1956

Acute gaucher's disease with neurological manifestations

Frederick William Karrer
University of Nebraska Medical Center

ACUTE GAUCHER'S DISEASE WITH NEUROLOGICAL MANIFESTATIONS

REVIEW OF THE LITERATURE
REPORT OF A CASE

FREDERICK WILLIAM KARRER

Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

March 25, 1956

Omaha, Nebraska

TABLE OF CONTENTS

INTRODUCTION

The infantile form of Gaucher's disease with neurologic manifestations is a very rare disease. It has only been recognized in the past thirty years. Before this time no cases are recorded in the literature.

In 1882, the well-known dermatologist, Gaucher (16), described the case of a woman, age 32 years; whose illness dated back to seven years of age. This form of splenic anemia he termed, "primary idiopathic hypertrophy of the spleen." Today this form of the disease is known as Chronic Gaucher's disease.

In 1907, Schlagenhaufer (48) described this entity as a systemic disease of the reticulo-endothelial system. Today we recognize the underlying feature of Gaucher's disease as a disturbance in the metabolism and storage of a particular lipoid substance, called Kerasin. (Gordon and Kaufman 22)

In 1924 Reuben (41) called attention to the relative frequency of Gaucher's disease occurring in childhood, and in addition pointed out the relationship existing between age of onset and the duration of the disease. Three years later in 1927, Oberling and Woringer (36), reported on the outstanding differences between the

manifestations of the disease in infancy and in adults and older children. They reported four cases in infants all of which showed striking neurological symptoms. At autopsy in these cases, they point out that "unique" changes were noted in the cerebral cortex.

The term "acute Gaucher's disease" was coined, in 1928, by Rowland (44) in order to distinquish this form of the disease from the more chronic type in older children and adults, which was previously known.

The acute or infantile type is according to Rowland (43), a rare form of the disease with clinical and pathologic features somewhat different from those of the chronic type. It is characterized by striking familial tendency, by the development of neurological symptoms due to progressive de-cortication, short duration and early fatal termination, in contrast to the chronic type.

This paper is concerned only with the acute form of the disease with neurologic manifestations. A thorough review was attempted in an effort to report all the recorded cases of this form of the disease. One case seen at the University of Nebraska College of Medicine in 1955 is summarized. The review of the literature was quite difficult, due to the several languages in which these cases are reported. In the following tabular

form we have listed all the cases found, with age at onset of symptoms, age at death and any noted neurologic symptoms. A thorough review of the literature was made by Aballi and Kato (1) in 1938 and they reported 17 cases with neurologic symptoms. In all of these cases the onset of symptoms was in the first six months of life. Twenty-five additional cases from the literature have been added to those reviewed by Aballi and Kato (1).

Because of the rarity of this form of the disease this case should eventually be recorded in the literature in an effort to add to our meager knowledge of the entity.

AUTHOR	SEX	ONSET Mo	1st SEEN Mo	DEATH Mo	AUTOPSY	NEUROLOGICAL SYMPTOMS
1. Rusca(45) 1921	M	6	11	12	x	Rigid neck, strabismus, hypotonia.
2. Gerstl(18) & Kraus(30) 1921	F	6	7	12	x	Hypertonicity, convergent strabismus, mental retardation, laryngeal spasm.
3. Kohn(1) 1921	F	B	9	9	x	Some neurological involvement.
4. Reber(40) 1924	M	6	6	8	x	Neck rigidity, dysphagia laryngeal spasm, hypertonicity, exaggerated deep tendon reflexes.
5. