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Storage Disorders (4-Feb-2003)

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Storage diseases, or lysosomal enzymopathies are rare, degenerative disorders which, in the majority of cases result from a genetically-determined defect of a specific lysosomal acid hydrolase enzyme. There is subsequent accumulation and storage of substrate(s) within the cytoplasm of neurons throughout the nervous system, as well as in cells in other organs. Neurons are typically involved since they are post-mitotic, permanent cell populations [1]. Peripheral nerves are affected in some lysosomal enzymopathies. Most storage diseases have an autosomal recessive mode of inheritance, affect both males and female animals, have an onset early in life, manifest diffuse neurological dysfunction, and have a progressive, inexorable course, leading to death. These conditions tend to be infrequently seen in clinical practice and most published reports emanate from institutions where colonies are maintained for research as animal models of human disease. Lysosomal storage diseases in dogs and cats have been categorized as follows [1]:

Sphingolipidoses
Gangliosidosis
Globoid Leukodystrophy
Gaucher's Disease
Sphingomyelinosis (Niemann-Pick Disease)
Niemann-Pick Disease Type A
- Phenotypic Variant of Niemann-Pick Disease Type A
Niemann-Pick Disease Type C
Glycoproteinoses
Fucosidosis
Mannosidosis
Galactosialidosis
Mucopolysaccharidoses
Mucopolysaccharidosis Type I
Mucopolysaccharidosis Type II
Mucopolysaccharidosis Type III A
Mucopolysaccharidosis Type III B
Mucopolysaccharidosis Type VI
Mucopolysaccharidosis Type VII
Mucolipidoses
I-cell Disease
Miscellaneous
Glycogenoses
- Glycogenosis Type Ia
- Glycogenosis Type II
- Glycogenosis Type III
- Glycogenosis Type IV
- Glycogenosis Type VII
Ceroid Lipofuscinosis

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Ceroid lipofuscinosis (neuronal ceroid lipofuscinosis, or ceroidosis) is a putative neurodegenerative lysosomal storage disease associated with accumulation of lipofuscin and its related pigment, ceroid, in many organs, including neurons and glial cells of the CNS. The lipopigment complexes in ceroid lipofuscinosis and those reported with normal aging are biochemically different. Neuronal ceroid lipofuscinosis occurs as an autosomal recessive trait in English Setters [2], Tibetan Terriers [3,4], and Border Collies [5]. Males and females are affected. There have been sporadic case reports in a variety of breeds, including Chihuahua [6], Dachshund [7], Terrier-cross [8], Saluki [9], Corgi, as unpublished data, see [10], Japanese Retriever [11], Blue Heeler [12,13], Yugoslavian Sheepdog [14], Dalmatian [15], Cocker Spaniel [16-19], Poodle [20], Gordon Setter [21], Polish Owczarec Nizinny [22], and Miniature Schnauzer [23]. Ceroid lipofuscinosis has also been reported in cats [24-27].

The underlying pathogenesis remains unclear. In some forms of the disease in people, ceroid lipofuscinosis is considered to represent a lysosomal storage disorder characterized by the absence of a specific protease activity, e.g., a deficiency of pepstatin-insensitive acid proteases has been reported in classical late-infantile neuronal ceroid lipofuscinosis in children, but not in Tibetan Terriers, English Setters, or Border Collies with ceroid lipofuscinosis [28]. Some researchers suggest that this

neurodegenerative disease is associated with the disease process rather than storage of fluorescent lipopigment per se, and that the pathogenesis may involve mitochondria rather than a primary defect of lysosomal catabolism [29,30,267]. Lysosomal accumulation of subunit c of mitochondrial ATP synthase has been found in these three canine breeds, as well as in most forms of the disease in people [4,29,31]. Subunit c has also been identified in an affected cat [25]. Another class of neuronal ceroid lipofuscinosis is suggested by the finding of storage of sphingolipid activator proteins (SAPs) A and D, but not the c subunit, in affected Miniature Schnauzer dogs [32,33]. In people, five disease genes have been isolated [34]. Two of these (CLN1 and CLN2) encode lysosomal enzymes palmitoyl-protein thioesterase and tripeptidyl peptidase 1. The remaining three (CLN3, CLN5 and CLN8) encode putative membrane proteins of unknown function. A molecular genetic study on English Setters with ceroid lipofuscinosis did not indicate any linkage between the canine form of the disease and homologues of human CLN3 or CLN2 genes [35], and another study eliminated CLN3 as the locus for the disease in English Setters [36].

Clinical signs usually occur in young adult or mature animals between 1 and 9 years of age, although most animals are under 2 years of age. Signs are extremely variable but will usually include some form of abnormal behavior (e.g., aggression, depression, dullness, hyperactivity, loss of learned behavior, and acral mutilation) and visual impairment. These signs are often seen between 1 and 2 years of age. Other signs may include generalized ataxia, head tremors, seizures, and tetraparesis. Signs tend to slowly evolve over several years, especially in Tibetan Terriers [3], often with an accompanying loss of condition. The course in English Setters may be quicker with death within a year of initial signs [37]. The visual loss appears to be cortical, since, in contrast with human neuronal ceroid lipofuscinosis, severe retinopathy does not develop in most affected dogs [37-40]; however, retinal lesions appear to be more severe in Tibetan Terriers [4], in whom one of the early signs is nyctalopia (night blindness). Cocker Spaniels are clinically affected in adulthood and show progressive hind limb paresis, incoordination, and deficient postural reactions and proprioception [16]. Visual deficit is not a feature of the disease in the adult Dachshund [7,41].
Hematology, blood chemistries, urinalysis, CSF, and skull-spinal radiographs are normal, although autofluorescent sea-blue histiocytes have been described in bone marrow aspirates from affected English Setters [42]. Electrocardiographic changes have been reported in some affected dogs [43]. In contrast with early onset ceroid lipofuscinosis in English Setters, plasma carnitine concentrations are not decreased in the late-onset disorder in Tibetan Terriers [271]. Ophthalmoscopy may reveal a pigmented central retinal atrophy [16]. Early diagnosis of affected dogs has been reported with the use of quantitative ocular fundic autofluorescence [44]. Electroretinography has shown that the c-wave is typically either decreased in amplitude, lacking or replaced by a negative wave in English Setter dogs and Polish Owczarec Nizinny dogs with ceroid lipofuscinosis and associated damage of the retinal pigment epithelium [22]. These c-wave changes were seen early in the disease, when the a- and b-waves of the electroretinogram were still within normal limits. Computed tomography of the brain may show dilatation of the ventricles and atrophy of the cerebral cortex [45,46]. Since many cell types are affected by lipopigment accumulation, skin biopsies offer a useful antemortem diagnostic test [15].

Grossly, the cerebrum and/or cerebellum may be atrophic [1]. Microscopically, neuronal ceroid lipofuscinosis is characterized pathologically by distention of large and small neurons with fine granular storage material that stains gray to pale yellow with hematoxylin and eosin, bluish-black with Sudan Black and Luxol Fast Blue, orange with Sudan III, is periodic acid-Schiff (PAS) positive, and shows yellow autofluorescence with ultraviolet light. Affected neurons are distributed throughout the brain and spinal cord (including neurons of the peripheral nervous system), the intensity of which varies with the particular canine breed involved [1], e.g., Purkinje cell pigmentation is slight compared to that in large pyramidal cells of the cerebral cortex in Cocker Spaniels [16]. Loss of functional neuronal cytoplasm results from increasing pigment accumulation. Nerve cells may eventually die and disappear, with subsequent reactive astrogliosis [37]. This is especially evident in cerebellar Purkinje cells [1,3], although this was not observed in affected older Dachshunds [7]. In Cocker Spaniels, degenerative changes are reportedly more common in medulla and spinal cord [16,47]. Axonal spheroids occur in variable numbers throughout the brain and spinal cord [1,16]. Wallerian type degeneration may be seen, along with widespread swelling of astrocytes, and abundance of lipopigment-laden and vacuolated macrophages [3]. Histochemical and immunocytochemical methods have demonstrated abnormal neuronal mitochondria and loss of GABAergic neurons and synapses in cortex and cerebellum of affected English Setters [30]. Ultrastructurally, lipofuscin granules may appear as electron dense bodies with multilamellar profiles, bodies with fingerprint patterns, zebra crystalloids, or curvilinear profiles within neuronal membrane-bound cytosomes [9,13]. Macrophages tend to have more vacuolar cytosomes and less lipofuscin [1]. Storage inclusions may also be observed in retinal ganglion cells, autonomic ganglia, and cells in kidney, liver, pancreas, and smooth muscle fibers [18]. A distinct syndrome occurs in some Cocker spaniel dogs in which there is a generalized accumulation of a lipofuscin-like pigment with such a heavy accumulation in smooth muscle that the intestine and other organs have a brown discoloration [16-18]. In some cats, pigment deposition appears to be restricted to neural tissues [26].
Prognosis is guarded to poor. Attempts to treat the canine disease using allogeneic bone marrow transplantation have so far

been unsuccessful [48].

