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The Lipidoses: Morphologic Changes in the Nervous System in Gaucher's Disease, GM_2 Gandliosidoses and Niemann-Pick Disease

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ABSTRACT

The present paper presents, in tabular form, most of the inborn errors of lipid metabolism (exclusive of the hyperlipoproteinemias); some may, with further studies, be removed from this category. Three of the lipidoses and their subtypes which are associated with severe neurologic disorders are discussed, i.e., infantile Gaucher's disease, Niemann-Pick disease and the GM_2 gangliosidoses.

Particular emphasis is placed on the importance of careful biochemical and enzymatic studies of either surgical or autopsy material of any patient suspected of having one of the lipidoses. Only by such studies can an exact diagnosis of virtually all of these inborn errors of lipid metabolism be established. Such a diagnosis is important, since in many instances an antenatal diagnosis is possible by demonstration of the enzymatic defect in cells grown in tissue culture from the amniotic fluid.

Introduction

The lipidoses, here defined as inborn errors of metabolism characterized by an increase of one or more lipids in the tissues, and sometimes in the plasma as well, are usually transmitted as autosomal recessive characteristics, with only the homozygously involved person having the overt disease. Fabry's disease, which will not be discussed further in this paper, is, however, transmitted by an X-linked mode of inheritance. Many of the lipidoses are associated with severe mental and motor retardation, sometimes accompanied by blindness. The stored lipid(s) are generally ones normally present in the body which have accumulated as the result of an enzymatic defect which precludes their normal catabolic cycle; the nature of many of these enzymatic defects has been elucidated only within the past 5 to 10 years and can often be demonstrated not only in the tissues in which the major morphologic changes are present but also in other viscera, in circulating leukocytes, in fibroblasts grown in tissue culture and in cells grown from tissue cultures of amniotic fluid. Thus, an antenatal diagnosis of many of the lipidoses is now possible. In table I is an incomplete listing of the lipidoses, only a few of which will be discussed in this manuscript. In some of those included in this tabulation, the nature of the enzymatic defect is currently unknown and in some, e.g., Farber's disease, the nature of the stored substances is not entirely clear. Thus, it is

TABLE I

The Lipidoses

Gaucher's disease
Infantile or cerebral
Adult or non-cerebral
Tay-Sachs disease (GM_2 gangliosidosis type 1)
Sandhoff's disease (GM_2 gangliosidosis type 2)
Juvenile GM_2 gangliosidosis (GM_2 gangliosidosis type 3)
GM_1 gangliosidosis type I (Landing's disease: pseudo-Hurler's disease)
GM_1 gangliosidosis type II (juvenile GM_1 gangliosidosis; Derry's disease)
Niemann-Pick disease
Classical infantile form (Group A)
Non-cerebral form (Group B)
Late infantile form (Group C)
Nova Scotian form (Group D)
Fabry-Anderson disease (angiokeratoma corporis diffusum)
Globoid cell leukodystrophy (Krabbe's disease)
Metachromatic leukodystrophy (sulfatide leukodystrophy)
Late infantile
Juvenile
Adult
"Variant" form
Refsum's disease (phytanic acid storage disease)
Cholesteryl ester storage disease
Cerebrotendinous xanthomatosis
Tangier disease (familial high density lipoprotein deficiency)
Abetalipoproteinemia (Bassen-Kornzweig syndrome)
Wolman's disease
Sudanophilic leukodystrophy
Farber's disease

quite possible that some of those here tabulated may be subsequently removed from the classification of lipidoses.

Gaucher's Disease

Gaucher's disease is characterized by the accumulation of glucocerebrosides in the cells of the reticuloendothelial system. Infrequently, presumably similar deposits have been identified in neurons in the central nervous system in infants with the cerebral (infantile) form of the disease.[1]

Chronic, non-cerebral or the adult form of Gaucher's disease, which accounts for at least 80 percent of the recorded instances of this disorder, involves principally Ashkenazi Jews. Its manifestations are predominantly those of hypersplenism and osseous changes, e.g., vague pains in the bones, sharply localized pain as the result of pathologic fractures, kyphosis secondary to collapse of vertebral bodies, or pain, limp and limitation of motion, sometimes followed by osteoarthrosis as a result of destruction of the femoral head. Since it is not accompanied by neurologic manifestations, it will not be discussed further here, except as to its enzymatic relationship to the infantile form of Gaucher's disease.

Acute, infantile or cerebral Gaucher's disease has no predilection for Jews. It is a very rare disorder characterized by the early onset of impaired mental and motor development, prominent neurologic manifestations and abdominal enlargement secondary to hepatosplenomegaly. Hyperextension of the neck, strabismus, hypertonicity, dysphagia, apathy or somnolence with catatonia, increased deep tendon reflexes and laryngeal spasm are among the more common neurologic manifestations. These usually appear by the age of six months and, rarely, some may be present at birth. There may be microcytic anemia as well as thrombocytopenia. The serum acid phosphatase is increased, most of it being non-tartrate-inhibitable. Increased amounts of glucosylceramide are present in the urinary sediment.[5] Roentgen examination of the chest often reveals a hazy reticular or coarse, miliary-like pattern. Aspirates of the bone marrow almost always reveal typical Gaucher cells, the morphology of which is indistinguishable from that encountered in the adult, non-cerebral form of the disease. The disease is usually rapidly fatal, most of the patients dying by the age of one year.

