

The Pathology of the Feline Model of Mucopolysaccharidosis I

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Five cats with feline α -L-iduronidase-deficient mucopolysaccharidosis were studied. Membrane-bound cytoplasmic inclusions were present in central nervous system neurons, hepatocytes, chondrocytes, vascular and splenic smooth muscle cells, bone marrow leuko-

cytes, and fibroblasts of the skin, eye, and cardiac valves. The lesions in these cats closely resemble those described in human patients with mucopolysaccharidosis I H (Hurler syndrome). (Am J Pathol 1983, 112: 27-36)

THE GENETIC MUCOPOLYSACCHARIDOSES (MPSs) are a group of diseases that result from defects in glycosaminoglycan (GAG) metabolism. At present, there are 12 subclassifications in man, each of which has a characteristic combination of clinical signs, urinary GAG excretion, and a specific lysosomal enzyme deficiency.¹⁻³

Two of these subclasses, MPS I and MPS VI, have been described in domestic cats.⁴⁻⁷ This report describes the pathologic features of MPS I in cats and compares the lesions in cats with those described in man.

Materials and Methods

Five cats clinically affected with MPS I were studied. The animals excreted excess dermatan and heparan sulfate in the urine,⁴ and the activity of the enzyme α -L-iduronidase in peripheral leukocytes was markedly decreased (2.7, 2.3, 2.3, 0.4, and 2.0 nmol/hr/mg protein in leukocytes versus 48.8 nmol/hr/mg protein in leukocytes from normal animals).⁴ All 5 were white domestic short-haired cats. Four were produced within the animal colony at the School of Veterinary Medicine, University of Pennsylvania, by outcrossing an obligate carrier female to a normal male and then performing brother-

sister matings (Figure 1, Animals 1-5). At the time of death 2 of the animals, a male and a female, were 10 and 12 months of age (Figure 1, Cats 2 and 1, respectively). One female was 2 years of age (Cat 3), and 2 males were 2 years 6 months and 2 years 9 months of age (Cats 5 and 4, respectively).

Two animals died (Animals 3 and 4), 2 were killed by the intravenous administration of an overdose of barbiturate (Animals 1 and 2), and 1 cat was killed by exsanguination under ketamine anesthesia (Animal 5). Unfixed tissue samples were frozen in liquid nitrogen, sectioned on an IEC CTF microtome cryostat, and stained with periodic acid-Schiff, toluidine blue, or oil red O. Tissue samples for light-microscopic examination were fixed in 10% buffered formalin, paraffin-embedded, sectioned, and stained with hematoxylin and eosin (H&E), Bodian, luxol blue-periodic acid-Schiff-hematoxylin, trichrome phos-

Supported by NIH Grants AM-25759, EY-3400, EY-1583, GM-25279 (2T32-HD-07105), Genetics Center Grant GM-20138, and March of Dimes Birth Defects Foundation Grant I-578.

Accepted for publication February 18, 1983.

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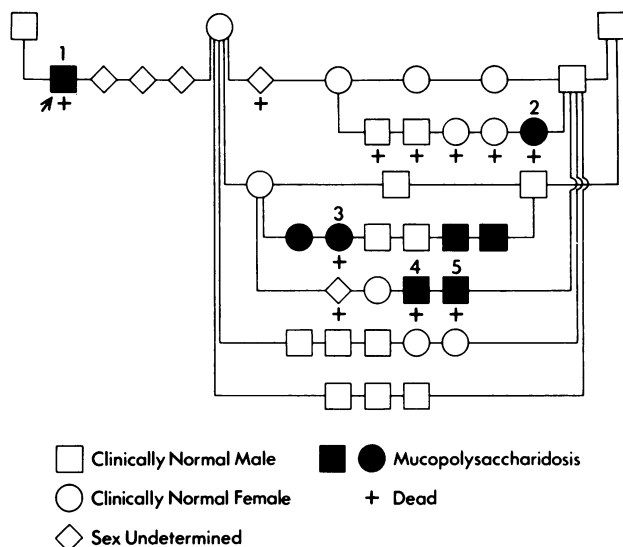


Figure 1—The pedigree of the family of cats with MPS I. The mother of the propositus (arrow, Animal 1) was mated to a normal, unrelated male. Brother-sister matings produced animals 2, 3, 4, and 5.

photungstic acid-hematoxylin, or azure II–methylene blue. Tissue samples for ultrastructural examination were fixed overnight in cacodylate-buffered glutaraldehyde at 4 C, postfixied in osmium tetroxide, dehydrated, and embedded in Spurr's medium⁸ or Epon. One-micron-thick sections were stained with azure II–methylene blue for light-microscopic examination. Ultrathin sections (silver interference) were taken from selected areas, stained with uranyl acetate and lead citrate, and examined with a Zeiss EM 9S-2 transmission electron microscope.

