. Most skeletal muscles can be hypertrophied, especially proximal limb muscles, neck muscles and tongue. Signs are worse in cold weather. In older animals, an increasing period of exercise is necessary for muscle relaxation to occur. Percussion of muscles results in formation of dimples. This reaction is elicited in conscious and anesthetized dogs, and in those administered neuromuscular blocking agents. In kittens, the gait is also stiff and stilted (limbs tend to be abducted), especially in the hind limbs, and signs are also worse in cold weather and improve with exercise [410,411]. There may be marked non-painful enlargement of proximal appendicular muscles. When startled, all four limbs become extended and kittens fall into lateral recumbency. Other signs seen on being startled include third eyelid prolapse, spasm of the orbicularis oculi muscle, lip retraction, and ear flattening. Masticatory muscle spasms may result in trismus, which may lead to dysphagia. Dysphonia and inspiratory stridor (sometimes with cyanosis) is seen occasionally. Some kittens have a coarse meow. Electromyographic studies in dogs and cats are characterized by trains of repetitive discharges which wax and wane in frequency, producing an audible "dive-bomber" or motorcycle sound. These myotonic discharges are independent of neural control and persist even under general anesthesia [412]. A regional curare test for evaluating muscle discharges without subjecting animals to general anesthesia has been reported [413]. Motor and sensory nerve conduction velocities are normal. Myopathic changes are mild and typically non-specific with occasional fiber hypertrophy, centralized nuclei, and focal necrosis. Histochemical stains and dystrophin immunocytochemistry are normal in dogs and cats. A deficiency in type I fibers has been reported in Staffordshire Terriers [399]. Mild dilatation of transverse tubules have been seen in affected kitten muscle by electron microscopy [410]. No abnormalities are seen in peripheral nerves. Serum creatine kinase levels are normal or slightly elevated. Hypocholesterolemia has been reported in one affected Chow Chow [400], while serum cholesterol levels were normal in kittens [411]. Diagnosis is based on signalment, clinical and electrodiagnostic data. Prognosis is guarded, although myotonia congenita does not appear to be progressive. Membrane stabilizing agents including procainamide (at 40 mg/kg PO qid) and mexiletine (at 8.3 mg/kg PO tid), as well as quinidine and phenytoin, may result in significant improvement in clinical signs [406]. These drugs act by blocking voltage-dependent sodium channels thereby decreasing membrane excitability (drugs acting on the chloride channel are not presently available). Note that these membrane stabilizing drugs have a high risk of side-effects in cats [411]. To date, no treatment has been necessary in the affected kittens (close supervision is advised, however). Anesthesia may also be a risk in affected animals due to difficulty in endotracheal intubation associated with an inability to open the mouth to a wide angle, enlargement of the tongue and pharyngeal muscles, or narrowing of the glottis due to muscle spasm or paralysis [400,406,410,411]. Potassium bromide may be contraindicated in dogs with myotonia congenita [414].

Adult-onset myotonic myopathy has been reported as an idiopathic condition in several dogs, including a 3 year old Rhodesian Ridgeback dog [415], a 3 year old Boxer [416], and 11 and 13 year old female Poodles [417]. Clinical signs and electrodiagnostic findings are similar to those seen in dogs with myotonia congenita. Serum CK levels are elevated. Histopathological changes tend to be much more obvious, and these may include fiber size variation, fiber splitting, occasional myonecrosis, many fibers with internalized nuclei, and type I fiber deficiency. Note that similar changes have been noted in adult dogs with myotonia congenita. Immunohistochemical staining is positive for dystrophin [416]. No changes are seen in peripheral nerves. Clinical (e.g., weakness, stiff gait with short stride, tonic extension of all limbs and falling, palpably firm skeletal muscles and myotonic dimpling) and electromyographic evidence of myotonia has been observed in dogs exposed to herbicides containing 2,4-dichlorophenoxyacetic acid (2,4-D) or 2-methoxy-3,6-dichlorobenzoic acid (dicamba or MCPA), and serum CK levels may be markedly elevated [418-421].