Thanatopsy reveals severe splenomegaly, the weight of the spleen often being ten or more times that expected. The liver is similarly but not so massively enlarged. Histologically large numbers of Gaucher cells are present in the reticuloendothelial cells of the spleen, liver, bone marrow, lymph nodes, tonsils, thymus and Peyer's patches. In the lungs, similar cells may be present both in the alveolar septa and spaces. These cells, in contrast to most of the lipidoses, are not vacuolated, but instead tend to have a

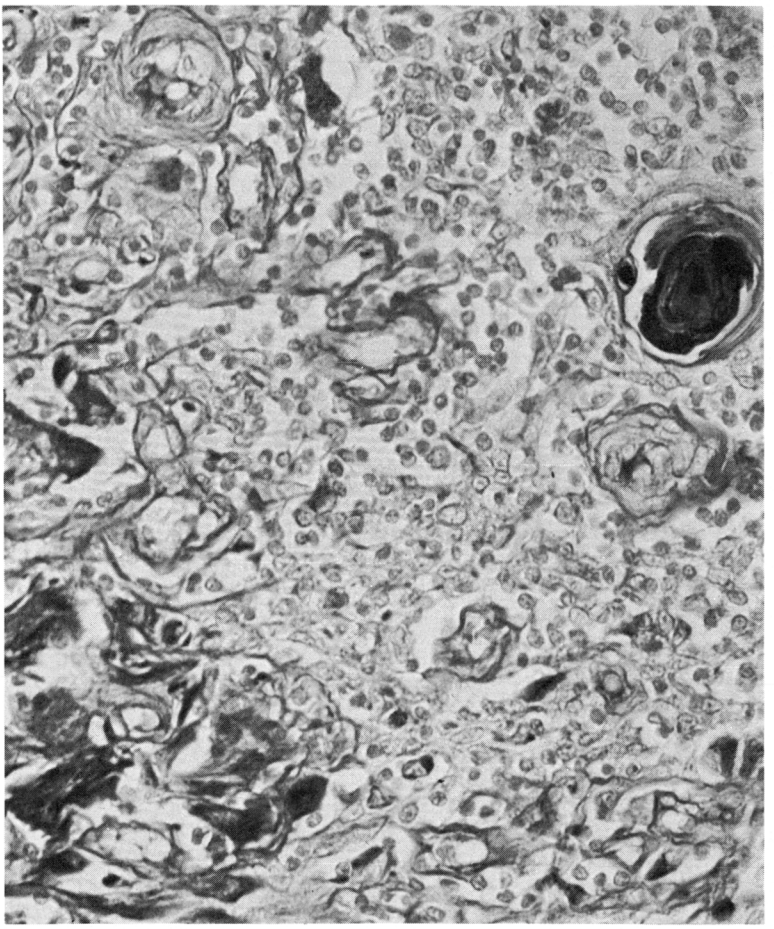

Figure 1. Infantile Gaucher's disease. Section of the thymus reveals a Hassell's corpuscle on the right and Gaucher cells with a fibrillary type of cytoplasm on the left. Periodic acid Schiff × 390.

fibrillary type of cytoplasm (figure 1). They are large, pale cells, 20 to 100 micra in diameter, with one or more dark, eccentrically placed nuclei. The fibrillary cytoplasm stains a bright rose purple by the periodic acid leukofuchsin (Schiff) technique following fixation in formalin and embedding in paraffin as well as after freeze drying.[16]

In spite of the prominent neurologic manifestations, specific changes in the central nervous system are often absent. There is, however, usually widespread degeneration of neurons with chromatolysis and neuronophagia and, by electron microscopy, "Gaucher bodies" are sometimes identifiable in the cytoplasm of the shrunken neurons.[1] Small accumulations of Gaucher cells may be present in the leptomeninges and in Virchow-Robin spaces.

The enzymatic defect responsible for the adult or noncerebral and the infantile or cerebral form of Gaucher's disease is qualitatively similar. In the adult form, glucocerebrosidase activity is present but is greatly reduced, whereas in the infantile form it is virtually absent. The two diseases, nevertheless, appear to be distinct entities, and adults with Gaucher's disease do not give birth to infants with the acute, cerebral form of the disease. Heterozygous carriers may be detected by enzyme assays performed on extracts of skin fibroblasts grown in tissue culture as well as upon sonicated white blood cell preparations;[2] heterozygous carriers of the adult form of the disease may also be de-

tected by the demonstration in tissue cultures of the skin of giant fibroblasts containing metachromatic material.[4]

Tay-Sachs Disease

Tay-Sachs disease (GM_2 gangliosidosis Type I) was initially described in 1881 by Waren Tay, a British ophthalmologist.[32] In 1884, he noted the occurrence of the disease in two siblings of the infant first reported by him[33] and in 1892 he reported a fourth instance of the same disease in a different family.[34] Sachs, a New York neurologist, described the clinical and pathologic findings in a child with this disease in 1887[23] and in 1896 designated the illness as amaurotic family idiocy.[24] Prior to this last report, however, Kingdon[11] in 1892 had reported an additional patient and had collected from the literature[6,8,12,15,23,35] and from personal correspondence 10 to 12 infants and young children with the disease, including the one described by Sachs[23] as well as another one Sachs was following; Kingdon's report substantiated the disease as a clinical entity and, if eponymic terms are desirable (as indeed in some instances they may be) the disorder might appropriately be referred to as Tay-Kingdon-Sachs disease.