Fucosidosis

Fucosidosis is a lysosomal storage disease resulting from a deficiency of the enzyme α-L-fucosidase responsible for metabolism of glycoasparagines with terminal fucose residues [49]. As a consequence of this enzyme deficiency, there is an intralysosomal accumulation of substrate (fugoglycoproteins, oligosaccharides, and glycosaminoglycans) in various tissues including central nervous system (CNS), peripheral nervous system (PNS), kidney, pancreas, lymph nodes and lung. Fucosidosis occurs in English Springer Spaniels and has a worldwide distribution with reports from Australasia, the United Kingdom, and North America [50-54]. The disease is transmitted as an autosomal recessive trait [55].

Clinical signs are seen in young English Springer Spaniels and are characterized by progressive motor and mental deterioration. From 6 to 12 months of age, affected dogs may be anxious, apprehensive, and slow to learn. Ataxia, hypermetria, and proprioceptive deficits may be noted after 12 to 18 months [51]. Hearing, visual, and menace deficits may develop from 18 to 24 months, followed by severe incoordination over the next 6 months. During the third year of life, the bark frequently becomes monotonal and hoarse and dysphagia may be present, sometimes accompanied by regurgitation (although without evidence of megaesophagus). Most dogs over 24 months of age have episodic pendular nystagmus elicited by positional change of the head. Death is not uncommon in animals 3 to 4 years of age [54]. Enlarged ulnar nerves can be palpated in dogs with advanced disease. In Canada, a confirmed case of fucosidosis has been reported in a 10 month old English Springer Spaniel in which the initial problem was visual impairment [56]. Affected male dogs are infertile because of decreased total sperm output, low sperm motility, and morphologic abnormalities of the spermatozoa [57,58]. In contrast, affected females reproduce successfully, although estrus cycles are abnormal.

Hematological studies indicate that up to 40% of lymphocytes have marked cytoplasmic vacuolation. Bone marrow macrophages show vacuolation also. CSF analysis is usually normal (WBC count, protein), although vacuolated mononuclear cells may be detected [54]. Clinically affected homozygotes have < 5% of normal enzyme activity in tissues, leukocytes, plasma, or cultured skin fibroblasts while carriers have approximately 50% of normal activity [54,55,59]. Motor and sensory nerve conduction studies are normal and no EMG abnormalities are present [54].

A notable gross autopsy finding is the pronounced enlargement of various nerves, associated with edema, fibroplasia, and aggregates of vacuolated endoneurial macrophages [1]. The cervical vagus is the most severely enlarged, sometimes measuring 10 mm in diameter [54]. Other involved nerves include optic, trigeminal, hypoglossal, glossopharyngeal, and spinal nerve roots, especially those supplying the brachial plexus. Dorsal root ganglia can also be enlarged. The lesions in the CNS are characterized by extensive cytoplasmic vacuolations and swelling of many neurons and supporting glia throughout the brain and spinal cord. Loss of neurons may be detected, especially of cerebellar Purkinje cells, and neurons in cuneate and gracile nuclei. Numerous vacuolated macrophages are found in the meninges. Axonal spheroids are frequently seen, especially in hypothalamic, cerebellar, cuneate, and gracile nuclei, usually associated with hypertrophic astrocytes [1]. Many phagocyte-like cells with a foamy, vacuolated, PAS-positive cytoplasm are present either free in the parenchyma or as pronounced cuffs around large vessels. Endoneurium and perineurium of peripheral nerves are infiltrated by foamy macrophages and nerve fibers are separated by edematous, finely fibrillar ground substance. There are minimal degenerative changes in peripheral nerves. Vacuolation is also found in cells of most visceral organs. Ultrastructurally, the vacuoles are seen either as membrane-bound, rounded cytosomes with an empty interior, or as amorphous, faintly stained material. Lectin staining of various paraffin-embedded tissues from human and canine fucosidosis has demonstrated a species-specific histochemical variability [60]. Unlike several other lysosomal storage diseases, Golgi staining of cortical pyramidal neurons in dogs with fucosidosis failed to demonstrate evidence of ectopic dendrite growth, although there is GM2-like immunoreactivity limited to glia and/or to non-pyramidal neurons [61].

Prognosis is guarded to poor. There is no treatment at present; however, treatment strategies in established colonies of dogs with fucosidosis are being assessed as a potential animal model for gene therapy and enzyme replacement therapy [62-71]. Bone marrow engraftment in dogs with fucosidosis has resulted in increased levels of alpha-L-fucosidase enzyme activity in leukocytes, plasma, and neural and visceral tissues, accompanied by a rapid improvement in the peripheral nerve and visceral lesions of fucosidosis and a more gradual improvement in the CNS pathology [72]. Long-term engraftment from an early age reduced the severity and slowed the progression of clinical neurological disease. In this study, transplantation after the onset of clinical signs was not effective.

The molecular defect underlying canine fucosidosis has been identified [73] and a polymerase-chain-reaction (PCR)-based diagnostic test for fucosidosis in English Springer Spaniels is now available, enabling detection of both carriers and homozygotes [71,74,75]. Using this screening test, fucosidosis can be controlled and ultimately eradicated from the English Springer Spaniel population [74].

Galactosialidosis

An adult-onset lysosomal storage disorder has been reported in a 5 year old Schipperke dog with progressive cerebellar and central vestibular signs [76]. It is characterized by cerebellar atrophy with extensive loss of Purkinje and granular cells, and hydrocephalus. Enlarged and vacuolated neurons are observed in spinal cord, brain and autonomic ganglia. Ultrastructurally, enlarged secondary lysosomes filled with lamellated bodies are present in neurons and empty enlarged vacuoles are found in pancreatic centroacinar, ductal, and islet cells. Neurons stain with luxol fast blue, PAS, Concanavalia ensiformis agglutinin, and are autofluorescent. These findings are consistent with an accumulation of glycolipids containing terminal beta-galactosyl and alpha-sialyl residues, and N-linked oligosaccharides. Tissue activity of lysosomal beta-galactosidase was 50% of normal and the activity of beta-hexosaminidase was elevated. Brain lipid-bound sialic acid level was twice normal, with a small increase of GM1-ganglioside, but there was a significant elevation of GM2- and GM3-gangliosides. In addition, significant elevations of sialylated and non-sialylated oligosaccharides were noted. These clinical, biochemical and pathological findings are similar to those observed in human patients with adult-onset galactosialidosis.

Gangliosidosis

Ganglioside storage diseases are inherited (autosomal recessive) defects of lysosomal hydrolase enzymes that result in accumulation of gangliosides (glycosphingolipids that are major constituents of plasma membranes in a variety of cells, especially neurons) and glycolipid substrates of these hydrolases within lysosomes of most neurons and glia throughout the nervous system [77-79], including brain, spinal cord, and autonomic ganglia.

In dogs and cats, several gangliosidoses have been identified and categorized according to the enzyme deficit and degree of visceral involvement. GM1 gangliosidosis has been reported in cats (Siamese, Korat, and Domestic Shorthair), and dogs (English Springer Spaniel, Portuguese Water dog, mixed-breed Beagle, Alaskan Huskies, Shiba, and cross-breed dogs) [77,79-93]. The accumulation of ganglioside in the brain is due to deficiency of acid β-galactosidase. In people, there are infantile (type 1), juvenile (type 2), and adult (type 3) variants of GM1. GM2 gangliosidosis has been reported in German Shorthair Pointers, Japanese Pointers, mixed-breed cats, and Korat cats [94-101]. Four major enzymatic variants of GM2 gangliosidosis are recognized in people based on their defective subunits or activator protein [100,101]:

a. Type B, or Tay Sachs disease, due to deficiency of hexosaminidase A;
b. Type O, or Sandoff's disease, due to deficiency of hexosaminidase A and B;
c. Type AB, due to deficient or defective GM2 activator; and
d. Type B^{-1}, due to a mutation in the α-subunit of β-hexosaminidase.

Massive accumulation of ganglioside occurs in all animals with GM2 gangliosidosis; however, the biochemical defect varies. A marked deficiency in activity of hexosaminidase A and B is reported in Korat cats (similar to Sandoff's disease in people). In the Japanese Spaniel, the biochemical basis is thought to be due to attenuation in stimulatory activity of the GM2 activator (similar to Type AB in people), and β-hexosaminidase activity may be 12 fold higher than that in normal brain [100]. In a report of GM2 gangliosidosis in a German Shorthair Pointer, massive accumulation of GM2 ganglioside was found in the brain and in other organs; however, β-hexosaminidase activity in plasma, liver, kidney and brain was normal, suggesting either an activator protein disorder or a B^{-1} variant [101]. A partial deficiency of β-hexosaminidase activity has also been reported in this breed [99].

In most of the gangliosidoses, total ganglioside content of brain is high in clinically affected animals. Asialo (sialic acid free) derivatives of the gangliosides also accumulate in brain and liver [79]. High levels of other neutral glycosphingolipids may also be found. In some instances, different substrates are stored in neural and visceral tissues, probably reflecting the heterocatalytic activity of the deficient enzyme. For example, English Springer Spaniels and Portuguese Water dogs (PWDs) with GM1 gangliosidosis reportedly store GM1-ganglioside, asialo-GM1, and oligosaccharides in brain but only the PWDs store glycoproteins containing polylactosaminoglycans in visceral organs, and neither breed stores them in the brain [89]. Visceral storage of glycolipids and glycoproteins occurs in canine and feline GM1 gangliosidoses. Visceral involvement was not observed in the Japanese Spaniel with GM2 gangliosidosis [98], but in a report of GM2 gangliosidosis in a German Shorthair Pointer, storage of ganglioside was observed in liver, kidney, and spleen [101].