Results

Clinical History

The affected animals raised in the animal colony were identified at weaning (6 weeks) by the Berry Spot test⁹ for excessive urinary glycosaminoglycans, shown previously to be dermatan sulfate and heparan sulfate by cellulose acetate electrophoresis.⁴ Typical facial dysmorphism was present at weaning, but because of the normal facial variability in domestic short-haired cats, it was not as striking as that seen in Siamese cats with MPS VI (Maroteaux–Lamy syndrome). As adults, all 5 affected cats had facial dysmorphism, with a thick neck, large head, frontal bossing, depressed nasal bridge, and small ears. Each affected cat had diffuse bilateral corneal clouding resulting from fine granular opacities present at all levels of the corneal stroma when observed by retroillumination or slit-lamp biomicroscopy. Toluidine-

blue-stained leukocytes in peripheral blood smears did not contain prominent granules as seen by light microscopy. A Grade IV/V holosystolic heart murmur compatible with mitral insufficiency was detected in Animals 1 and 5.

The radiographic features of this disease were characterized by bilateral hip subluxation, fusions and widening of the cervical vertebrae, and pectus excavatum. Dwarfing was not seen; in fact, these cats, particularly the males, were larger than unaffected sex-matched relatives of the same age.

All animals exhibited hind-leg gait abnormalities compatible with the degree of skeletal disease. Neurologic examination showed no abnormalities prior to 2.5 years of age. Until that age the animals appeared neurologically intact, active, alert, and responsive. Two animals developed neurologic abnormalities at 2.5 years of age. One exhibited clonus in response to the patellar myotonic stretch reflex at the time it was killed (2.5 years). The oldest animal (2 years 9 months) developed hind-limb paralysis with extensor tone, exaggerated hind-limb reflexes with clonus, abnormal fore-limb gait, and lack of a menace response. In this animal the neurologic abnormalities were observed to be slowly progressive over a 6-week period.

Pathologic Findings

Liver

The liver of each animal was enlarged, with a prominent lobular pattern and an increased firmness. By light microscopy, the hepatocytes of the oldest animal had multiple, clear cytoplasmic vacuoles and an eccentrically located nucleus. The hepatocytes in the remaining animals had a finely granular, eosinophilic cytoplasm without prominent vacuolation. The Kupffer cells in all animals were large, with a lacy, eosinophilic or clear cytoplasm. Seen by electron-microscopy, hepatocytes contained membrane-bound cytoplasmic inclusions, which contained granular material or lamellar bodies (Figure 2). Kupffer cells were filled with electron-lucent or granular inclusions, which often appeared to have coalesced.

Spleen

The spleens were enlarged and firm, with a gray-white capsular surface, which, histologically, was thickened. Ultrastructurally, the smooth muscle cells of the trabeculae contained membrane-bound cytoplasmic inclusions linearly arranged and extending from the perinuclear region along the long axis of the cell. Many of these inclusions contained membranous cytoplasmic inclusions or "zebra" bodies.

Central Nervous System

The meninges were more opaque than normal, and the lateral cerebral ventricles of the brain of 2 of the 5 cats (Figure 1, Cats 3 and 5) were larger than normal.

A spherical 5-mm pale, white-gray mass, characterized histologically as a meningioma, was observed in the tela choroidea of the third ventricle in Cat 4. Of the 5 cats, 3 had meningiomas in the tela choroidea of the third ventricle. In addition, other smaller meningiomas were present throughout the meninges, some containing psammoma bodies.

By light microscopy, neurons in virtually every area of the central nervous system, including the spinal cord, medulla oblongata, pons, midbrain, diencephalon, cerebellum, and cerebral cortex were swollen with cytoplasmic vacuoles (Figure 3). Many of these cytoplasmic vacuoles stained with oil red O, indicating the presence of lipid. The numbers of cells affected and the number and size of cytoplasmic vacuoles present in CNS neurons varied between animals. The brain stem was severely affected in all animals; the cortex and cerebellum were most severely affected in the 2 cats (Animals 3 and 4) that died spontaneously. Neuronal loss and astroglyosis was most severe in those cortical areas adjacent to thickened leptomeninges. In these focal areas the

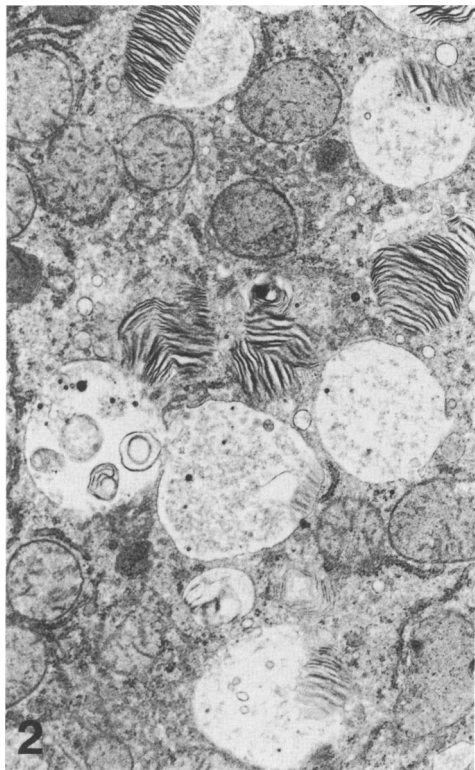


Figure 2—Electron micrograph of the membrane-bound, cytoplasmic inclusions present within a hepatocyte from Cat 1. The inclusions contain granular and lamellar material, which can be present in the same inclusion. (Uranyl acetate and lead citrate, $\times 4800$)