Among certain ethnic groups the disease is not a rare one, the carrier rate in Eastern Europian (Ashkenazi) Jews being estimated as 1:30, in Sephardic Jews as 1:100 and in Yemenite Jews and non-Jews as 1:300.[27] Affected infants are apparently normal at birth but usually manifest evidences of the disease at about six months of age. Abnormal sensitivity to sound (hyperacusis) in the form of a characteristic extension response is the most common initial manifestation and is often present within the first two months.[25] This is followed by inability to sit, inattentiveness and abnormal movements of the limbs or head. Failure of ocular fixation or abnormal eye movements are usually apparent early in the course of the disease. The classic cherry-red spot in the macula is not present in the neonatal period but may already be visible by the second month of life.[26] It is present at some time in the course of the disease in almost all of the patients but may disappear when the disease is prolonged. The infant becomes flaccid with increased reflexes and obvious blindness, followed by increasing dementia, intense spasticity with greatly increased reflexes, extensor plantar responses and seizures. A completely vegetative state is finally reached, with death usually occurring by three or four years of age.

Although the measurements of the head are initially normal, in patients surviving more than 18 to 24 months after the onset of symptoms there is usually a progressive increase in its size, its circumference at the time of death often being about 20 percent above normal. This is not primarily the result of hydrocephalus, although initially there may be slight dilation of the lateral and of the fourth ventricles. Subsequently, however, although dilation of the fourth ventricle and atrophy of the infratentorial structures persist or increase, there is usually diminution of the lateral ventricular enlargement accompanied by a significant increase of supratentorial tissue.

The percentage of vacuolated lymphocytes in the peripheral blood tends to increase with the duration of the disease. In smears of the blood fixed for 24 hours in a solution containing 4 percent formaldehyde and 1 percent calcium chloride, some of the vacuoles stain positively with Oil-Red O or Sudan Black B.[29] Hexosaminidase A is absent not only from the brain but also from the liver, kidney, skin, fibroblasts derived from tissue cultures of the skin and from plasma and leukocytes of affected persons. It is also absent in cells derived from tissue culture of the amniotic fluid of affected fetuses as well as from certain other of their tissues.[22] Levels of hexosaminidase A in plasma and leukocytes of heterozygous carriers are intermediate between those of homozygous affected persons and controls.[20,31]

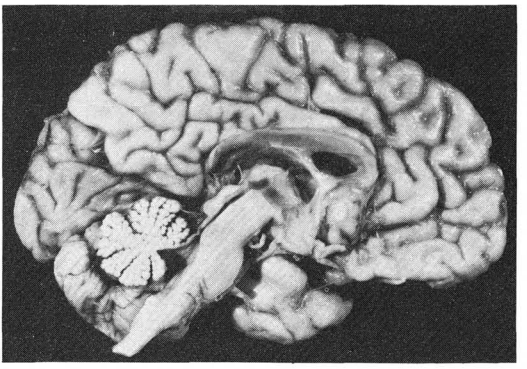

Figure 2. Cerebellar atrophy in Tay-Sachs disease. Note the prominent, widely separated folia of the cerebellum.

At necropsy, morphologic changes are confined to the eye, central and autonomic nervous system. Chemically, however, increased concentrations of the ganglioside GM_2 can be identified not only in the brain, but also in such varied sites as the heart, liver and spleen, indicating the generalized nature of the metabolic disorder. The brain of an infant dying within about a year after the onset of symptoms may be of normal or slightly decreased weight. In those surviving longer, however, and especially those dying two or more years after the onset of symptoms, the weight of the brain is usually increased, sometimes being more than 50 percent greater than normal. The brain is of firm consistency, resembling in the fresh state one which had been fixed in formalin. Although early there is apt to be mild to moderate cerebral atrophy with narrowed gyri and broad sulci, in those surviving longer the cerebral hemispheres are apt to be unusually voluminous with full gyri and sulci which are no longer widened. Atrophy of the brain stem and cerebellum becomes progressively more severe with advancing disease and the folia of the cerebellum are widely separated (figure 2). In the more advanced disease, the lateral ventricles, although occasionally slightly dilated, are more often of normal size or even slightly small, in contrast to the dilated fourth ventricle. This later, megalencephalic phase of the disease is the result of expansion of the cerebral white matter, within which there may be irregular cystic areas of encephalomalacia surrounded by demyelinated and edematous tissue. The normally sharp line of demarcation between the grey and white matter is usually obscured, but in some areas the cortex may appear to be separated from the underlying "white matter" by linear areas of encephalomalacia. Upon closer inspection, however, it is apparent that this separation is actually deep in the cortical layer rather than at the junction of cortex and white matter (figure 3).

Histologically, the usual layers of the cerebral cortex are initially quite well preserved. Subsequently, however, they be-

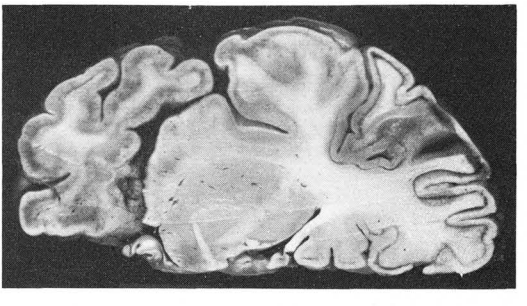

Figure 3. Laminar necrosis in the cerebral hemisphere of a child with Tay-Sachs disease. Note the linear dark area of necrosis in the deep cortical zone, in some areas superficially suggesting separation between the grey and the white matter.