Secondary myotonia occurs in several other myopathic disorders in dogs, including hyperadrenocortical (Cushing's) myopathy, hypothyroid myopathy, Labrador Retriever hereditary myopathy, and the dystrophinopathies in dogs and cats (see muscular dystrophy). In these conditions, electrophysiological evidence of myotonic-like discharges may be seen and heard [72,75,137,174,181,263,295,309,398,412,413,422]. However, since these discharges typically do not wax and wane, they have been termed "pseudomyotonic" or "bizarre high frequency discharges" [412]. An overlap of true myotonic and pseudomyotonic discharges may occur in some instances. For example, Duncan and colleagues reported that of 5 dogs with Cushing's disease, waxing and waning discharges were recorded in four dogs, and pseudomyotonic potential in one dog [71]. Curiously, myotonic discharges that waxed and waned were noted in one study of dogs with fibrotic myopathy [36]. Note that clinical myotonia may occur secondary to Cushing's disease in some dogs, with signs including stiffness, muscle hypertrophy, muscle dimpling, rigid epaxial muscles, arching of the back, ears drawn back, and tongue protrusion [71,72,75,417].

Nemaline Myopathy

In people, nemaline myopathy is a disorder characterized morphologically by the presence of rods (nemaline bodies) in muscle cells. Various forms of the disease have been reported, including congenital, childhood-onset and adult-onset, and both autosomal dominant and autosomal recessive cases have been documented [423]. Three genetic mutations have been identified as the cause of nemaline myopathy: the gene for slow alpha-tropomyosin 3, the nebulin gene, and the actin gene. Nemaline myopathy appears to be most commonly associated with the autosomal recessive form caused by mutations in the nebulin gene [424]. The pathogenesis of nemaline myopathy is still unclear although recent molecular genetic studies suggest that rod formation is secondary to contractile dysfunction [425]. The main component of the nemaline bodies is α -actinin [426]. Nemaline myopathy has been infrequently reported in animals. In 1986, Cooper and associates reported on nemaline myopathy in 5 cats, of either gender, derived from 4 litters from the same mother, thus suggesting possible autosomal recessive mode of inheritance [427]. Clinical signs were observed in cats (a specific breed was not reported) between 6 months and 1.5 years of age. Cats appeared extremely apprehensive. Signs included mild weakness, reluctance to move, and a crouched, jerky hypermetric gait when prompted to move. Following a short period of movement, some cats appeared fatigued and panted. In some animals there was skin twitching and muscle atrophy (especially in scapular and gluteal muscles, and occasionally, in masticatory muscles). Patellar reflexes were consistently depressed or absent. Other spinal reflexes, along with sensation, were normal. Electrodiagnostic studies and cerebrospinal fluid analyses were normal, although mild increase in serum CK and lactate dehydrogenase levels were seen in some cats. Prognosis was poor. Clinical signs persisted for up to a year after signs first began, but did not appear to progress. However, muscle atrophy did progress, and cats became inappetent, lost condition, and were eventually euthanized. Pathological findings were characterized by presence of large numbers of nemaline rods in skeletal muscle fibers (while all muscles examined were abnormal, the changes were most apparent in the proximal forelimb muscles), marked fiber size variation, atrophy of type 1 and type 2A fibers, internalized nuclei, and fiber splitting. In some muscles, core-like lesions were seen characterized by disorganization of the internal structure producing a swirling pattern and particularly evident on NADH-TR-stained myofibers. Rods stained red with trichrome stain and were aligned along the long axis of muscle fibers (in some instances measuring up to 5.7 μ m in length). Rod numbers varied from a few to many (that filled some fibers) and were in subsarcolemmal or central locations. Rods were most common in atrophic type 1 and type 2A fibers. Predominance of type 1 fibers, typically a feature of the human disease [428,429], was not observed. Ultrastructurally, there was myofibrillar disarray. Rods were electron-dense and showed bi-directional periodicity (approximately 17 nm along the axis and 8 nm transversely) in longitudinal sections, and a lattice-like arrangement in cross-sections. Rods appeared to arise from Z-bands and the smallest rods consisted of localized expansions of the Z-band. No lesions were seen in extraneural tissues, brain, spinal cord, or peripheral nerves. Nemaline rods have been experimentally-induced in cats by tenotomy [425]. Congenital and adult-onset nemaline myopathies have also been reported in several dogs, including a 12 week old female Silky Terrier [230], a 10 month old Border Collie, an 11 year old Schipperke with a 5 year history of gait abnormalities [430]. Clinical signs are somewhat variable but may include exercise intolerance and limb tremors, stiff-stilted gait (in hind limbs or in all four limbs), and spasmodic limb jerking. In some instances, a plantigrade stance has been noted in the thoracic limbs, there may be generalized muscle hypertrophy, and sometimes absence of patellar reflexes along with decreased withdrawal reflexes. In one affected dog,