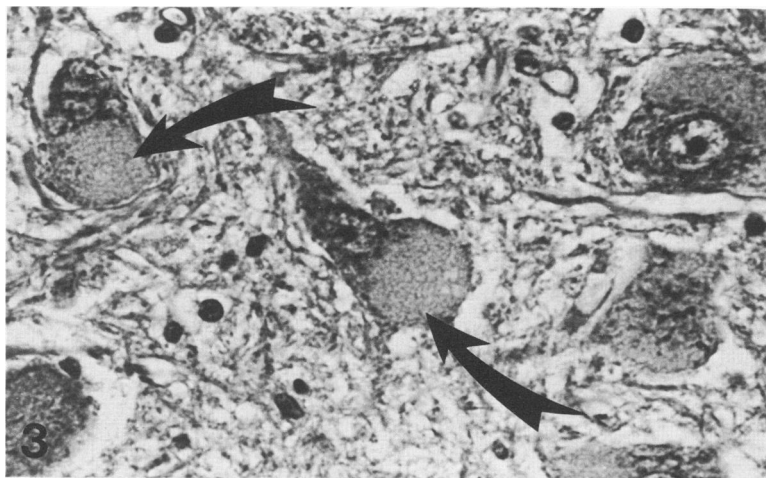
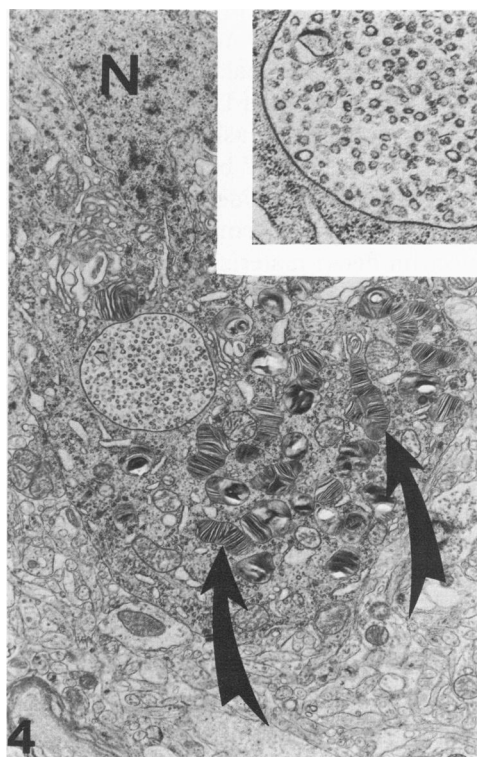


Figure 3—Light micrograph of neurons in the nucleus of the facial nerve of Cat 3. Note the cell distortion due to an increase in granular cytoplasm (arrows). (H&E, $\times 100$) **Figure 4**—Electron micrograph of a cortical neuron from Cat 5. Note the numerous "zebra" bodies in the cytoplasm and the large membrane-bound structure containing inclusions that resemble swollen synaptic vesicles (inset). The significance of this structure is not known. N, nucleus. (Uranyl acetate and lead citrate, $\times 4750$)



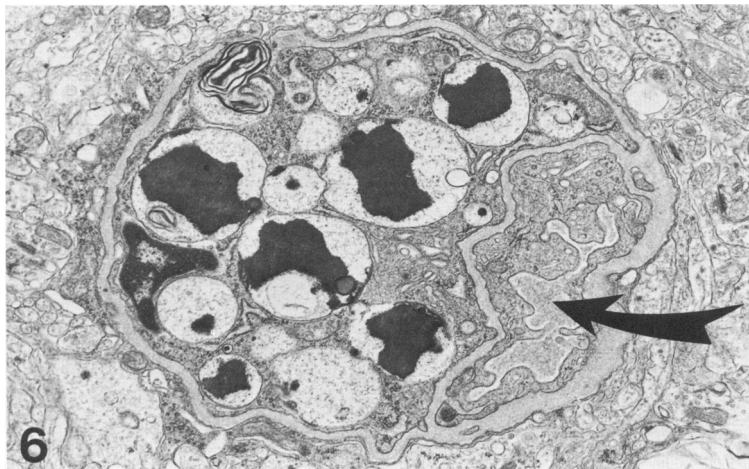


Figure 5—Electron micrograph of membrane-bound “zebra” bodies in the cytoplasm of a cortical neuron from Cat 5. (Uranyl acetate and lead citrate, $\times 9500$)
Figure 6—Electron micrograph of a vessel from the cortex of cat. Note the vascular lumen (*arrow*) and the large membrane-bound inclusions within the perithelial cytoplasm. The inclusions contain granular, lamellar, and irregular dense material. (Uranyl acetate and lead citrate, $\times 4750$)

meninges contained an increased amount of collagen and mononuclear cells having extensive, vacuolated cytoplasm. Perivascular cells throughout the CNS were highly vacuolated, with large, clear vacuoles surrounding vessels of all sizes.