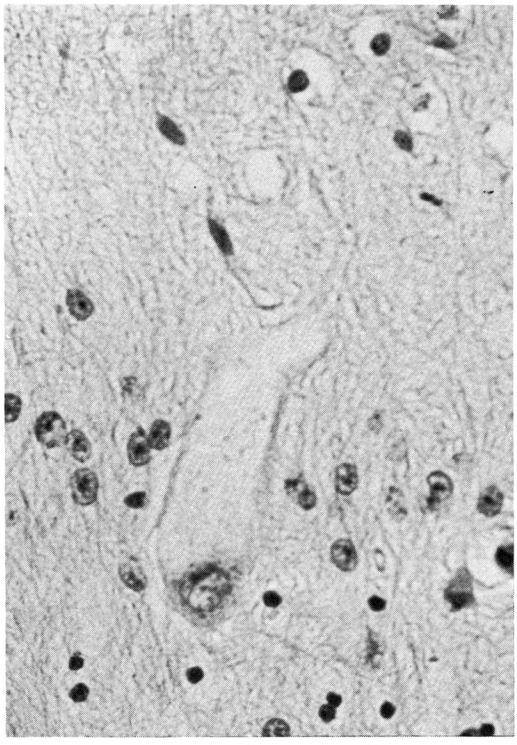

Figure 4. Purkinje cell in Tay-Sachs disease. Note the swollen, "antler-like" expansion of the dendrite extending into the molecular layer. Hematoxylin and eosin × 513.

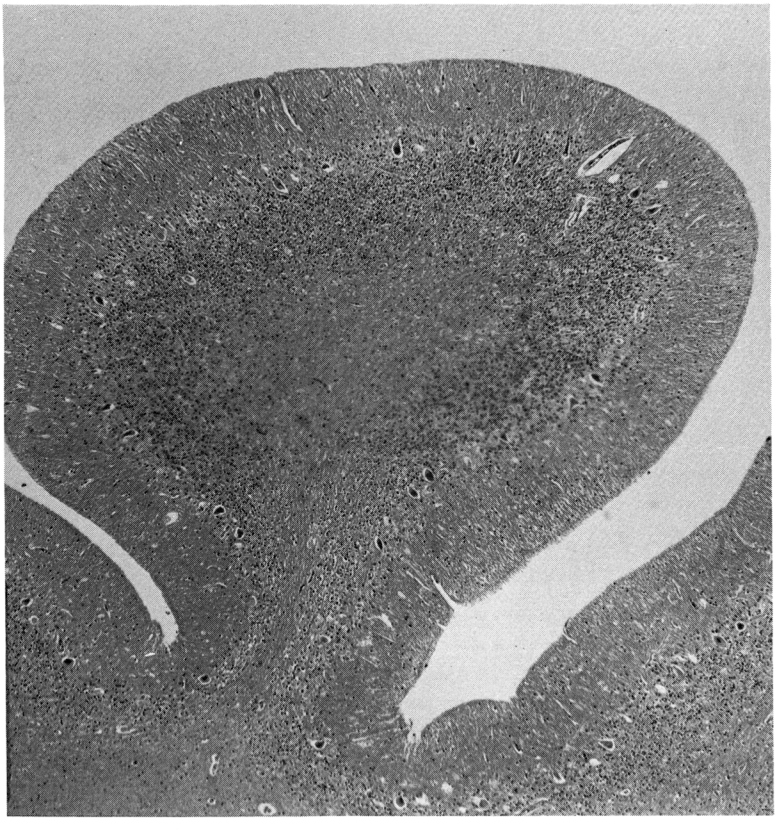

Figure 5. Cerebellar folium in Tay-Sachs disease. Note the paucity of cells in the granular layer. Hematoxylin and eosin × 60.

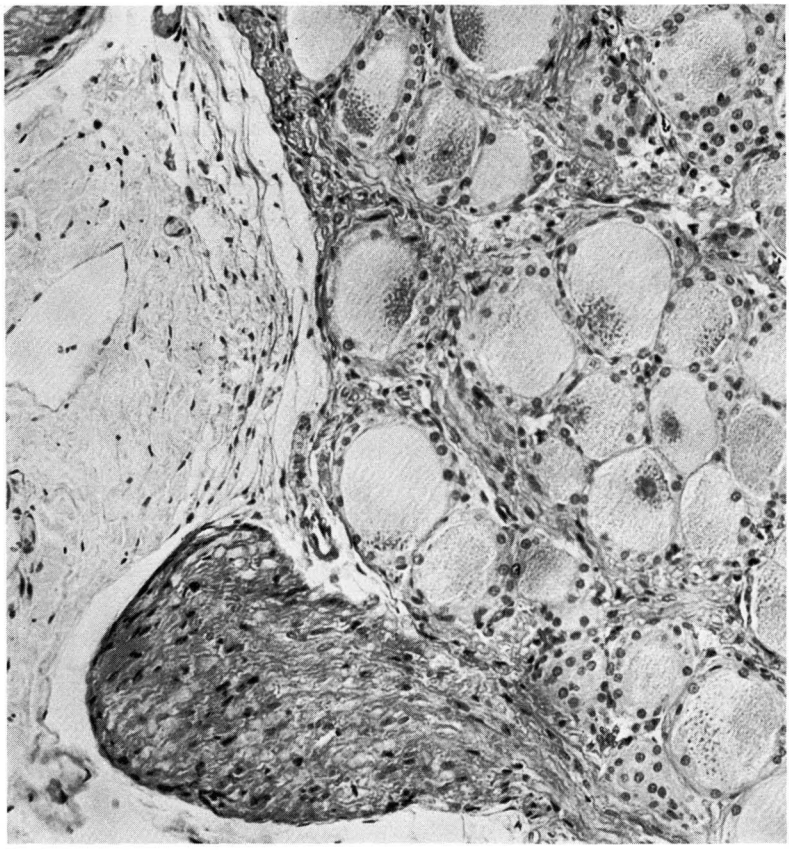

Figure 6. Gasserian ganglion in Tay-Sachs disease. Note the swollen, balloon-like neurons. Hematoxylin and eosin × 186.