there was a history of dysphagia/choking, the tongue was protruded, and the dog assumed a "begging" position after mild exercise [230]. EMG changes in these young dogs were usually mild (occasional fibrillation potentials and positive sharp waves), and nerve conduction velocities were normal. Muscle changes in affected dogs include presence of numerous rods, especially in atrophic type 1 fibers. Type 1 fiber predominance was reported in one dog with most fibers having a lobulated appearance [430]. Ultrastructural findings are similar to those seen in cats. As in people, rods are not exclusive to nemaline myopathy and have been seen in normal canine muscle in fibers adjacent to thick fibrous septa/tendinous insertions [431], occasionally in adult dogs associated with hypothyroidism [137,432] and Cushing's syndrome [430] (although concurrent hypothyroidism may have complicated the Cushing's syndrome in this report), and in older Golden Retrievers with muscular dystrophy [264]. The significance of the rods in these various other canine myopathies remains to be determined.

Polyglucosan Myopathy

A myopathy may be found in some dogs with progressive myoclonic epilepsy (see Lafora's disease that is characterized by presence of periodic acid-Schiff positive polyglucosan inclusions in a variety of tissues including skeletal muscle, peripheral nerve, and CNS).

Toxic Myopathy

There have been sporadic reports of a severe myopathy in dogs associated with ingestion of dog food contaminated with monensin, a coccidiostat and feed additive used for chickens and cattle [24,433]. In one report in which 17 dogs were exposed, 14 died [24]. Clinical signs included polydipsia, polyuria, dark urine, vomiting, lethargy/weakness, anorexia, dehydration, and diarrhea. In cases we have seen, morphological changes are characterized by acute necrosis, muscle fiber degeneration, fiber atrophy, regeneration, and fibrosis. Organophosphates have been incriminated in skeletal muscle necrosis in dogs (see organophosphate/carbamate toxicity).

Vitamin E Myopathy

Vitamin E (alpha tocopherol) myopathies (variously termed white muscle disease, nutritional myopathy, and nutritional myodegeneration) have been reported in sheep, cattle, pigs, horses, and poultry (often in conjunction with selenium deficiency), but only rarely in dogs or cats [434-438]. This myopathy is associated with low dietary levels of vitamin E, although similar clinical signs and pathology occur in dogs with experimental vitamin E and selenium deficiency [439]. Selenium is an integral part of glutathione peroxidase and its function is closely involved with that of vitamin E. Clinical signs include of vitamin E (vitamin E/selenium) myopathy include weakness, dysphagia, sialosis, dysphonia, stiff stilted gait, difficulty in rising from a recumbent position, and inability to raise heads. Sudden death is reported in newborn puppies. Signs may be exacerbated with exercise. Serum muscle enzymes are often elevated, especially CK levels [440]. Skeletal muscle lesions tend to be bilaterally symmetrical and may affect individual or several muscle groups. Grossly, the affected muscle is paler than normal and distinct chalky longitudinal striations may be visible. Pathological findings are characterized by necrosis, phagocytosis, proliferation of sarcolemmal nuclei, loss of striations, and fiber regeneration. Mineralization may be seen in necrotic muscle fibers. Myocardial necrosis is also a feature of vitamin E/selenium deficiency [434,435,439,441]. Diagnosis is based on historical, clinical, and histopathological data. Animals usually recover rapidly after selenium and/or vitamin E replacement therapy. A confirmed case of a myopathy due to a deficiency of vitamin E has been reported in a 2 year old female cat that was fed a diet consisting almost entirely of boiled Norwegian coley [442]. Muscles in the pelvic limbs were swollen, hot and very painful on palpation. Histological muscle changes were similar to those reported in dogs. Complete clinical recovery occurred within 14 days following correct dietary management and multivitamin supplementation (especially vitamin E additives). Recent studies [19] suggest that vitamin E does not appear to play a role in sled dogs developing exertional rhabdomyolysis. For more information on vitamin E and the CNS, see vitamin E deficiency.

Myasthenia Gravis

Myasthenia gravis (MG) is a disorder of the neuromuscular junction and both acquired and congenital forms of the disease are recognized in animals and in humans.