Seen by electron microscopy, the perikaryon in neurons from the thalamus, cortex, cerebellum, medulla, and spinal cord were packed with membrane-bound, lamellar inclusions similar to what have been described as “zebra” bodies (Figures 4 and 5). Perivascular cells contained large vacuoles, which were electron-lucent or contained granular or irregular electron-dense material (Figure 6).

Eye

Intracytoplasmic vacuoles were present in fibroblasts in the cornea, sclera, choroid, conjunctiva, trabecular meshwork, iris stroma, and ciliary processes. Affected cells showed increased cytoplasmic volume and altered cellular contours. In some cells, the variable size of the vacuolated inclusions suggested fusion of intracellular inclusions. The corneal endothelial cells contained numerous small vacuoles throughout the cytoplasm but were not hypertrophied (Figure 7). The ultrastructural appearance of these vacuoles was variable and, to some extent, dependent on the tissue of origin. Those in the keratocytes appeared electron-lucent, with a faint residual

granular matrix; in other tissue the fibroblast inclusions appeared more granular. Seldom were lamellar bodies found in association with the vacuolated inclusions (Figure 8).

Vacuolated intracytoplasmic inclusions were also present in tissues of neuroectodermal origin. Although in the nonpigmented epithelia of the ciliary processes the inclusions were most distinct as seen by light microscopy (Figure 9), electron microscopy indicated that both pigmented and nonpigmented cells were affected. Similarly, the pigmented iridal epithelium also contained vacuolated inclusions.

In tissues stained by azure II–methylene blue, the nonpigmented retinal pigment epithelium (RPE) contained homogeneous blue inclusions, indicating GAG, bounded by a slightly darker limiting membrane (in the cat, the retinal pigment epithelium overlying the tapetum lucidum is not pigmented). These inclusions occupied most of the cell’s cytoplasm but did not result in hypertrophy. The pigmented RPE had similar inclusions, but these were less distinct. Ultrastructurally, the inclusions in both pigmented and nonpigmented RPE cells were similar; single membrane-bound granular inclusions were abundantly distributed throughout the cytoplasm.

No abnormalities were found in the retinal photoreceptors. In contrast, the perivascular glial cells associated with the capillaries in the outer plexiform

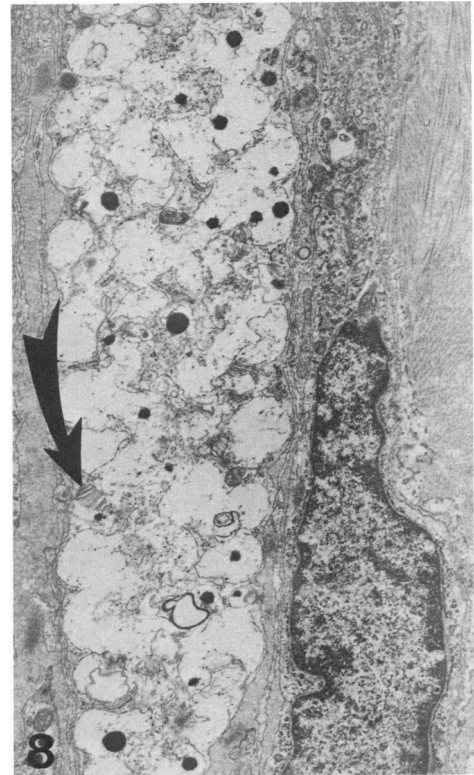
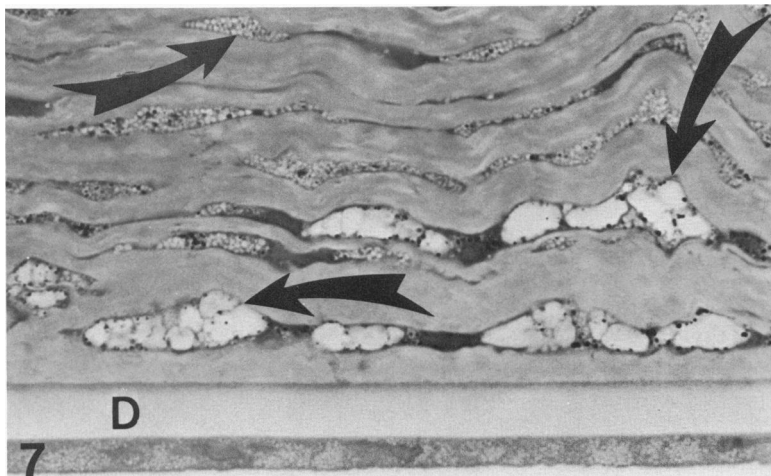


Figure 7 — Although all stromal keratocytes show an intracellular accumulation of inclusions (*arrows*), only those anterior to Descemet's membrane (*D*) are hyperthrophied. Numerous small vacuolated inclusions are present in the endothelium. (Azure II-methylene blue, $\times 800$) **Figure 8** — The cytoplasm of a choroidal fibroblast is filled with membrane-bound inclusions; most are electron-lucent, with a residual granular matrix. Lamellar bodies are visible in some of the inclusions. (Uranyl acetate and lead citrate, $\times 9200$)

layer were greatly distended, and the cytoplasm was filled with large pale inclusions. The ganglion cells and their axons were normal (Figure 10).