come disorganized as the result of extensive loss of neurons. Almost all of the cortical neurons are tremendously enlarged with pale, granular or vacuolated cytoplasm resulting in a balloon-like appearance. In many of the cells the nucleus is not visible, being displaced to the periphery and not included in the plane of the section. With long-standing disease there is a progressive loss of neurons and proliferation of microglia, some of the phagocytes containing neutral fat and others lipid with the same or even more intense staining characteristics than that in the swollen neurons. Finally, few or no neurons remain in the cortex, which now consists largely of astrocytes, glial fibers and microglia.

In sections stained with hematoxylin and eosin the balloon-like neurons cannot be differentiated from those seen in Neimann-Pick, Hurler-Hunter, or Farber's disease, GM_1 gangliosidosis[19] or possibly Wolman's disease. The staining reaction of these cells is somewhat variable, but in general they stain somewhat more intensely with the usual stains for fat, e.g., Oil-Red O and Sudan Black B, in paraffin sections of formalin fixed tissue than in frozen sections of tissue similarly fixed.[14] They stain intensely by the periodic acid Schiff technique in frozen sections of formalin fixed material, but this property is usually lost following embedding in paraffin. In electron micrographs, the lipid granules are concentrically laminated bodies referred to as membranous cytoplasmic bodies.

The cerebellum is similarly affected by the storage of lipids in its neurons, the Purkinje cells being swollen and their dendrites in the molecular layer often showing antler-like ex-

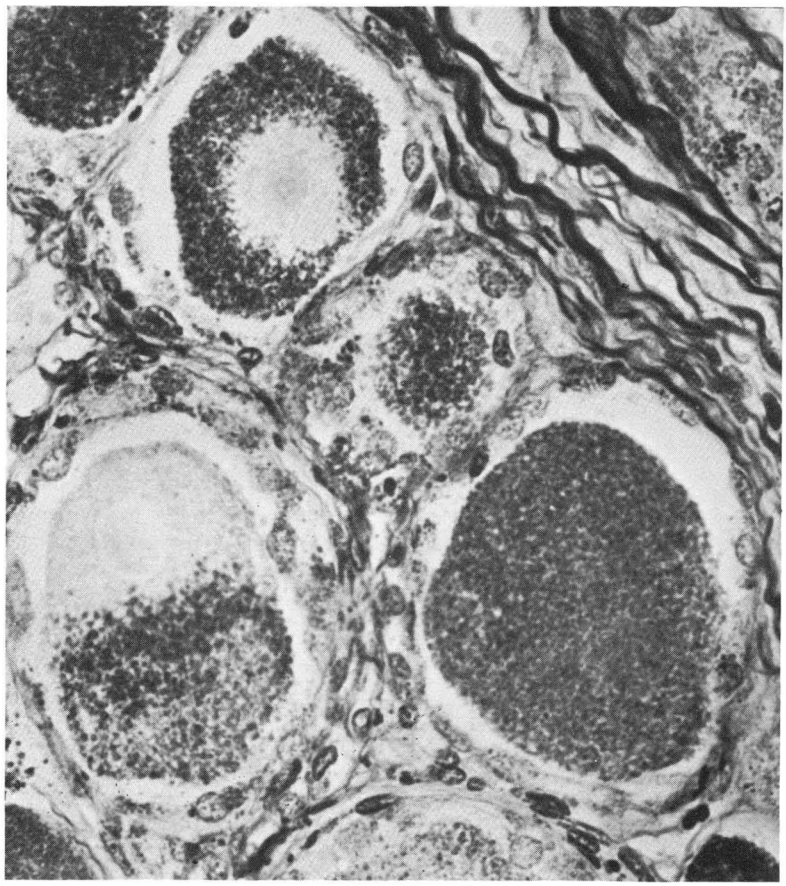

Figure 7. Gasserian ganglion in Tay-Sachs disease. Swollen, granular neurons stained by the periodic acid methenamine silver technique after fixation in formalin and embedding in paraffin. × 513.

pansions filled with lipid (figure 4). The cells of the granular layer, however, do not reveal the distended appearance of the cerebral cortical neurons. With advanced disease the granular layer virtually disappears (figure 5) and only rare Purkinje cells can be found. Storage of lipid is also present in the thalamus and basal ganglia, in the brain stem, spinal cord, dorsal root ganglia (figures 6 and 7), in the neurons of the autonomic nervous system, including those of Auerbach's and Meissner's plexuses and in the posterior lobe of the pituitary. In the retina, the ganglion cells are swollen with lipid, especially near the fovea, and there is a reduction of ganglion cells at the margins of the fovea.[7] The cherry-red spot thus appears to result from accentuation of the normal color of the choroid in the fovea[10] as a result of accumulation of lipid in cells about its margins. In the protracted disease, when the ganglion cells have disappeared, the cherry-red spot may no longer be apparent.

Sandhoff's Disease

Sandhoff's disease (GM_2 gangliosidosis Type 2) appears to bear no predilection for Jews. Clinically and, for the most part morphologically, it is similar to Tay-Sachs disease, although scattered vacuolated histiocytes may be present in the viscera, in contrast to GM_2 gangliosidosis type 1. Deposits of lipid may also be present in renal tubular epithelial cells.[18] The enzymatic defect consists of absence of both hexosaminidase A and B. It is mentioned here only to emphasize the fact that morphologic studies

of any storage disease of the central nervous system are, by themselves, incomplete; for exact diagnoses, they must be accompanied by careful biochemical and enzymatic analyses.

Juvenile GM_2 Gangliosidosis

Juvenile GM_2 gangliosidosis (GM_2 gangliosidosis type 3) apparently results from partial deficiency of hexosaminidase A.[17,21] There is no predilection for Jews, and cherry-red spots have been absent as have vacuolated lymphocytes in the peripheral blood; blindness tends to be a late feature. Ataxia, loss of speech as well as mental and motor deterioration usually begin between two and six years of age. Decerebrate rigidity ensues, with death occurring from 5 to 15 years of age. At necropsy, the neurons are distended and balloon-like, as in Tay-Sachs disease, but by electron micrography they are filled with pleomorphic lipid bodies and only a few of the membranous cytoplasmic bodies seen in Tay-Sachs disease.

Niemann-Pick Disease

Niemann-Pick disease is an uncommon group of disorders characterized by the accumulation of a phospholipid, sphingomyelin, and of cholesterol in cells of the reticuloendothelial system and usually in parenchymal cells as well. The increased levels of cholesterol seen later in the disease may not be apparent early in fetal life and, thus, may be secondary to the disordered sphingolipid metabolism.[28]

GROUP A

The classical infantile form of the disease, which comprises about 85 percent of all persons with Niemann-Pick disease, has been designated as Group A. Here the metabolic lesion is the result of extreme diminution or absence of the enzyme sphingomyelinase. The enzymatic defect can be demonstrated in a variety of sites, including liver, spleen, kidney, leukocytes, tissue cultures of fibroblasts derived from the skin or bone marrow of affected persons as well as cells grown in tissue culture of amniotic fluid of affected fetuses.[28] Heterozygous carriers can be identified using sphingomyelinase assays performed on sonicated white blood cell preparations.[2]

The classical, infantile form of Niemann-Pick disease (Group A) affects predominantly but not exclusively Jews. Clinical manifestations are usually apparent by the age of six months and may even be present at birth. Icterus is often a prominent finding, first appearing immediately after birth or during the neonatal period and usually disappearing after three or four months. Hepatosplenomegaly may be present at birth, and abdominal enlargement is usually apparent during the first several months of life. Multiple small transient xanthomas of the skin are sometimes present and there may be mild generalized lymphadenopathy. A cherry-red spot similar to that seen in Tay-Sachs or Sandhoff's disease is present in perhaps somewhat more than one-third of the affected persons; it sometimes involves only one eye. Failure to thrive, vomiting, cough, fever, irritability, extreme emaciation as well as progressive mental and motor retardation occur; death usually ensues by the age of three years.

Roentgen examination often reveals diffuse granular or reticular densities throughout the lungs. Vacuolated lymphocytes are often demonstrable in smears of the peripheral blood or bone marrow and smaller numbers of these are sometimes present in the blood of the parents.[9] Foamy histiocytes can usually be identified in smears of the bone marrow.

The foam cells of Niemann-Pick disease are large cells, 15 to 90 micra in diameter, usually containing a single nucleus which may be located eccentrically or near the center of the cell; multinucleated cells are occasionally present. The cytoplasm, as seen in smears of the bone marrow or in sections

fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin, is characteristically distended with innumerable minute droplets of relatively uniform size. In some of the cells, however, larger vacuoles of variable size may be present. The histochemical reaction of the deposits within the foam cells may be of distinct benefit in attempting to establish a diagnosis, but again, an exact diagnosis is dependent upon chemical and enzymatic analyses and not only upon histochemical findings. In general, in frozen sections of fresh tissue or of material fixed only briefly in chilled calcium formalin or gluteraldehyde the cells stain positively with Sudan Black-B and Oil-Red-O; their reaction to the periodic acid Schiff stain is variable but they may be stained red. The intensity of the color following Sudan and periodic acid Schiff stains may be diminished but it is not usually abolished in sections which have been embedded in paraffin. By electron microscopy, the cells contain round or oval residual bodies, some of which contain discrete myelin figures consisting of concentric osmophilic layers. These alternate with clear, osmophobic layers.

Postmortem examination of an infant or child with classical (Group A) Niemann-Pick disease reveals severe emaciation and abdominal enlargement secondary to hepatosplenomegaly. The spleen, which may be as much as ten times its expected weight, is usually more firm and of lighter color than normal. The liver, which is not so extensively enlarged as is the spleen, is firm and yellowish, sometimes with a distinct green discoloration. Lymph nodes, especially in the mesentery may be somewhat enlarged and yellow to grey. Yellow flecks or nodules may be apparent beneath the visceral pleura.

The brain is usually decreased in weight and is unusually firm, its consistency being comparable to that of a brain which has been fixed in formalin. Closer examination reveals that the cortex is soft whereas the

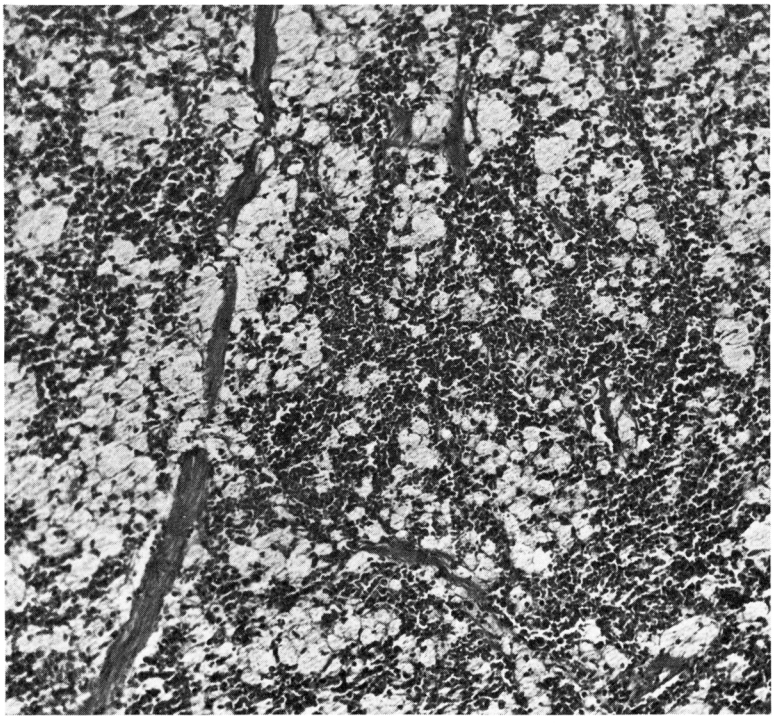

Figure 8. Spleen in Niemann-Pick disease, Group A. Numerous reticuloendothelial cells are distended with droplets of lipid (sphingomyelin). Hematoxylin and eosin × 142.

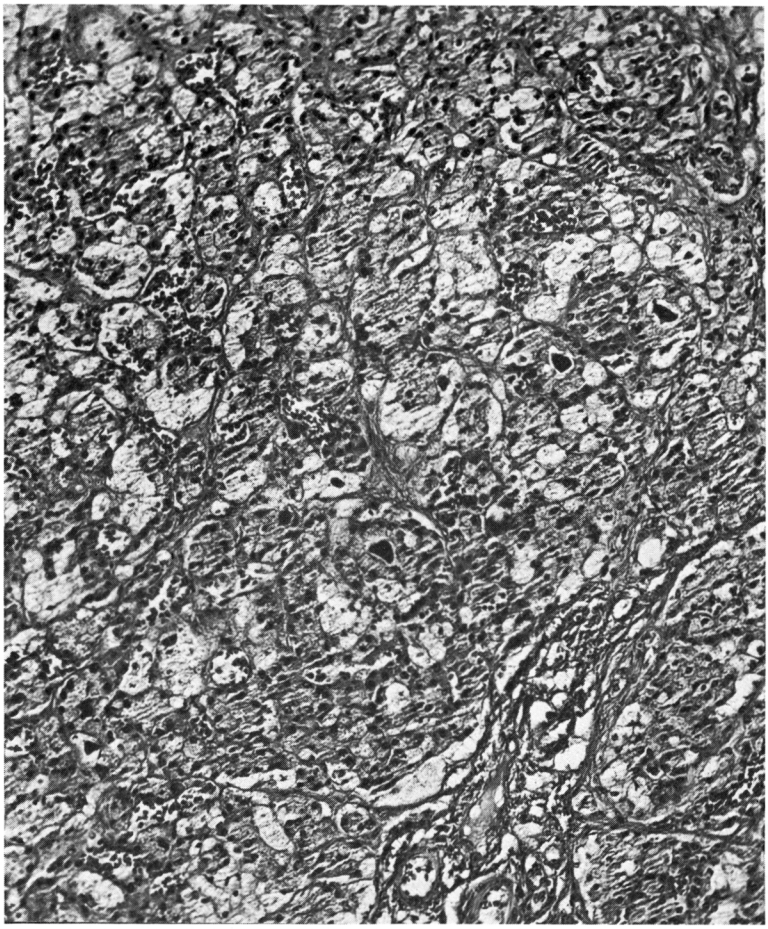

Figure 9. Liver in Niemann-Pick disease, Group A. Note distension with droplets of lipid of Kupffer cells as well as of hepatocytes about bile canaliculi. Hematoxylin and eosin × 142.

white matter is abnormally firm, the converse of the situation which usually occurs in Tay-Sachs disease.[3] The gyri are apt to be somewhat small and the sulci wide and deep. There is usually no significant ventricular dilatation.

Histologically, the foam cells of Niemann-Pick disease are widely distributed, involving not only the reticuloendothelial cells of the spleen (figure 8), liver, lymph nodes, bone marrow, tonsils, lymphoid aggregates of the gastrointestinal tract and thymus, but also those within connective tissue in a variety of sites as well as the parenchymal cells of almost any of the viscera. In the liver, differentiation of involved Kupffer cells from vacuolated parenchymal cells may be difficult but may be rendered possible by the grouping of the hepatic cells about bile canaliculi (figure 9). In spite of the extensive involvement of the liver which is apt to be present at necropsy, hepatic biopsy during the early stages of the disease may suggest only the diagnosis of neonatal (giant cell) hepatitis.