Acquired MG is now recognized as a common condition in dogs [443-448] (although it is less commonly reported in cats) characterized by failure of neuromuscular transmission due to reduction in number of functional nicotinic acetylcholine receptors (AChR) on the post-synaptic membrane of the neuromuscular junction [449-451]. This deficiency of receptors reduces the sensitivity of the postsynaptic membrane to the transmitter, acetylcholine. Acquired canine MG is an immune-mediated disease caused by production of antibodies (predominantly IgG) directed against acetylcholine receptors (AChR-ab) of the neuromuscular junction [452]. Reactive antibodies are usually demonstrable in the sera of dogs (approximately 98%) with acquired MG [443] and in most affected cats [453-457]. Antibodies reactive with muscle striations and other autoantibodies (see below) may coexist with a high titer of AChR-ab. Based on experimental and human clinical studies, MG involves both B and T cells (T cells and complement are involved in persistent B cell stimulation and in cell-mediated postsynaptic destruction of the neuromuscular junction, and there is antibody-induced blockade of the function of the remaining AChR molecules) [458,459]. In people, the thymus (either

hyperplastic or neoplastic) appears to play an important role in the pathogenesis of MG [459,460,531]; thymic dysfunction may occur in 75% of human patients with MG [461]. Acquired MG in dogs and cats also occurs in association with thymic dysfunction, including thymomas [451,456,462-473], other thymic abnormalities such as thymic cysts [457,474,534], or non-neoplastic thymic disease [474]. Some cysts (thymic or brachial cleft cysts) have apparent T-cell infiltration [534]. The reported incidence of thymoma is approximately 3% in dogs [448] but is much higher in cats, with an incidence ranging from 19 to 25% [444,475]. In these animals, the pathogenesis of the autoimmune response of acquired MG remains unclear but may be paraneoplastic and related to the recognized antigenic similarity between myoid cells of the thymus and receptor-bearing muscle cells at the neuromuscular junction. One theory is that disruption of the thymic lymphocytes or muscle cells may lead to an autoimmune attack against acetylcholine receptors and other skeletal muscle components [476,477]. Human patients with thymoma-associated MG may also produce autoantibodies to a variety of neuromuscular antigens, including the muscle protein titin, skeletal muscle calcium release channel (ryanodine receptor, RyR), and voltage-gated potassium channels [478,531]. Titin and RyR antibodies have been recently detected in dogs with thymoma-related MG, as well as in dogs with other forms of MG [451]. The presence of circulating RyR antibodies seems to be associated with a severe form of thymoma associated myasthenia gravis in human and canine patients [443,479]. Occasionally, MG may develop in dogs and cats after removal of the thymoma [468,480]. In dogs, acquired MG has also been reported in association with other tumors including cholangiocellular carcinoma [481], osteogenic sarcoma [482], anal sac adenocarcinoma [475], and non-epitheliotropic cutaneous lymphoma [483]. Acquired MG and polymyositis developed in one dog following fetal hematopoietic cell transplantation, along with presence of AChR-ab and immune complexes reactive with myoneural junctions [484]. Acquired MG has also been reported in dogs with hypothyroidism [485], and in hyperthyroid cats receiving tapazole (methimazole) therapy [486], a drug known to exacerbate MG in people [487]. Shelton states that she has identified MG in dogs with hypoadrenocorticism, thrombocytopenia, and hemolytic anemia [443].