Skin

The skin, particularly over the dorsal neck, was thickened. Seen by light microscopy, this thickening appeared to be due to an increase in dermal collagen rather than an increase in cell size due to lysosomal storage. The fibroblasts, however, contained small electron-lucent or granular cytoplasmic inclusions. Collagen and mast cells appeared normal.

Cardiovascular System

The atrioventricular heart valves and chordae tendineae were thickened, white, and nodular; and, in 4 of the affected cats, the aortic valves were also thickened. The valvular lesions were somewhat more severe in the animals with murmurs. Seen by light microscopy, the valvular cells were enlarged and round, with vacuolated cytoplasm. Seen by electron microscopy, these cells were packed with electron-lucent cytoplasmic vacuoles, some of which appeared to have coalesced. The nuclei of these cells were distorted in outline, having indentations in the nucleus (Figure 11). The myocardium contained plump, elongated connective tissue cells with small, dark nuclei

and vacuolated cytoplasm that separated myocardial fibers. Several intramural arteries in the 2 oldest animals were narrowed by the presence of large cells within the vessel wall. The aorta appeared normal grossly; but seen by light microscopy, the cells of the tunicae intima and media were enlarged, with a central nucleus and lacy eosinophilic cytoplasm. Seen by electron microscopy, these cells contained large numbers of membrane-bound granular inclusions, some of which appeared to have coalesced and which fit into indentations in the nucleus (Figure 12).

Bone Marrow

Ten to 20% of mononuclear and polymorphonuclear leukocytes were observed to contain small, granular, cytoplasmic inclusions, which were only visualized by electron microscopy (Figure 13). These inclusions were present in some granulocytes in association with the dense crystalloid material characteristic of the eosinophil.

Cartilage and Bone

The atlantooccipital joint and cervical intervertebral articulations were fused. Grossly, the femoral heads appeared normal. Histologically, the articular cartilage of the femoral head contained enlarged chondrocytes which had vacuolated cytoplasm.

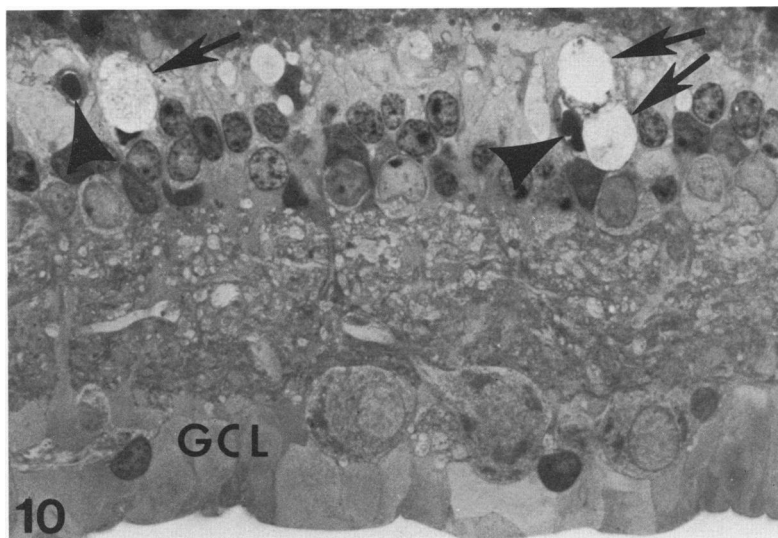
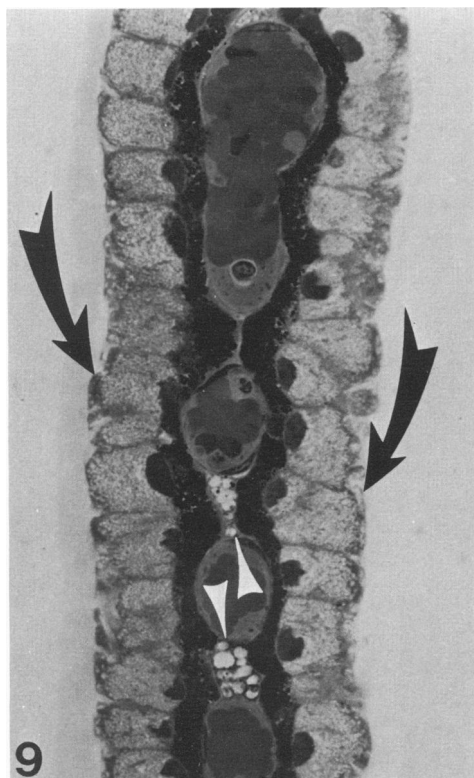


Figure 9—A longitudinal section of the ciliary process demonstrates swelling of the nonpigmented epithelium (arrows), accumulation of vacuolated inclusions, and apical displacement of nuclei. The pigmented epithelium is compressed. Stromal fibroblasts (arrowheads) contain vacuolated inclusions. (Azure II-methylene blue, $\times 640$) **Figure 10**—Glial cells (arrows) associated with capillaries (arrowheads) in the outer plexiform layer are distended and vacuolated. The three large ganglion cells present in the ganglion cell layer (GCL) are normal. (Azure II-methylene blue, $\times 800$)

Similar cells were observed in the cartilage of ribs, trachea, and large bronchi. Areas of trabecular bone in the femoral head contained islands of cartilage with an irregular matrix that stained unevenly. Seen by electron microscopy, the cytoplasm of articular chondrocytes contained membrane-bound inclusions, which were electron-lucent or contained granular or membranous material (Figure 14).

Smooth and Skeletal Muscle

The smooth muscle of the stomach and intestine and the skeletal muscle of the diaphragm appeared normal. However, the associated connective tissue cells were plump, with vacuolated cytoplasm, producing an apparent separation of myocytes. In the small intestine, these vacuolated cells were contiguous and produced a distinct band of separation between the submucosa and muscularis externa.

Discussion

Mucopolysaccharidosis I in man is presently divided into three syndromes: the Hurler Syndrome (MPS I H), the Scheie syndrome (MPS I S), and the intermediate phenotype Hurler/Scheie syndrome (MPS I H/S). Initially the Scheie syndrome, first described in 1962,¹⁰ was classified by clinical pheno-

type as MPS V. Subsequent biochemical findings clearly demonstrated that MPS I and MPS V were due to allelic mutations which produce a deficiency in α -L-iduronidase activity.¹¹⁻¹³ Because these two syndromes are caused by a deficiency in activity of the same enzyme, they have been reclassified as MPS I H and MPS I S, respectively. Individuals with a phenotype intermediate between the two syndromes are considered to be either compound heterozygotes or homozygotes for a third allelic mutation at the locus for α -L-iduronidase.¹⁴⁻¹⁷

The clinical and pathologic syndrome in cats with α -L-iduronidase deficiency has many features analogous to those observed in children with MPS I H, including the presence of facial dysmorphism, a large head, frontal bossing, and a depressed nasal bridge, excretion of excessive amounts of dermatan and heparan sulfates, diffuse bilateral corneal clouding, and mitral insufficiency. In affected cats, Alder-Reilly bodies have not been found in peripheral blood smears. Although often seen in children with MPS I H,¹⁸ these granules are not always easily demonstrated.¹⁹ The radiographic features of the disease are also similar to those seen in man, particularly the cervical and pelvic abnormalities.

One of the major clinical differences between MPS I H and MPS I S in man is the severity of

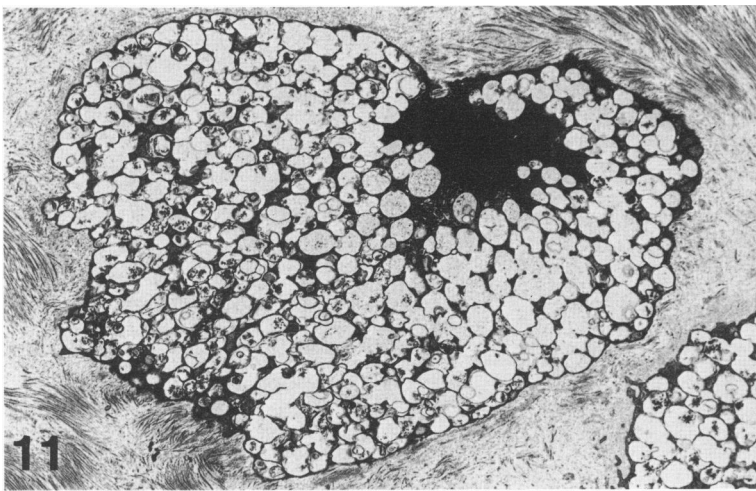


Figure 11—Electron micrograph of a cell from the mitral valve filled with membrane-bound inclusions, some of which fit into nuclear indentations. (Uranyl acetate and lead citrate, $\times 1900$) **Figure 12**—Electron micrograph of a cell from the aortic media from Cat 5, showing the large number of membrane-bound, granular cytoplasmic inclusions. (Uranyl acetate and lead citrate, $\times 1900$)



neurologic involvement.¹ Children with MPS I H are severely retarded, whereas individuals with MPS I S usually have normal intelligence. Patients with MPS I H/S have been reported both with and without intellectual impairment. In cats, however, it is difficult to assess mentation in a way that would identify a deficit comparable to mental retardation in man. Psychomotor testing in cats with MPS I is made more difficult because of the severe skeletal lesions and corneal clouding. In addition, all of the cats studied were heterozygous or homozygous for the dominant white spotting gene, which has, as a pleiotropic effect, varying degrees of deafness.²⁰ The animals observed until 2.5 years of age appeared active, alert, and responsive; but because they had been raised in an animal colony, it was perhaps difficult to appreciate subtle differences that might be apparent in a more variable environment.

Another difference between MPS I S and MPS I H in man is the length of survival. Children with MPS I H usually die within the first decade, while those with MPS I S survive into their adult years. Cats with MPS I have survived to 2.5 years of age before demonstrating neurologic abnormalities. Two of the animals that were greater than 2 years of age apparently succumbed to the disease or its complications. Although these cats did live beyond puberty,

unlike most children with MPS I H, it would appear that the critical factor may be the age of the neuron, relative to the rate of GAG storage, rather than its age relative to sexual maturity. It is of interest to note that cats with GM₁ and GM₂ gangliosidosis, α -mannosidosis, and sphingomyelinosis do not survive beyond about 1 year of age.²¹⁻²⁴

The neuropathologic lesions of MPS I H in man are the most severe and diffuse; those of MPS I S are the least severe, and those of MPS I H/S are intermediate.^{25-28,49} The degree of neuronal involvement has been reported to be extensive in MPS I H.^{26,27} The neurons of the cortex and brain stem had cytoplasm distended by excessive material, positive for lipid by special stains, within cells in various stages of degeneration and shrinkage. Gliosis was present in the white and gray matter. In contrast, patients with MPS I S had normal neurons with no secondary degeneration or gliosis.²⁵ In a case of MPS I H/S, neuronal storage was not present in the cerebral cortex or cerebellum; however, storage was present in the spinal cord and the brain stem.²⁷ In another case classified as MPS I H/S, occasional large neurons with granular inclusions were observed in the cerebral cortex, basal ganglia, cerebellum, brain stem, and spinal cord.¹⁴ A third case had no neuronal storage.⁴⁹ The degree of ventricular dilatation appeared most

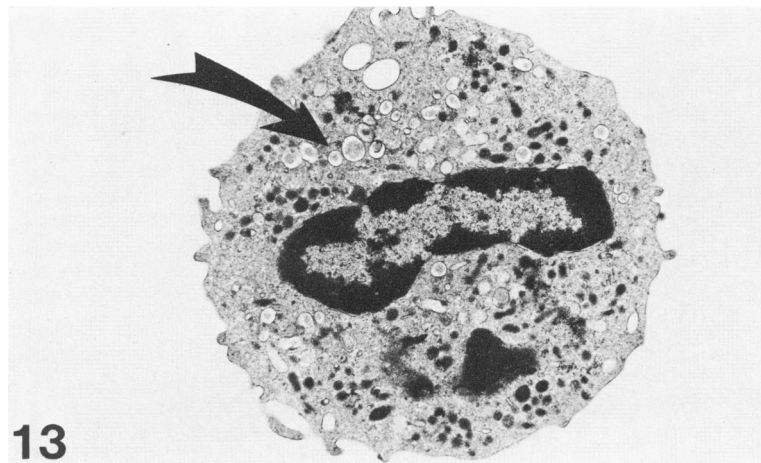


Figure 13— Electron micrograph of a bone marrow neutrophil of Cat 1. In addition to the normal granules present within the cytoplasm, there are larger inclusions that contain granular material (*arrow*). (Uranyl acetate and lead citrate, $\times 8500$)

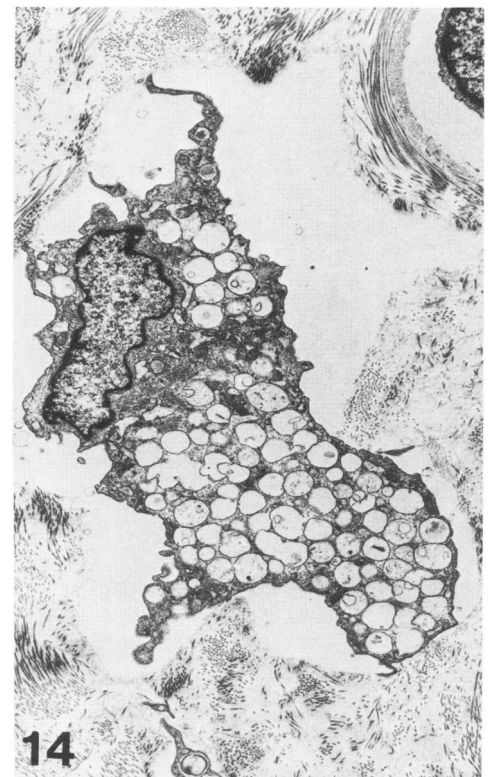


Figure 14— Electron micrograph of a chondrocyte from the articular surface of the femur of Cat 5. Note the distorted cellular outline and the cytoplasmic inclusions, some of which contain granular material. (Uranyl acetate and lead citrate, $\times 1900$)

marked in cases of MPS I H and H/S, compared with MPS I S. It would appear that, on the basis of the degree and distribution of neuronal lesions, the cats with MPS I most closely resemble human patients with MPS I H.