Clinical signs of GM1 gangliosidosis are first noted in dogs around 4 to 5 months of age and in cats from 2 to 5 months of age. In animals with GM2 gangliosidosis, onset of clinical signs is from 1 to 3 months of age in kittens, 6 to 12 months of age in German Shorthair Pointers, and around 18 months of age in Japanese Spaniels. Stunted growth and failure to eat may be noted early in life. Neurological signs are very similar in both species and are highlighted by their relentlessly progressive nature [79]. Cerebellar-like signs of ataxia-dysmetria, discrete head tremor, loss of balance, and abnormal nystagmus are often the first signs observed, followed by spastic paraplegia or tetraplegia, visual impairment, depression, sometimes dementia, seizures, aggression, and death. Corneal clouding has been seen in feline GM1 and GM2 gangliosidosis associated

with proteoglycan storage in corneal endothelial cells and fibroblasts [83,102]. Proportional dwarfism has been reported in English Springer Spaniel (these dogs also have coarse facial features, including ocular hypertelorism or increased width between the eyes), Portuguese Water dog, and Alaskan Husky puppies [90,103]. In addition, skeletal lesions such as deformed, irregular and abnormally widened intervertebral disk spaces, have been reported in English Springer Spaniels and Portuguese Water dogs [89]. Some cats with GM1 gangliosidosis manifest facial dysmorphia and hepatomegaly.
Note that clinical signs in cats with panleukopenia (parvo) virus-induced cerebellar hypoplasia and the gangliosidoses are similar; however, cats with the former disorder typically show signs at birth or shortly thereafter and the signs remain relatively static. Several electrodiagnostic abnormalities have been reported in cats with GM1 gangliosidosis, including slow spinal evoked potentials in cats over 200 days of age and prolonged latencies of brainstem auditory evoked responses in cats over 90 days of age [104], findings consistent with the hypothesis that at least some of the abnormalities in cats with this lysosomal enzymopathy may be associated with altered CNS synaptic activity [105] (see also neurotransmission derangement, below). Motor and sensory nerve conduction velocities were normal and no abnormal spontaneous potentials were found by needle EMG [104].

Gross changes are usually not present although the liver may appear swollen and pale [1]. Microscopically, the storage material produces widespread neuronal distension (in CNS, autonomic ganglia, and retina) with a foamy to granular cytoplasm due to tightly packed vacuoles that displace the Nissl substance. Nuclei are eccentrically placed and there may be variable neuronal loss. Astrocytes may be similarly affected. Vacuoles in frozen sections often stain positively with Luxol fast blue and Grocott's method, PAS, and Sudan Black [1]. Axonal spheroids are variably seen in white matter in GM1 and GM2 gangliosidosis [106]. These structures may involve axons of inhibitory GABAergic neurons, suggesting that a resulting defect in neurotransmission in inhibitory circuits may be an important factor underlying brain dysfunction in animals with gangliosidosis [107]. Abnormal myelin development in the CNS (based on magnetic resonance imaging, white matter histopathology, and immunostaining) has been reported in dogs (English Springer Spaniel and Portuguese Water Dog) with GM1 gangliosidosis [108] and in cats with Sandhoff-like GM2 gangliosidosis [109]. In Alaskan Huskies with GM1 gangliosidosis, mild demyelination and axonal degeneration were accompanied by a significant astrogliosis in the gray matter and a significant loss of oligodendrocytes in the gray and white matters [90]. I have observed paranodal demyelination in up to 10% of single teased peripheral nerve fibers from some cats with GM2 gangliosidosis. Wallerian degeneration has also been reported in peripheral nerves, ventral and dorsal nerve roots, and in dorsal funiculi of all spinal cord segments in a 2 year old mixed breed dog with GM2 gangliosidosis (due to a presumed defect or deficiency of hexosaminidase activator protein) [257]. Ultrastructurally, cells are packed with membrane-bound vacuoles containing a membranous, lamellar material arranged in whorls, called membranous cytoplasmic bodies, or stacks of membranes in parallel arrays that have been termed zebra bodies [110]. The axonal spheroids are filled with electron-dense bodies, degenerating mitochondria, tubulovesicular profiles but little or no storage material [1]. Endothelial cells and perivascular macrophages in many organs are vacuolated in the gangliosidoses, including endoneurial macrophages in nerves from cats with GM2 gangliosidosis. The vacuoles tend to be empty or contain variable amounts of fibrillar or granular remnants of oligosaccharides which have been washed out during tissue fixation [1]. Golgi and ultrastructural studies reveal the presence of conspicuous enlargements (meganeurites - a manifestation of the storage process) located between the axon and cell body which appear to give rise to neurites and dendritic spines in cortical pyramidal neurons in canine and feline gangliosidoses [98,105,106,111]. These structures are postsynaptic to afferent fibers of unknown origin, are thought to contribute to neuronal dysfunction, and their distribution varies with cell type and brain region. The meganeurites are distended with membranous cytoplasmic bodies [111].

Skeletal lesions in English Springer Spaniel, Portuguese Water dog, and Alaskan Husky puppies are characterized by retarded endochondral ossification and osteoporosis [90,103]. Older puppies have focal cartilage necrosis within lumbar vertebral epiphyses. At the cellular level, lesions are characterized by chondrocytic hypertrophy and lysosomal accumulation of storage compounds. Premature thymic involution has been demonstrated in feline GM1 gangliosidosis [112].
In animals with peripheral nerve lesions, there may be slow motor nerve conduction velocities and reduced amplitude of evoked muscle potentials [257]. A tentative diagnosis is suggested by presence of cytoplasmic inclusions in peripheral blood leukocytes. In animals with GM1 gangliosidosis, oligosaccharides may be detected in urine in abnormally high quantities. Definitive diagnosis requires biochemical identification of the storage product and absence or marked reduction in activity (e.g., only 3 to 5% of the activity seen in homozygous normals) of specific lysosomal enzymes required for hydrolysis of accumulated compounds (e.g., chromatographic analyses may indicate a 5 to 10 fold increase in ganglioside storage). Note that the enzyme level in clinically unaffected heterozygotes is approximately 50% that of normal animals. Antemortem diagnosis can be made by enzyme assay of whole skin, cultured skin fibroblasts, liver, and purified leukocytes. Neonatal diagnosis using enzyme assays of placenta and umbilical cord has been reported in GM1 gangliosidosis [89]. Postmortem diagnosis is made most reliably by enzyme assay of brain. Prognosis is grave. There is no definitive treatment at present but

different strategies that have been tested in animal models include gene transfer and cell engraftment of neural stem cells engineered to express the specific enzyme deficiencies [113]. Allogeneic bone marrow transplantation early in life was found to be ineffective in canine GM1 gangliosidosis [114].
A suspected lysosomal storage disease has been reported in Abyssinian kittens in which the clinical signs are very similar to those reported above [115-118]. In human patients with gangliosidosis, peripheral nerve lesions are usually not significant, although motor neuronopathy tends to be common in late onset GM2 cases [258].

Gaucher's Disease
Gaucher's disease, or glucocerebrosidosis, is a rare lysosomal storage disease caused by a deficiency of glucocerebrosidase (glucocerebroside β-glucosidase) that catalyzes the hydrolysis of glucocerebroside to ceramide and glucose [119]. A form of Gaucher's disease (similar to the type 2, infantile form in people) has been reported in Australian Silky Terriers [120-122]. Clinical signs reportedly occur around 4 to 6 months of age, are progressive, and are characterized by severe incoordination, wide-based stance, stiff gait, generalized tremors, hyperkinesis, and hypermetria. No gross findings have been noted in brain or spinal cord. Microscopically, the cytoplasm of many neurons in the brain, but not in the spinal cord, is distended and has a foamy, finely vacuolated appearance that often contains weakly eosinophilic, PAS-negative granules [122]. Nissl granules appear lost or peripherally displaced. Neurons of the dorsal and lateral thalamic nuclei and the dorsal hippocampus are especially affected, with less severe changes occurring in cerebral cortical gray matter, inferior colliculus, oculomotor nucleus, cochlear nucleus, trigeminal motor nucleus, superior olivary nucleus, dentate nucleus, fastigeal nucleus, and ventral pontine gray matter. Gaucher cells (foamy, distended macrophages) are found in the cerebellar granule cell layer that may be mildly to severely atrophic. In addition to variable granule cell loss, degenerating Purkinje cells may be noted. At all levels of the brain there is mild to moderate spongy vacuolation of white matter and breakdown of myelin sheaths. The most severely affected areas include central white matter of the cerebral hemispheres, corpus callosum, optic tracts, cerebral peduncles, trapezoid body, central cerebellar white matter, and spinocerebellar and corticospinal tracts. Axonal spheroids may be seen, especially in ventral pontine gray matter. Gaucher cells are also found in several visceral organs, including liver (without signs of hepatomegaly) and lymph nodes. Ultrastructurally, the storage material in neuronal cytosomes appears laminated (zebra-like bodies) with variable fine fibrillar material. These structures, as well as twisted tubular material, are also seen in Gaucher cells.
Premortem diagnosis can be established by determining enzyme activity in leukocytes. Negligible β-glucosidase activity can be determined at pH 4.0 to 4.25 [123]. Postmortem diagnosis is made most reliably by enzyme assay of brain and liver as well as finding elevated levels of glucocerebroside, especially in liver [122]. Prognosis is poor. There is no treatment at this time.

Globoid Leukodystrophy
Globoid cell leukodystrophy (Krabbe's disease or galactocerebrosidosis) is a rare lysosomal storage disease that results in progressive degeneration of white matter of the CNS and PNS. The disease is caused by mutations in the gene for the lysosomal enzyme galactosylceramidase (GALC) (or galactocerebroside β-galactosidase), which results in an accumulation of psychosine (galactosylsphingosine), a lipid that is highly toxic to oligodendrocytes and Schwann cells [124-127].
Globoid cell leukodystrophy is inherited as an autosomal recessive trait in young (3 to 6 month-old) West Highland White Terriers (WHWT) and Cairn Terreirs [128-136]. The disease also has been reported in a 4 month old Beagle [137] a 2 year old Poodle [138], a 4 year old Basset Hound [139], 4 month old Blue Tick Hounds [140], two Pomeranians - 5 1/2 months and 14 years of age [139,141] and in Domestic Shorthair and Longhair kittens [142,270]. Recently, the condition has been reported in Irish Setter puppies around 6 weeks of age [143].
The clinical signs associated with this disease are variable and may reflect a multifocal syndrome. Animals often present with either signs of an ascending posterior paralysis or signs of a cerebellar syndrome, or both. Signs of a neuropathic syndrome are infrequently observed (e.g., in Irish Setters) and include depressed spinal reflexes, reduced muscle tone, and muscle atrophy. As the disease progresses, signs of a cerebral syndrome may be observed (including behavioral abnormalities, depressed mentation, visual deficits, etc.). In terminal cases, usually prior to 1 year of age, animals may become prostrate, demented, anorexic, and cachectic [134]. The progression of clinical signs appears more rapid in Irish Setters. Partial motor seizures characterized by repetitive jaw movements, muscle twitching, licking and chewing movements, fly biting and opisthotonus have been observed in some affected Irish Setters. Prolonged postrotatory nystagmus can be induced by rotating affected animals [144].

Results of ancillary aids usually are non-specific. Hematology, blood biochemistry, ophthalmology and spinal-skull radiography are normal. Analysis of CSF, however, can reveal an elevated protein level with cell counts usually within normal limits (albuminocytologic dissociation). Mononucleated or multinucleated PAS-positive cells are sometimes identified in CSF [145]. Magnetic resonance and magnetization transfer imaging in affected dogs are compatible with diffuse,

symmetrical white matter disease [146,147], while electrodiagnostic testing may reveal an abnormal brainstem auditory evoked response, abnormal spontaneous muscle activity (fibrillation potentials and positive sharp waves), and slow motor nerve conduction velocities [144,146]. Electroencephalographic traces also may be abnormal.
Grossly, involved regions of fixed white matter of the CNS are gray and soft compared to normal white matter, while leukodystrophic peripheral nerves may appear normal or enlarged and whiter than normal nerves [134]. Ventricles may be enlarged 2 to 3 times normal size in some animals [148]. Significant lesions typically are confined to the white matter of the nervous system where any level of the brain and spinal cord may be affected, although lesions were limited to the brainstem and spinal cord in an older Basset Hound [139], and subcortical lesions were minimal in the affected Beagle [137]. Lesions tend to be symmetrical but with variable intensity at different levels within the neuraxis. In WHWT and Cairn Terriers, most severe changes may be seen in central and gyral white matter of the cerebrum, optic tracts, corpus callosum, fimbria, subcortical and adjacent folial white matter of the cerebellum, and outer one-half of the funiculi of the spinal cord [148]. The disease is characterized by destruction of white matter and replacement by aggregates (often in a perivascular fashion) of nonsudanophilic, nonmetachromatic, PAS-positive macrophages called "globoid cells", usually with accompanying hypertrophic astrocytes. Globoid cells are CD68 and ferritin positive, verifying their monocytic origin [270]. Myelin stains weakly in affected areas and there may be loss of oligodendrocytes. Axons are lost in the larger globoid cell collections. Changes in gray matter are minimal. In peripheral nerves, lesions may be typified by multifocal presence of segmental demyelination, variable axonal degeneration, and endoneurial accumulation of globoid macrophages [144,149,150]. In a recent study, a significant increase in the G-ratio (axon diameter divided by fiber diameter) was identified in affected dogs suggesting a decrease in total fiber diameter which appeared to be due to myelin loss or hypomyelination [144]. Ultrastructurally, intracytoplasmic vacuoles in Schwann cells and macrophages may contain myelin debris and characteristic twisted or straight-to-arched tubular inclusions [133]. Endoplasmic reticulum is often dilated and there may be evidence of mitochondrial degeneration [150].

Antemortem diagnosis may be suggested by nerve biopsy and demonstration of the characteristic ultrastructural inclusions [144,149,150] and established by levels of GALC activity in blood leukocytes of affected dogs or from cultured fibroblasts - the mean enzyme activity is reportedly 18% of the activity in normal dogs, whereas heterozygous carriers have a mean enzyme activity of about 50% of normal [151]. A screening test for clinically normal heterozygote carriers among WHWT and Cairn terriers, based on the molecular defect, has been established and provides rapid and accurate genotyping for all WHWT and Cairn terriers using any tissue sample available [152]. A similar DNA-based PCR test is available for Irish Setters [143]. Mutation analysis for carrier identification is superior to measurement of GALC activity because of the wide range of GALC values in peripheral blood leukocytes [127]. PCR testing will also facilitate prenatal diagnosis based on small fetal tissue samples (e.g., chorionic villus biopsy and amniotic fluid cells). Lipid analysis of brain reveals marked elevations in psychosine [127]. Deficient enzyme activity may also be found in liver and kidney [151].
Researchers and clinicians at the University of Pennsylvania, School of Veterinary Medicine, are investigating treatment strategies. To date, studies have shown successful transduction of cultured skin fibroblasts from an affected dog and normal canine bone marrow using a retroviral vector containing the human GALC cDNA [127]. However, intracerebral inoculation of an affected dog with transduced bone marrow stromal cells did not result in improved brain pathology (Dr. Charles Vite, personal communication, 2001).

Glycogenosis
Glycogen storage diseases or glycogenoses, are uncommon disorders in dogs and cats. These diseases represent inborn errors of metabolism due to deficient activity of one of the enzymes involved in glycogen metabolism. The enzyme defects result in inadequate glycogen utilization and accumulation of glycogen of normal or abnormal chemical structure within various tissues, including muscle.

Glycogenosis Type Ia - a Von Gierke-like disease associated with glucose-6-phosphatase (G-6-Pase) deficiency has been reported in related Toy Breed puppies between 6 and 12 weeks of age [153], with signs of depression, coma, hypothermia, hypoglycemia, hepatomegaly and histological evidence of excessive glycogen accumulation in liver, kidney and sometimes myocardium, [154,155]. G-6-Pase deficiency has recently been reported in two 47-day-old littermate Maltese puppies presented for necropsy with a history of failure to thrive, mental depression, and poor body condition, [156] and the genetic mutation has been identified [157]. Gross findings included small body size and emaciation, severely enlarged pale livers, and pale kidneys. Histologically, there was marked diffuse vacuolation of hepatocytes with large amounts of glycogen and small amounts of lipid. Renal tubular epithelium was mildly to moderately vacuolated. Biochemical analysis showed that levels of G-6-Pase were markedly reduced in liver and kidney and that glycogen content was increased in liver. A colony has been established by crossbreeding Maltese and Beagle dogs carrying a mutated, defective G-6-Pase gene [158]. Puppies from this colony exhibited tremors, weakness, and neurologic signs when hypoglycemic. They had postnatal growth retardation

and progressive hepatomegaly. Biochemical abnormalities included fasting hypoglycemia, hyperlactacidemia, hypercholesterolemia, hypertriglyceridemia, and hyperuricemia. Microscopic and biochemical findings were similar to those found in the Maltese puppies [158]. Gene therapy has resulted in sustained G-6-Pase expression and improvement in liver histology and in biochemical parameters [266].

Glycogenosis Type II - or Pompe's disease in people, due to acid α-glucosidase enzyme deficiency, has been reported in related Lapland dogs [154,159-161]. Clinical signs developed in animals after 6 months of age and were characterized by progressive muscle weakness, frequent vomiting and regurgitation, megaesophagus, dysphonia, persistent panting and cardiac abnormalities. Death occurred before the age of 2 years. Electromyographic studies revealed prolonged insertion activity, bizarre high frequency discharges, and occasional fibrillation potentials and positive sharp wave activity. The main lesions consisted of massive glycogen accumulation in membrane-bound vacuoles (glycogenosomes), involving most organs (including cerebral cortex and skeletal, cardiac, and smooth muscle) [160]. The disease has an autosomal recessive mode of inheritance [162] and may be confirmed by low leukocyte activity of acid α-glucosidase. The enzyme protein is present in affected tissues, although in an inactive form [163]. Heterozygous animals may be identified by their partial deficiency of acid α-glucosidase in leukocytes [162]. Prognosis is poor. There is no treatment.