Acquired MG has been observed in adult dogs of all sizes, but more commonly in medium-to-large breeds, and particularly in German Shepherds, Golden Retrievers, and Labrador Retrievers [448,452,463]. In one report, the relative risk of acquired MG in different breeds of dogs was highest in Akitas [448]. Newfoundlands may also be predisposed to acquired MG [488]. A bimodal age of onset (<5 years and >7 years) has also been reported in affected dogs [452], and spayed female dogs may have heightened risk [448] (a bimodal incidence peak is also seen in people: second and third decades in women, and fifth and sixth decades in men [459]). In one review of cats with acquired MG, Abyssinians and a close relative, Somalis, usually > 3 years of age, seemed to be overrepresented (gender was not a risk factor) [444]. A spectrum of clinical signs occurs in animals with MG, along with some variations between cats and dogs. Signs in dogs are often characterized by generalized muscle weakness/fatigability that is exacerbated by exercise. Additional signs may be lameness, collapse, regurgitation, drooling, ventroflexion of the head, and tremors. Megaesophagus is also commonly seen (presumably associated with the presence of striated muscle along the entire length of the esophagus in dogs), being as high as 88% in one survey [448]. Note that apart from fatigue/skeletal muscle weakness, neurological deficits may be minimal in some affected dogs [471]. In one study involving 1154 dogs, generalized MG was reported in 57% of cases [448]. Focal forms of MG have also been recognized in dogs, with an incidence ranging from 26% to 43% of all cases of MG [447,448,489]. Focal signs may include megaesophagus, pharyngeal paralysis and/or decreased palpebral reflexes, but without evidence of appendicular weakness [470,489-491]. Facial and laryngeal muscle weakness may also be observed. Focal MG in dogs may occur with thymoma [470]. Approximately 25% of dogs presented with idiopathic megaesophagus have increased serum titers of AChR-ab [489,492]. Idiopathic cardiac conduction disturbances (e.g., 3rd degree heart block) have been reported in some dogs with MG (with and without thymomas and with generalized and focal MG) [469]. A severe, fulminating form of MG has also been recognized in dogs clinically characterized by frequent regurgitation of large quantities of fluid associated with megaesophagus, rapid loss of muscle strength leading to recumbency that is not abated by rest, and marked respiratory distress [447,493]. Several of these dogs have had thymoma [493]. In a recent report involving 5 dogs with fulminating MG, titin and RyR antibodies were found [451]. In cats, signs often include progressive lameness, weakness, drooling and ventroflexion of the head [454,456,494]. Other signs may include head and body trembling (which may be related to exercise in some cats, but in others, it may be seen at rest), crouching posture, dysphagia, regurgitation, weight loss, and voice change. Megaesophagus/esophageal motility dysfunction may be present [454,495]. In a recent review of 105 cats with MG (diagnosis based on positive AChR-ab in serum samples), clinical data indicated that signs of generalized weakness without megaesophagus occurred in approximately 30% of cats, generalized weakness and megaesophagus/dysphagia occurred in 20%, generalized weakness associated with thymoma occurred in approximately 26%, while focal forms of MG, including megaesophagus and dysphagia, without signs of generalized weakness, occurred in approximately 15% of cats [444]. Some cats manifest stiff, choppy movements in all limbs, and after a few steps, they crouch to sternal recumbency and rest their heads on their forepaws. Many cats have facial weakness and are unable to close their eyelids (accompanied by lack of menace and absent palpebral reflex). Third eyelids may be protruded. Neurological examination may reveal normal sensation, intact tendon reflexes but diminished withdrawal reflexes, poor postural reactions, and proprioceptive deficits [455,457]. In human patients, MG has been classified into 4 grades: ocular disease (grade I), generalized weakness of mild (grade IIa) or moderate intensity (grade IIb), severe generalized disease (grade III), and fulminating disease/myasthenic crisis with respiratory failure (grade IV) [459]. Pathological findings (at the light microscopic level) in muscle are minimal but in our laboratory we have seen scattered angular, atrophic fibers in several muscle samples from dogs and cats with MG,