Cortical pyramidal neurons demonstrating meganeurites with spines and spine synapses have been described in a case of MPS I H in man.²⁹ Neural tissue from Cat 5 has been examined by the same Golgi staining technique, revealing cortical pyramidal neurons with axon hillock enlargement, as well as meganeurites which often possessed spines or neurites.³⁰

Perivascular zones of the central nervous system (CNS) in all three MPS I syndromes have been reported to contain delicate fibrillar networks and large cells with vacuolated cytoplasm.²⁵⁻²⁸ By electron microscopy, pericytes and perivascular macrophages in a case of MPS I S had large collections of compact, concentric membrane fragments. Both of these changes were observed in the cats with MPS I.

The meninges in all three syndromes are reported to be thickened and to contain numerous large clear cells. However, meningiomas have not been reported in children with MPS I. These lesions in cats are of interest because, although meningiomas have been described in cats, they are found almost exclusively in

animals older than 9 years of age.³¹ It is remarkable that multiple meningiomas were present in 3 of 5 animals that were less than 3 years of age. The significance of this finding is, at present, unclear.

Hepatosplenomegaly and cytoplasmic vacuolation of hepatocytes and Kupffer cells has been described in man with MPS I H, I S, and I H/S.^{14,25,27,28,32,33,49} Similar lesions were present in these cats. The reports of splenic pathology in MPS I S and I H indicate considerable numbers of vacuolated cells present in the sinusoids associated with connective tissue, particularly adjacent to blood vessels.^{25,28} Similar cells in splenic sinusoids were not observed in the feline model. Splenomegaly appeared related to lysosomal storage within smooth muscle trabeculas.

The ocular lesions present in the affected cats were similar to those reported for MPS I H.³⁴ Glycosaminoglycan storage, indicated by the accumulation of intracytoplasmic inclusions, was present in most ocular tissues. A difference, however, exists in the extent of retinal abnormalities found in the two species. Whereas patients with MPS I H had vacuolated ganglion cells, degenerate photoreceptors and abnormal pigment epithelium, the MPS-I-affected cats did not. This may represent a species difference in the expression of the metabolic disease. Alternatively, since retinal pigmentary degeneration is not a ubiqui-

tous finding in all MPS I H patients, this finding in the feline may represent one of the variant human phenotypes.^{35,36}

Reported abnormalities in the skin of patients with MPS I H have included fibroblasts and macrophages bloated with inclusions, and similar changes present in Schwann cells, smooth muscle cells, keratocytes, and the secretory coils of the eccrine sweat glands.^{37,39} Some keratocytes, less than 20%, had occasional swollen cytoplasm. Other than a general increase in skin thickness and the presence of inclusions within dermal fibroblasts, the skin was normal in affected cats.

In MPS I H in man, mitral valves have been described as pearly white, thickened, and beaded, with similar changes present in the chordae tendineae.⁴⁰ Seen by electron microscopy, the cells of the mitral valve were large, irregular, and contained clear vacuoles whose membranes were often broken. Occlusion of the coronary arteries has been reported in MPS I H. By electron microscopy, smooth muscle cells in the inner media and intima of the aorta were distended by cytoplasmic vacuoles.^{41,42} Similar valvular and vascular pathology has been reported in MPS I S and MPS I H/S.^{14,25,49} The cardiovascular lesions of the feline model resemble those of human MPS I.

White blood cells in MPS I H have been shown to contain multiple, clustered cytoplasmic vacuolations, particularly in lymphocytes and large mononuclear cells.^{43,44} These inclusions were not visualized by light microscopy in the feline model. By electron microscopy, 20–38% of peripheral blood lymphocytes in human patients contained vacuoles. Inclusions present in bone marrow cells from affected cats were similar in structure, but fewer in number, than those described in man.

In MPS I H in man, a characteristic abnormality in bone and cartilage is the presence of large chondrocytes filled with lysosomal vacuoles and growth plates, which are focally disrupted by large areas of connective tissue.⁴⁵ Electron-microscopic study has revealed huge chondrocytes with smooth periphery and innumerable densely packed cytoplasmic vacuoles, which appeared empty or contained a few delicate filaments.^{46,47} These vacuoles often coalesced. Cysts in the femoral head have been described in MPS I S.⁴⁸ Although bone cysts have not been observed in the feline, the histologic and ultrastructural lesions in cartilage and bone resemble those described in man.

Feline MPS I, with its clinical, biochemical, and pathologic similarities to MPS I in man, should prove to be a useful model in the study of lysosomal

storage disease pathogenesis and approaches to therapy. Animals with this disease survive comfortably for several years, thus allowing chronic therapeutic trials.

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Acknowledgments

The authors thank Drs. J. T. McGrath, J. W. Northington, M. H. Goldschmidt, and J. E. Kritchevsky for their invaluable assistance in interpretation of clinical and pathologic aspects of this disease and J. Collenberg, K. Notarfrancesco, and J. McGrane for their excellent technical assistance.