Glycogenosis Type III - or limit dextrinosis, a glycogenosis similar to Cori's disease in people, is associated with a deficiency of the debranching enzyme amylo-1,6-glucosidase (reduced to between 0 and 7% of normal activity) and has been reported in German Shepherds and Akitas [164-167]. Muscular weakness and exercise intolerance was noted as early as 2 months of age. Other clinical signs included progressive abdominal distention as a result of hepatomegaly. Abnormal glycogen-like material occurred in liver, muscle (smooth, cardiac and skeletal) and neurons and glial cells of the CNS [154]. The stored substance lay freely dispersed in the cell cytoplasm without any indication of lysosomal storage [164]. The molecular basis for this disease has been characterized and a PCR screening test is available for diagnosis [259,260].

Glycogenosis Type IV - (Andersen disease, amylopectinosis), an inherited (autosomal recessive) deficiency of the glycogen branching enzyme α-1,4-D-glucan: α-1,4 glucan 6-glucosyl transferase, has been reported in a family of young Norwegian Forest cats [168,169]. Two cats developed fever, generalized muscle tremors, bunny-hopping gait, and weakness at 5 months of age which progressed to tetraplegia by 8 months of age. Fever disappeared at 8 months of age. Severe generalized muscle atrophy with contracture of the caudal antebrachial and cranial thigh muscles were present at the time 2 cats were euthanized (at 8 and 13 months). The older cat had ventricular hypertrophy. Abnormal fibrillation potentials were recorded in most muscles of one cat. The third cat died at 5 months of age before clinical signs developed. In another report, an unrelated Norwegian Forest cat had similar clinical signs beginning at 5 months of age [170]. In addition, this cat developed generalized, tonic-clonic seizures.
Microscopically, glycogen storage disease type IV is characterized by granular to globular intracytoplasmic storage of PAS-positive, diastase-resistant material that stains blue with hematoxylin and eosin and purple-blue with Lugol's iodine and is found in many organs, including skeletal muscle. Stored material was found in neurons throughout the CNS and PNS including dorsal and ventral horns, dorsal root ganglia, sensory and motor nuclei throughout the brainstem, Purkinje cells in the cerebellum, ganglion cells of the retina, autonomic ganglia, and myenteric plexi of the intestinal tract [168]. Accumulation of abnormal glycogen is accompanied by severe degeneration in the CNS and PNS, skeletal muscle, and heart. There is extensive loss of axons and myelin in peripheral nerves, spinal cord white matter, and cerebellar peduncles [171]. In peripheral ganglia and neurons within the CNS in which there is extensive storage, there is loss of neuronal cell bodies and astrogliosis. Ultrastructural evaluation of the stored material demonstrates irregular, non-membrane bound, finely granular cytoplasmic deposits [168,171]. Analysis of the glycogen in affected cats indicates less branching than normal and branching enzyme activity less than 10% of normal levels in liver and muscle [168]. Partial deficiency was found in muscle and leukocytes of the parents of affected cats. The molecular basis for this disease has been characterized and a PCR screening test is available for diagnosis [259,260].

Glycogenosis Type VII - an inherited (autosomal recessive) deficiency of phosphofructokinase (PFK), comparable to type VII glycogen storage disease in people, is recognized in English Springer Spaniels less than 12 months of age [172-175]. Muscle and erythrocyte PFK activities are deficient [174,175]. Characteristically, enzyme-deficient dogs have compensated hemolytic anemia and sporadic episodes of intravascular hemolysis with hemoglobinuria. Typically, clinical signs of muscle or CNS disease are not features of this disorder; however, muscle cramping has been noted in affected field trial dogs and in hunting dogs, both in the USA and in Europe [176,177]. Further studies are needed to determine if the behavioral abnormality observed sporadically in some affected dogs (called "Springer rage" syndrome by the breeders) is related to PFK deficiency. Interestingly, a severe, progressive myopathy characterized by weakness and muscle atrophy has been reported in an 11 year old PFK-deficient English Springer Spaniel [178]. Muscle changes included large accumulations of basophilic

floccular material in hematoxylin and eosin sections that stained strongly with PAS. Ultrastructurally, the non-membrane bound deposits were composed of short granular filaments, 8 to 12 nm in diameter and 100 to 160 nm in length, small granules, and amorphous material. Based on staining characteristics, the deposits were thought to represent an amylopectin-like polysaccharide with possible sialic acid residues. Total PFK activities were markedly reduced when assayed in skeletal muscles of this dog. In contrast with other PFK-deficient dogs, muscle glycogen in this animal was not increased above that of normal dogs [178].

A PCR-based diagnostic test has been developed for detecting dogs with PFK deficiency and clinically normal carriers [177,179]. Preliminary treatment attempts using bone marrow transplantation have shown promise. An identical condition, having the same molecular mutation, has been found in American Cocker Spaniels [180]. Screening for PFK deficiency is recommended for English Springer Spaniels with suspicious clinical signs and before using any for field trials or breeding in order to prevent the further spread of this hereditary disorder [177].

A suspected glycogen storage disease that was accompanied by growth retardation, progressive muscular weakness, atrophy of pelvic limbs, and death has been reported in cats between 1 and 4 months of age [181]. There was hepatomegaly, splenomegaly, and focal necrosis of muscle and elevated serum creatine kinase and aldolase activity. Glycogen-like material occurred in reticuloendothelial cells, liver and muscle cells.

Mucolipidoses

I-cell Disease - I-cell disease is a rare lysosomal storage disease caused by a deficiency of the enzyme N-acetylglucosamine-1-phosphotransferase (GlcNAc-phosphotransferase) recently reported in cats [261,262] and considered homologous to I-cell disease (or mucolipidosis type 3) in humans [199]. The disease is characterized by facial dysmorphism, large paws in relation to body size, dysostosis multiplex, and poor growth. Affected cats appear dull, ataxic, and may have decreased muscle tone. Radiographic abnormalities are seen as early as 2 weeks of age and lesions include long bone metaphyseal flaring, radial bowing, and antebrachial-carpal joint luxation. Fusion of cervical and lumbar vertebral bodies develop within the first 5 months of life. In some severely affected cats, spina bifida and hemivertebraw have been noted. Retinal degeneration may be detected around 2 - 3 months of age. The condition has an autosomal recessive mode of inheritance and affected cats either die or require euthanasia within 1 day to 7 months of age. The urine mucopolysaccharide spot test is negative. The enzyme GlcNAc-phosphotransferase is deficient in leukocytes and cultured fibroblasts. Inclusion bodies have been detected in cultured fibroblasts but not in white blood cells. Inclusions have also been seen in endothelial cells and chondrocytes. Storage lysosomes contained oligosaccharides, mucopolysaccharides, and lipids. Tissues most affected are bones, cartilage, skin, and other connective tissues. Parenchymal cells of liver and kidney are unaffected, as is skeletal muscle. Few cerebral cortical neurons show lipid inclusions and peripheral nerves appear normal. It should be noted that the subtle neurologic signs in affected cats are believed to be secondary to the orthopedic changes [262].

Mannosidosis

Mannosidosis is a lysosomal storage disease resulting from a deficiency of the enzyme alpha-D-mannosidase in various organs, including brain, kidney and liver. Lysosomal alpha-D-mannosidase is involved in the catabolism of N-linked glycoproteins through the sequential degradation of high-mannose, hybrid, and complex oligosaccharides [182]. In feline alpha-mannosidosis, the accumulated oligosaccharides primarily represent intact oligomannosyl moieties of N-linked glycans rather than the products of residual alpha-mannosidase activity [183]. As a consequence of this enzyme deficiency, there is intralysosomal accumulation of glycoprotein-derived, mannose-rich oligosaccharides. This rare disease has been reported in a 7 month old Domestic Shorthair (DSH) cat [184,185], in Domestic Longhaired (DLH) cats aged between 7 and 15 months [186], and in Persian kittens [187-189]. There is considerable heterogeneity among these reports regarding clinical onset, clinical course, and pathology. All cats have signs of apparent cerebellar dysfunction, including ataxia-dysmetria and intention tremors. However, stillbirths and neonatal deaths may occur in Persian litters and many affected animals may not survive the first 6 months of life [189]. Some affected cats show gingival hyperplasia, bizarre behavior, such as running in circles, jumping without provocation, and standing in the water bowl, and progressive dementia and apathy [187]. Other findings include corneal changes, open suture lines in calvaria, thymic aplasia, hepatomegaly, and polycystic kidneys. In the DSH cat, thoracic limb deformation due to lateral dysplasia of the carpus was noted at 4 months of age [184]. Other findings included radiographic abnormalities of the spine and long bones, cataracts and tapetal changes, hepatomegaly, lymphadenopathy, and thickened peripheral nerves. In DLH cats, additional clinical signs such as lurching, falling, opisthotonus, paraplegia, megaesophagus and systolic heart murmur have been reported; however, none had evidence of hepatomegaly, skeletal deformities or ocular abnormalities [186].