sometimes with small, focal aggregations of lymphocytic cells (lymphorrhages). Lymphocytic myositis has been reported/suspected in some affected dogs and cats with thymomas [456,466,469,496-498]. No changes are found in peripheral nerves. Immunocytochemical methods (e.g., staphylococcal protein A-horseradish peroxidase) may reveal presence of immune complexes localized at neuromuscular junctions [449]. Ultrastructural studies in human cases of MG indicate decreased number of acetylcholine receptors, widening of the synaptic space, and flattening of the regular undulations in the muscle cell membrane at the motor end-plate [460,461]. A significant reduction in muscle acetylcholine receptors has been shown biochemically in dogs with acquired MG [450]. Diagnosis is based on clinical signs, EDX evidence of decremental response of the compound muscle action potentials after repeated nerve stimulation (consistent with a postsynaptic transmission defect), serological testing for autoantibodies, and amelioration of signs following administration of the short-acting anticholinesterase edrophonium chloride (Tensilon), using a dosage of 0.1 - 0.2 mg/kg, IV in dogs and 0.25 - 0.5 mg IV in cats, total dose (anticholinesterase drugs inhibit the enzymatic elimination of acetylcholine, thereby increasing its concentration at the postsynaptic membrane). Neostigmine methylsulfate (Prostigmin) at 40 µg/kg, IM or 20 µg/kg IV may also be used in dogs. Following injection, an animal that has been previously recumbent may be restored immediately to normal activity, which will last for a few minutes before muscle weakness gradually returns. However, some dogs with MG may not respond, while dogs with other neuromuscular disorders may be responsive. It has been reported that the Tensilon test has not proven useful in the diagnosis of focal MG [489]. Note also that a decremental response to nerve stimulation is not always detected in dogs and cats with acquired MG [456,467]. Chest radiography, ultrasonography, or specialized imaging techniques (CT, MRI) may demonstrate a mediastinal thymic mass. EMG testing is normal, as is hematology, blood biochemistry, urinalysis and CSF analysis. Definitive diagnosis can be made using radioimmunoassays for detection of serum acetylcholine receptor antibodies that appear to be specific for acquired MG in dogs [475]. This test (a positive antibody titer in dogs is > 0.6 nmol/L; and > 0.3 nmol/L in cats) will detect nearly all cases of generalized MG [443]; lower serum titers reportedly occur in animals with the focal form of MG [489]. High serum AChR-ab titers were reported in dogs with acute fulminating MG [493]. It should be noted that the assay is not necessarily correlated to the severity of clinical signs in any affected animal, results may be negative in a small percentage of animals with generalized (<2%) or focal forms, and serum titers are decreased by immunosuppressive therapy >7 - 10 days [475,489]. Clinical improvement of signs may be associated with decreasing AChR-ab titers, and remission of signs may occur when titers reach < 0.6 nmol/L [489]. Recently, molecular cloning of the canine nicotinic acetylcholine receptor alpha- subunit gene has been reported along with development of an ELISA assay to facilitate diagnosis of MG in dogs [499]. In people, nearly all cases of MG can be diagnosed using a combination of tests, including AChR-ab titers, repetitive nerve stimulation studies, and single fiber EMG demonstration of increased "jitter" [459]. Prognosis is guarded, especially in dogs with thymoma [471]. Also, dogs with the acute fulminating form of MG appear to have a very guarded prognosis associated with propensity for developing aspiration pneumonia [493]. The presence of circulating RyR antibodies in dogs with various forms of MG may have negative prognostic significance (see above) [451]. Medical treatment usually entails a trial and error approach to the drug(s) used, dosage, frequency, or combination. Long-acting anticholinesterase drugs such as pyridostigmine bromide (Mestinon) may result in clinical control. Dosages range from 30 to 60 mg, PO, two or three times a day in dogs. Dosage depends on the severity of signs and on the size of the dog. In cats, oral pyridostigmine bromide syrup, starting at 2.5 mg bid, has been successful. Overdose in animals can produce a cholinergic crisis with signs of muscarinic (hypersalivation, lacrimation, urination, defecation, pupillary constriction, bradycardia respiratory paralysis), nicotinic (muscle fasciculations, tremors, stiff gait), or CNS (anxiety, hyperactivity, anorexia, generalized seizures) stimulation. Administration of atropine (at 0.2 - 0.4 mg/kg IV, slowly over 5 minutes) will reduce the muscarinic signs. Some animals with acquired MG may become refractory to anticholinesterase therapy after a period of successful treatment. However, Shelton and associates have recently reported spontaneous clinical and immunologic remission in 47 of 53 dogs treated only with anticholinesterase therapy (no immunosuppressive drugs were used) within an average of 6.4 months [475]. Interestingly, various neoplasms developed in the 6 remaining dogs that did not go into remission. It has been stated that anticholinesterases provide only symptomatic relief and have no effect on the underlying immunological dysfunction [500]. Accordingly, some cats have been treated aggressively with immunosuppressive doses of corticosteroids, e.g., prednisolone, 2 mg/kg, bid, for several months, followed by gradual reduction every 2 months over a 12 to 16 month period, has resulted in complete remission of signs and withdrawal of all therapy [455]. In some dogs and cats, combination of corticosteroids and anticholinesterases has been necessary [456,467]. In a report of acquired MG in a cat, successful management involved thymectomy in conjunction with long-term immunosuppressive corticosteroid therapy [457]. The efficacy of the corticosteroid treatment is probably related to both suppression of the immune response and to a direct facilitatory presynaptic action. One caveat is that corticosteroids may initially worsen clinical signs in some instances and steroid induced polydipsia can exacerbate the problem of regurgitation [471,475]. Azathioprine, alone or with pyridostigmine, has been used successfully to treat dogs with MG [501]. Another dog was successfully treated using plasmapheresis and corticosteroids [502]. In one report, surgical removal of a thymoma in a 10 year old mixed breed dog resulted in rapid remission of signs; however, the thymoma recurred 6 months post-operatively [470]. Treatment strategies in people with MG including anticholinesterase inhibitors (typically pyridostigmine), thymectomy, corticosteroids, cytotoxic agents (azathioprine, cyclosporine), plasma exchange, and intravenous pooled immune globulins have led to a low mortality rate and favorable prognosis for most patients (although lifelong immunomodulating therapy may be needed) [459]. It is recommended that the following drugs be avoided in animals