In the central nervous system, ballooning of neurons is comparable to, but not usually so widespread as that seen in Tay-Sachs disease (figure 10). In sections fixed in formalin and embedded in paraffin, the cells stain weakly or not at all by the periodic acid Schiff technique;[13] they are weakly positive with Sudan IV or Sudan Black B. The neurons in the myenteric plexuses may resemble those in the central nervous system in routine sections but their reaction to the

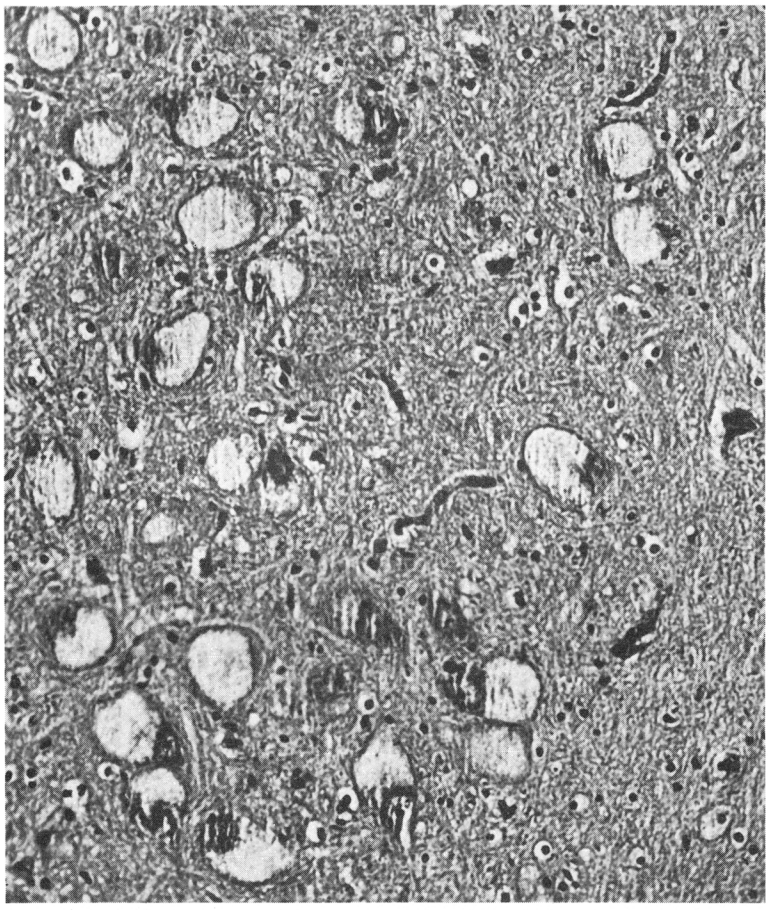

Figure 10. Ballooning of neurons in the brain in Niemann-Pick disease, Group A. Hematoxylin and eosin × 219.

Sudan stains tends to be somewhat less intense.[14]

It is apparent that there are many similarities as well as certain striking dissimilarities between the classical infantile form of Niemann-Pick disease and Tay-Sachs disease. Indeed, for some time it was believed by some that Niemann-Pick disease represented simply a different or systemic manifestation of Tay-Sachs disease. Genetic, biochemical, enzymatic and electron micrographic studies now clearly demonstrate that these are distinctly different disease entities.

GROUP B

Group B Niemann-Pick disease is associated with severe hepatosplenomegaly, usually noted at two to five years of age, diminished but not absent sphingomyelinase activity and absence of neurologic manifestations. Since it is the neural involvement which is primarily responsible for the extremely grave prognosis in most persons with Niemann-Pick disease, these patients may survive well into childhood or, possibly, into adult life. It is not clear, however, whether this Group B is a single disorder or whether some of the very few adults reported as having Niemann-Pick disease represent a different disorder. Since neurologic manifestations are not a feature of these patients, they will not be discussed further.

GROUP C

Patients with Group C Niemann-Pick disease tend to have visceral deposits which

are not so massive as those in Groups A and B. Neurologic manifestations usually begin somewhat later than in those with the classical infantile form of the disease, usually having their onset at two to four years of age, but sometimes as late as ten years. Death usually occurs between six and 13 years of age.

GROUP D

Patients with Group D Niemann-Pick disease have in common the fact that they all have been derived from families living in a small area near Yarmouth, Nova Scotia. Their disorder is characterized by a protracted course with neurologic abnormalities progressing slowly to severe disability and death usually in late childhood. There is some evidence to indicate that the extensive deposits of foam cells in these patients may decrease with advancing age.

Summary

It is apparent that this discussion has been limited to only a very few of the inborn errors of lipid metabolism which may be associated with severe neurologic defects. Some of the other lipidoses are listed in table I. For a more detailed discussion of these and other disturbances of lipid metabolism, comprehensive and detailed studies are described elsewhere.[30]

Particular emphasis is here made on the importance of careful biochemical and enzymatic studies of either surgical or autopsy material of any patient suspected of having one of the lipidoses. This is not to detract from the importance of morphologic and histochemical studies, which continue to add to our knowledge of disease processes. However, just as a bacteriologic diagnosis of the type of meningitis should not be made simply by the gross and histologic appearance and location of the subarachnoid exudate, but rather by careful microbiological studies, so also an exact diagnosis of virtually all of the inborn errors of lipid metabolism can be firmly and unequivocally established only by detailed chemical and enzymatic analyses of the tissues, performed by competent and highly skilled personnel.

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