Microscopic lesions are characterized by extensive vacuolation of neurons and glial cells of the nervous system (more in astrocytes than oligodendrocytes), as well as in spinal and enteric ganglia [186]. Numerous vacuolated macrophages may be seen in peripheral nerves and in perivascular spaces of the CNS, and in a variety of parenchymal organs. Poor myelination of the cerebral white matter (especially in the corona radiata) and axonal spheroid formation (torpedoes, neuroaxonal dystrophy)

in cerebral and cerebellar white matter, thalamic radiations, and cerebellar roof nuclei have been observed in Persian kittens, while abnormally thin myelin was noted in DSH cats. Neither these changes nor the extensive vacuolation of hepatocytes and pancreatic acinar cells seen in Persian and DSH cats, were observed in the DLH cats [186], although abundant axonal spheroids were found ultrastructurally in DLH cats. Immunocytochemical studies showed that the spheroids reacted positively with glutamic acid decarboxylase, the synthetic enzyme for the inhibitory neurotransmitter, gamma- aminobutyric acid [107]. Extensive Purkinje cell loss was seen only in the DLH cats. In all cats, ultrastructural findings indicate that most neurons contain empty membrane-bound vacuoles or only small amounts of finely granular material. Some neuronal cytosomes have linear membranous profiles and vesicular or lamellar, membranous cytoplasmic bodies [184,186]. Lipofuscin-like inclusions may be seen in larger neurons. Vacuoles are present in CNS vascular endothelial cells and pericytes. Neuritogenesis, as determined by Golgi staining, is not as prominent in cortical neurons of mannosidosis cats as it is in other storage disorders, such as gangliosidosis, sphingomyelinosis, and mucopolysaccharidosis; however, meganeurites, secondary neurite formation, and various types of dendritic changes have been observed [190]. Very similar changes have been reported in swainsonine-induced feline α-mannosidosis [191].

Diagnosis is based on demonstrating a deficiency of acidic α-mannosidase in brain, liver or kidney, or detecting mannose-rich oligosaccharides in urine [192]. A three-fold increase in the level of alpha-D-mannoside has been reported in liver and brain of affected cats [193]. Lectin histochemistry on formalin-fixed, paraffin-embedded tissue sections is also a simple, reliable method for diagnosing alpha-mannosidosis [194]. Cytoplasmic vacuolation is seen in blood lymphocytes and monocytes in Giemsa-stained blood smears [188]. It is possible to distinguish between heterozygous and affected kittens by using enzyme assay and oligosaccharide determination in placenta: α-mannosidase activity is < 10% of control in affected kittens, and < 50% in heterozygous kittens [195]. Prognosis is poor. Treatment strategies are being investigated in colonies of affected cats. The cDNA encoding lysosomal alpha-mannosidase has been cloned in the Persian cat, and not surprisingly, in accordance with the variable clinical and pathological features, genetic studies have shown there is molecular heterogeneity for feline alpha-mannosidosis [196]. Researchers at the University of Pennsylvania, School of Veterinary Medicine, have also reported that retrovirus vector transfer of a new human alpha-mannosidase cDNA resulted in high-level expression of alpha-mannosidase enzymatic activity in deficient human and feline fibroblasts [197]. In a recent study by this group using Persian crossbred cats with a four base pair deletion in the gene encoding alpha-mannosidase [198], there was evidence of defective myelination in both CNS and PNS. Magnetic resonance imaging of the brains of affected cats revealed diffuse white matter signal abnormalities throughout the brain. Quantitative magnetization transfer imaging showed a 8 - 16% decrease in the magnetization transfer ratio in the white matter of affected cats compared to normal cats indicating myelin abnormalities. Histology confirmed myelin loss throughout the cerebrum and cerebellum. Affected cats showed slow motor nerve conduction velocity and increased F-wave latency. Single nerve fiber teasing revealed significant demyelination-remyelination in peripheral nerves. Ultrastructural findings in peripheral nerves included presence of numerous membrane-bound vacuoles within Schwann cell cytoplasm, endoneurial and perineurial macrophages, endothelial cells, and pericytes. The cytosomes were either empty or contained a fine fibrillar material. Many myelinated fibers were thinly myelinated and there was scattered presence of onion-bulbs and naked axons [198]. A significant increase in the G-ratio (axon diameter divided by fiber diameter) was identified in affected cats suggesting a decrease in total fiber diameter associated with myelin loss and/or hypomyelination.

Mucopolysaccharidoses

The mucopolysaccharidoses are a diverse group of inherited lysosomal diseases that result from deficits in the metabolism of certain glycosaminoglycans or acidic mucopolysaccharides, such as dermatan, heparan, chondroitin, and keratan sulfates, which accumulate in various connective tissues, as well as in brain, and are excessively excreted in urine. Thirteen subclasses of mucopolysaccharidosis have been described in people [199]. Clinically these diseases are characterized by multisystem abnormalities including skeletal alterations (e.g., facial dysmorphism), limited joint mobility, corneal clouding, hepatosplenomegaly, and mental retardation. Similar signs have been seen in dogs and cats, but usually without neurological involvement, despite accumulation of incompletely degraded glycosaminoglycans in the CNS. The mucopolysaccharidoses described in cats and dogs are considered to be recessively inherited.

Mucopolysaccharidosis Type I (MPS I) - caused by a deficiency of alpha-L-iduronidase, has been reported in Domestic Shorthair cats less than 6 months of age [200]. Signs include lameness, broad face with depressed nasal bridge and frontal bossing, small ears, corneal clouding, and multiple bone dysplasia, including fusion of vertebrae over the cervicothoracic junction, pectus excavatum, and bilateral coxofemoral subluxation. Neurological signs are usually not seen or mild, however exaggerated myotatic reflexes, impaired pelvic limb proprioception, along with reduced cervical mobility range and apparent pain on cervical palpation have been recently described suggesting possible cervical myelopathy [265]. Slowing of CNS conduction, predominantly in the cervical spinal cord, as determined by somatosensory evoked potentials, is supportive of

some form of cervical cord dysfunction in affected cats [265]. Cats excrete excessive amounts of glycosaminoglycans in urine, and glycosaminoglycan storage is evident in fibroblasts and neurons. Gross postmortem findings include hepatosplenomegaly, opaque meninges, and lateral ventriculomegaly. Membrane-bound vacuoles, either empty or containing a fibrillar material or lamellar cytoplasmic inclusions (zebra-like bodies) are present in CNS neurons, hepatocytes, chondrocytes, vascular and splenic smooth muscle cells, bone marrow leukocytes, and fibroblasts of the skin, eye, and cardiac valves [201]. Activity of alpha-L-iduronidase is deficient, e.g., approximately 5% of that of control cats in cultured fibroblasts and leukocytes [202]. An ill-defined relationship between MPS I and meningiomas has been reported in young cats less than 3 years of age [203]. Enzyme replacement therapy (recombinant alpha-L-iduronidase) was effective in reversing storage in some tissues at the biochemical and histological level in MPS I cats, although the enzyme was not consistently detected in cerebral cortex, brainstem, or cerebellum and the histological appearance and ganglioside profiles did not improve [204]. The mutation causing MPS I in cats has been identified and characterized [205]. Feline MPS I resembles Hurler's disease in people.
In dogs, a similar enzyme deficiency has been noted in Plott Hounds [206,207], which more closely matches Hurler-Scheie syndrome in people, a form of alpha-L-iduronidase deficiency of intermediate severity [207]. Clinical signs are seen in dogs less than 6 months of age, and are similar to those seen in cats with MPS I: corneal clouding, abnormal facies, impaired mobility, pain upon handling, stunted growth, joint stiffness, cardiac changes, and hepatosplenomegaly. Neurons at all levels of the CNS have varying degrees of cytoplasmic vacuolation, but neuronal loss or necrosis is not appreciable. There is vacuolation of perivascular mononuclear cells in the CNS, and leptomeninges are thickened and hypercellular [208]. Ultrastructural findings are similar to those seen in affected cats with both empty membrane-bound vacuoles and lamellar structures resembling zebra bodies. Cytoplasmic vacuolation, usually involving fibroblasts or fixed tissue macrophages, occurs in most extraneural tissues. Activity of alpha-L-iduronidase in the dogs is profoundly deficient (from 0 - 1% of the control mean values) in cultured fibroblasts and leukocytes [207]. Reduced levels of brain beta-galactosidase and increased levels of brain beta-hexosaminidase have been reported [208]. Increased amounts of dermatan sulfate and heparin sulfate are found in brain and many extraneural tissues (especially in liver) [208] and these glycosaminoglycans are excreted in urine. While Golgi impregnation studies in feline MPS I reveal that cortical pyramidal neurons may have axon hillock enlargements (meganeurites) and/or ectopic secondary neuritic processes, aspiny meganeurites without ectopic neurite growth have been reported in the canine disorder [209]. Fluorometric assays of alpha-L-iduronidase in serum are available for identifying affected, carrier, and normal dogs [210]. Allogenic bone marrow transplantation reportedly diminishes MPS I-related lesions in affected dogs [211,212]. In contrast, hematopoietic stem cell gene therapy has not produced clinical improvement in dogs [213,214].

Mucopolysaccharidosis Type II (MPS II) - or Hunter syndrome, has recently been reported in a 5 year old male Labrador Retriever with signs of progressive incoordination, visual impairment, and exercise intolerance [215]. Coarse facial features, macrodactylia, unilateral corneal dystrophy, generalized osteopenia, progressive neurologic deterioration, and a positive urine spot test for acid mucopolysaccharides suggested mucopolysaccharidosis. Intracytoplasmic vacuoles were most prevalent in epithelial cells, endothelial cells, and histiocytes of liver, kidney, thyroid gland, and spleen. Ultrastructural examination disclosed electron-lucent floccular or lamellar membrane-bound storage material characteristic of mucopolysaccharides. PAS-positive intracytoplasmic material was identified in multiple neurons in the medulla, pontine nucleus, cerebellum, and spinal gray matter horns. Biochemical assays identified a deficiency in iduronate-2-sulfatase (IDS) activity in cultured dermal fibroblasts compared with normal dogs. Hair root analysis for IDS showed that the dam was a carrier of X-linked Hunter syndrome and that a phenotypically normal male littermate of the affected dog was normal.