with MG (acquired or congenital) since they may further impair neuromuscular transmission [443]: aminoglycosides, phenothiazines, methoxyflurane, magnesium, and anti-arrhythmic agents.

Congenital MG in animals may occur as a postsynaptic or a presynaptic disorder. It has been described as a postsynaptic disorder in young dogs of several breeds: Jack Russell terrier [503,504], Springer Spaniel [505], and Smooth haired Fox terrier [506], usually appearing between the ages of 6 and 9 weeks, and with multiple cases occurring in a single litter. This form of congenital MG has also been reported in several cats, including a Siamese (5 month of age) and Domestic Shorthair cats (4 and 7 months of age) [453,507,508]. Congenital MG is inherited as an autosomal recessive trait in Jack Russell and Smooth haired Fox terriers [509,510]. The physiological basis of this form of congenital MG is the same as that of acquired MG; however anti-acetylcholine receptor antibodies are not demonstrable in serum or muscle in congenital MG. Ultrastructurally, there appears to be increased postsynaptic membrane density and shorter fold depths (possibly associated with abnormal trophic influences during synaptogenesis) [511]. Palmer and colleagues demonstrated a marked reduction in acetylcholine receptors (AChR) in skeletal muscle samples from Jack Russell terriers and Springer Spaniels with congenital MG [504,512]. In a related study, the low junctional membrane density of AChR in canine congenital MG was considered to represent a low insertion rate of AChR in the postsynaptic membrane rather than a primary inability of muscle to synthesize AChR, or an accelerated degradation of AChR in the postsynaptic membrane [513]. Clinical signs and electrophysiological findings of animals with postsynaptic congenital MG are similar to those described for acquired MG; however, signs of episodic weakness are often relentlessly progressive, ultimately leading to generalized weakness, muscle wasting and inability to ambulate, in spite of treatment. Megaesophagus has been observed only in the Smooth haired Fox terriers. Diagnosis is based on response to Tensilon (pyridostigmine bromide), using a dosage of 0.1 to 0.5 mg, IV. Mestinon (pyridostigmine bromide) is used for treatment at a dosage of 7.5 to 30 mg, PO, once daily. Clinical response to this drug is often erratic, with frequent relapses and animals may become refractory to treatment [504]. Accordingly, prognosis is guarded to poor in affected dogs. The prognosis of affected cats is uncertain because of insufficient numbers of reported cases; however, long-term treatment with pyridostigmine bromide syrup (1.5 mg, PO, bid) was beneficial in one cat [507]. Another congenital myasthenic disorder has been identified in Miniature Dachshund puppies around 5 - 6 weeks of age that is responsive to anticholinesterase therapy and resolves with maturation [443]. Presynaptic congenital MG has been reported in 12 to 16 week old Gammel Dansk Høsehund dogs, with autosomal recessive inheritance [514]. Signs are characterized by exercise-induced weakness, short strides with flexed limbs, head drooping, occasional falling, and crawling movements. Muscle tone and reflexes are normal during attacks, there is no facial weakness, no swallowing defect, no megaesophagus, and no change in voice. The condition is not progressive and some dogs have been followed for 6 years. No antibodies to acetylcholine receptors are found. Anticholinesterase treatment has no effect on muscle weakness or electrophysiological changes. The underlying defect is considered to be presynaptic and may be due to a defect in the synthesis of acetylcholine, impaired release of acetylcholine, abnormality of acetylcholine-induced ion channels, or deficiency of end-plate acetylcholinesterase. Specific electrophysiological patterns may be used to identify heterozygotes as well as myasthenic dogs [515]. In humans, congenital MG is relatively rare and has been classified as presynaptic, synaptic (with end-plate acetylcholinesterase deficiency), or postsynaptic (consisting of abnormal function or numbers of acetylcholine receptors [516]. Inherited cases are usually associated with autosomal recessive inheritance.

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