Mucopolysaccharidosis Type III A (MPS III A) - associated with a deficiency of the lysosomal enzyme heparan sulfate sulfamidase, has been reported in adult Wire-haired Dachshunds [216,217], and more recently, in New Zealand Huntaway dogs [273]. Around 3 years of age, dogs develop progressive neurological signs of ataxia and intention tremor. Dysuria may be seen late in the condition. Mentation remains normal throughout the course of the disease, which may extend over several years. A mucopolysaccharide storage is indicated by positive toluidine blue spot tests of urine. The diagnosis of MPS III A is confirmed by documentation of urinary excretion and tissue accumulation of heparan sulfate and decreased sulfamidase activity in fibroblasts and hepatic tissue. Mild cerebral cortical atrophy and dilation of the lateral ventricles may be grossly evident. Light microscopically, fibroblasts, hepatocytes, and renal tubular epithelial cells are vacuolated. Within the nervous system, cerebellar Purkinje cells, neurons of brainstem nuclei, ventral and dorsal horns, and dorsal ganglia are distended with brightly autofluorescent, PAS-positive, and sudanophilic material. Vacuolated macrophages may be seen in the meninges. Ultrastructurally, visceral storage presents as membrane-bound vacuoles with finely granular, variably electron-lucent contents. Neuronal storage appears as membranous concentric whorls, lamellated parallel membrane stacks, or electron-dense lipid-like globules. In one dog, additional lesions included calcium oxalate uroliths, severe secondary calcification of tissues including the brain, and storage deposits in some neurons [217]. This condition is being studied as a model of Sanfilippo

syndrome type A in people. The molecular defect has been identified in both canine breeds [218,273].

Mucopolysaccharidosis Type III B (MPS III B) - or Sanfilippo B syndrome, has recently been reported in Schipperke dogs in which pedigree analysis supported an autosomal recessive mode of inheritance [219,263]. In this report, clinical signs were seen in male and female Schipperkes around 3 years of age that were characterized by pelvic limb ataxia-dysmetria, wide-based stance, truncal swaying, occasional stumbling and falling, fine head intention tremor, and whole body tremor. The menace reaction was absent although pupillary light reflexes were normal, and peripheral retinal degeneration was noted. The condition was slowly progressive over several years. Granules in mononuclear blood cells stained positively with toluidine blue. The urinary mucopolysaccharidosis spot test was positive due to presence of heparan sulfate. Pathological findings revealed marked cerebellar atrophy, Purkinje cell loss, and neuronal and hepatic storage material that stained positively with toluidine blue and PAS. Activity of N-acetyl-α-D-glucosaminidase was <5% of normal. Other measured lysosomal enzyme activities were elevated. Note that the clinical signs described are similar to those seen in a 5 year old Schipperke with adult-onset galactosialidosis [76].

Mucopolysaccharidosis Type VI (MPS VI) - or Maroteaux-Lamy syndrome, has been reported in 2 to 3 month old Siamese cats [220], and recently in a 3 year old Siamese/shorthaired European cat [272]. This disorder, transmitted as an autosomal recessive trait, is caused by a deficiency of the enzyme arylsulfatase B (N-acetylgalactosamine-4-sulfatase) [221]. The clinical features of affected animals include small head, flat, broad facies, wide-spaced eyes, depressed bridge of the nose, corneal clouding, small ears, large forepaws, and a concave deformity of the sternum [222]. These signs are almost identical to cats with MPS I; however, Siamese cats have long bone epiphyseal dysplasia and toluidine blue-positive granules in circulating neutrophils. Signs of intracranial disease are usually not seen, although seizures have also been reported in a 2 year old Siamese cat with MPS VI [223]. Additional radiographic findings in Siamese cats may include long bone exostoses, severe spondylosis, severe osteoarthrosis of the articular facets of the entire spine, pectus excavatum, hypoplasia and fragmentation or abnormal ossification of the dens, and aplasia or hypoplasia of frontal and sphenoid sinuses. Hepatosplenomegaly is not a prominent feature [224]. Membrane-bound cytoplasmic inclusions have been noted in hepatocytes, bone marrow, granulocytes, vascular smooth muscle cells, and fibroblasts in skin, cornea, and cardiac valves. Lesions in CNS are reportedly restricted to mild ventricular dilatation, and perithelial cell vacuolation in the connective tissue of the meninges and choroid plexus, with membrane-bound inclusions in the cytoplasm of perivascular cells of the brain and spinal cord [224]. Neurons and glial cells are unaffected. It has been estimated that approximately 25% of immature cats with MPS VI develop clinical signs of a thoracolumbar syndrome secondary to cord compression from focal bony protrusions into the vertebral canal [222]. Signs are characterized by varying degrees of pelvic limb paresis that may progress to paraplegia, incontinence and depressed pain sensation caudal to the level of the thoracolumbar lesion. Spinal cord compression can be confirmed with myelography. Microscopic changes in the cord include myelin loss, Wallerian degeneration, astrocytosis, neuronal dropout, and neovascularization.
Affected cats with MPS VI excrete excess dermatan sulfate in the urine. Arylsulfatase B activity is less than 10% of normal in affected homozygous cats and 50% lower than normal in asymptomatic obligate heterozygous cats. Prognosis can be favorable in cats manifesting spinal cord signs with surgical decompression early in the course of the disease. The genetic mutation of this disorder has been identified and a rapid PCR-based screening method to genotype individuals has been developed [225]. It has been reported that two mutations within a feline mucopolysaccharidosis type VI colony cause three different clinical phenotypes [226]. Allogenic bone marrow transplantation can produce significant and sustained clinical and biochemical improvement in cats with MPS VI [227]. Resolution of corneal clouding and improvement in facial dysmorphia, walking ability, and better coat condition were reported, together with leukocyte arylsulfatase B activity and urinary dermatan sulfate excretion returning to normal. Enzyme replacement therapy in the MPS VI cat is also effective at reducing or eliminating pathology in most connective tissues, including bone development [228,229]. In one study, enzyme replacement therapy (recombinant feline N-acetylgalactosamine-4-sulfatase administered at a dose of 1 mg/kg of body weight), altered the clinical course of the disease in two affected cats treated from birth [230]. After 170 days of therapy, both cats were physically indistinguishable from normal cats with the exception of mild corneal clouding.
MPS VI has also been reported in several canine breeds, including Miniature Pinschers, Miniature Schnauzers, Chesapeake Bay Retreivers and Corgis [231,264] with clinical, radiographic, and biochemical findings similar to those seen in affected Siamese cats. Levels of both dermatan sulfate and chondroitin sulfate were increased in urine. Activity of arylsulfatase B was less than 1% of control values. The genetic mutation of this disorder has been identified and a DNA test is now available to distinguish between normal, carrier and affected animals [264].

Mucopolysaccharidosis Type VII (MPS VII) - associated with beta-glucuronidase deficiency has been reported in a dog, the offspring of a father-daughter mating [232]. Pelvic limb weakness was evident at 8 weeks of age and became progressively worse. The dog had a large head, a shortened maxilla, and corneal granularities. Most joints were extremely lax

and easily subluxated, with joint capsules that were swollen and fluctuant. The dog was alert and had apparently normal pain perception. No neurological signs were noted. At 13 months of age, there was radiographic evidence of extensive skeletal disease. The electrophoretic pattern of precipitated glycosaminoglycans indicated a predominance of chondroitin sulfate. The animal died suddenly from gastric dilatation. There was generalized hepatomegaly, thickening of the atrioventricular heart valves, and generalized polyarthropathy. Vacuolated cytoplasm was observed in hepatocytes, keratocytes, fibroblasts, chondrocytes and cells of the synovial membrane, retinal pigment epithelium, and cardiac valves. Neurons had cytoplasmic vacuoles. Electron microscopy demonstrated membrane-bound cytoplasmic inclusions in polymorphonuclear leukocytes, hepatocytes, synovium, heart valves and spleen. Levels of chondroitin sulphates were increased in urine. Tissue levels of beta-glucuronidase were very low. This disorder is similar to Sly syndrome in people. The biochemical and molecular defect in affected colony dogs have now been characterized [233,234] and a diagnostic screening test is available for detecting clinically normal carriers [235]. Bone marrow transplantation results in some improvement in the cardiovascular abnormalities in canine mucopolysaccharidosis VII [236], while gene transfer of low levels of beta-glucuronidase corrects hepatic lysosomal storage [237]. Recent studies indicate that neonatal gene therapy can prevent the clinical manifestations of MPS VII in dogs [268].

MPS VII has also been reported in a 12 to 14 week old male Domestic Shorthair cat with signs of walking difficulties (most of the weight was shifted to the front legs) and an enlarged abdomen. Facial dysmorphism, plump paws, corneal clouding, small ears, granulation of neutrophils, vacuolated lymphocytes, and a positive urine test for sulfated glycosaminoglycans suggested mucopolysaccharidosis. Activity of beta-glucuronidase was absent in leukocytes and markedly reduced in fibroblasts, thus establishing the diagnosis of mucopolysaccharidosis VII. Light microscopic examination revealed foam cells in virtually all organs examined, and electron microscopic examination showed pancytic storage of floccular material characteristic of mucopolysaccharides. Stored sphingolipids in the form of zebra bodies were seen in ganglion cells of the CNS and in smooth muscle cells of blood vessels. The molecular basis of feline beta-glucuronidase deficiency has been determined and a screening test is available for detecting clinically normal carriers in a breeding colony [238].

Sphingomyelinosis (Niemann-Pick Disease)

Sphingomyelinosis or sphingomyelin lipidosis denotes a heterogeneous group of lysosomal storage disorders marked by prominent organomegaly. In people, this condition is known as Niemann-Pick disease, and recent publications suggest there are several types (types A, B, C, D, and E) all of which have neurological involvement except types B and E [199]. Approximately 50% of the affected human patients with severe neurological signs belong in the type A group. Type C disease produces moderate neurological signs. The enzyme defect in types A, B, and C is sphingomyelinase; no defect has been identified as yet in type D disease, and the storage product in all types is sphingomyelin, a molecule containing a ceramide, a phosphoric acid ester, and choline [199]. Sphingomyelinase catalyses the hydrolysis of sphingomyelin to ceremide and phosphorylcholine.

In small animals, sphingomyelinosis has been reported in a 5 month old Miniature Poodle dog [239], a 5 month old Domestic Shorthair cat [240], in 3 to 4 month old Siamese cats [241], and in a 7 month old Balinese cat [242]. In the Siamese cats, the condition is inherited as an autosomal recessive trait. The disease results from a profound deficiency of lysosomal sphingomyelinase activity and is thought to be similar to **Niemann-Pick disease type A** [241,243], the most common and most severe form of Niemann-Pick disease that occurs frequently in individuals of Ashkenazi background [244]. Clinical signs in animals include ataxia, hypermetria, continuous head tremors, loss of equilibrium, and splaying of legs. Some animals manifest a stereotypic chewing behavior, lack of appetite and lack of interest in their surroundings. Signs can progress to visual impairment, total paresis and death before animals reach 1 year of age [241]. Hepatosplenomegaly has been seen in affected Siamese cats. In one report in an 11 month old Siamese cat, hepatomegaly but not splenomegaly was observed [245]. Pathological lesions are characterized by widespread cytoplasmic swelling and vacuolation of neurons in CNS and PNS, and foamy macrophages (so-called Niemann-Pick cells) in the bone marrow, lung, spleen, lymph nodes, liver, kidneys, adrenal glands and intestine. Storage material in the foamy cells of non-nervous tissues is reportedly different from those in affected cells of nervous tissues [246] where changes are most marked in Purkinje cells of the cerebellum, neurons of the cerebellar roof nuclei and hippocampus, and in dorsal roots and peripheral ganglion cells. In the spinal cord, affected neurons are especially numerous in the region of the ventral horns [240]. The neuronal changes are associated with nuclear margination and displacement of Nissl substance. Spheroids are commonly seen throughout the brain. Myelination of the brain and spinal cord is normal [242]. Ultrastructurally, neurons contain numerous membranous cytoplasmic bodies and occasional zebra-like bodies, while membranous and vacuolar profiles are reportedly more common in glial cells [242]. Membranous whorls are present in CNS endothelial cells and pericytes. Axonal spheroids contain membrane-bound dense bodies, mitochondria and variable membranous profiles. Many neurons in cerebral cortex, basal ganglia, amygdala, thalamus, and cerebellum show aberrant neurite growth and meganeurite formation, which may indicate dysfunction in the production and regulation of neuronal surface membranes [247]. Most lymphocytes and monocytes in blood smears contain cytoplasmic vacuoles.

A total deficiency of lysosomal (pH 5.0) sphingomyelinase is found in leukocytes, liver, and brain of the cats, although the activity of the microsomal (pH 7.4, magnesium-dependent) sphingomyelinase is normal in brain [241,243]. Cat brains contain an excess of GM2- and GM3-gangliosides, and a nine- to ten-fold excess of sphingomyelin and cholesterol occurs in liver of affected cats. Leukocyte sphingomyelinase levels are about half of the normal level in phenotypically normal littermates of affected kittens suggesting an autosomal recessive mode of inheritance [241].

Phenotypic Variant of Niemann-Pick Disease Type A - Characterized by a neuropathic syndrome, with mild or no CNS signs, has been observed in several related and unrelated Siamese cats [248]. Signs in affected animals include absent conscious proprioception, severely depressed to absent spinal reflexes, hypotonia, fine generalized muscle tremors (especially in pelvic limbs), a palmigrade-plantigrade stance, and moderate hepatosplenomegaly. Pain perception and cranial nerve function are normal. Motor nerve conduction velocities are markedly depressed. Positive sharp waves and fibrillation potentials are recorded only sporadically in muscles. While little changes are present in skeletal muscles, peripheral nerves show widespread myelin degeneration associated with many vacuolated macrophages interspersed within the nerve fibers. Remyelination and/or hypomyelination are prominent. Marked vacuolation and granular distension are seen in neurons, glial cells, endothelium, choroid plexus epithelium, and ependyma. Neurons in autonomic and dorsal root ganglia are similarly affected. Vacuolated macrophages, with metachromatic granules, are widely scattered throughout the CNS parenchyma. There is widespread infiltration of virtually every body system with distended granular macrophages. Biochemical analysis of CNS and viscera suggested that the condition in one of these cats was similar to Niemann-Pick disease type A in people [248]. In the other cats, a type A variant was suggested, based on less dramatic increase in sphingomyelin content in liver and kidney, modest increase in brain sphingomyelin content, and lack of detectable enzyme deficiency in known heterozygotes. All cats tested showed severe reduction in CNS and visceral lysosomal sphingomyelinase activity.

Niemann-Pick Disease Type C - Another form of sphingomyelinosis has been recognized in Domestic Shorthair cats, similar to the infantile form of Niemann-Pick disease type C (NPC) in people [249-251], an autosomal recessive neurovisceral lysosomal storage disorder in which cholesterol lipidosis results from defective intracellular transport of unesterified cholesterol. A recent study suggests that the underlying defect in the major form of human NPC and this feline model of NPC involve orthologous genes [252]. Affected animals manifest clinical signs around 6 to 9 weeks of age that are similar to those previously described above in cats with Niemann-Pick disease type A: ataxia-dysmetria, whole body tremor, intention tremor of the head, with progression over 4 to 6 months to moving in a crouched gait, loss of menace deficit, inability of cats to right themselves from lateral recumbency, and eventually, generalized disuse muscle atrophy [249]. Other CNS signs seen infrequently in some cats include depressed mentation, vestibular signs, anisocoria and hemiparesis. Affected cats have abdominal enlargement due to palpable hepatomegaly around 8 weeks of age, without clinical manifestations of liver disease [249]. Pathological findings in the CNS included distention and vacuolation of many neuronal cell populations in brain, spinal cord and ganglia, accompanied by extensive neuroaxonal dystrophy (eosinophilic axonal spheroids), especially in the cerebellar folia. Myelin loss and macrophage infiltration in the white matter of the spinal cord, particularly involving the spinocerebellar tracts have been observed in some cats [249]. Many foamy macrophages are found in liver, spleen, lymph nodes and lungs. Ultrastructural studies of affected tissues and organs show heterogeneous membranous inclusions. Immunocytochemical, histochemical, and Golgi studies indicate that gangliosides and unesterified cholesterol are differentially stored in neurons of the cerebral cortex, cerebellum, and hippocampus, as well as in liver [253]. Clinical neurological signs in feline NPC occur in parallel with neuronal structural alterations suggesting that GABAergic neuroaxonal dystrophy is a contributor to brain dysfunction in this disease [254]. In affected NPC cats, lipid analysis reveals excess cholesterol, glucosylceramide, lactosylceramide and phospholipids, including sphingomyelin, in liver [250]. In addition, levels of brain GM2- and GM3-gangliosides are increased. Sphingomyelinase activity in liver is partially deficient or low normal. Cultured skin fibroblasts have partially decreased sphingomyelinase activity and a decreased ability to esterify exogenous cholesterol [250]. Liver lipid analyses of obligate heterozygote cats demonstrates intermediate cholesterol and sphingomyelin concentrations. Furthermore, vacuolated skin fibroblasts, cortical neurons with intracellular inclusions immunoreactive for GM2-ganglioside, and ultrastructural studies with evidence of storage in liver and brain have been reported in heterozygote NPC cats [255].

Prognosis is poor in cats with sphingomyelinosis. Treatment strategies are being investigated in institutions containing colonies of cats with varying forms of sphingomyelinosis, e.g., therapeutic bone marrow transplantation in cats with NPC [249]. Dietary cholesterol restriction does not appear to alter disease progression in NPC-affected kittens [249,269].

A heterogeneous lipid storage disease similar to the human NPC has also been reported in a 9 month old boxer dog with progressive neurological abnormality [256]. Histological examination revealed marked neuronal storage throughout the CNS and histiocytic storage in the reticuloendothelial system. Ultrastructurally, the neuronal storage consisted of accumulation of concentric membranous inclusions and clusters of dense bodies. The biochemically unesterified cholesterol content was high in the liver and spleen. The brain showed increased levels of lactosylceramide and GM2 and GM3 gangliosides [256].

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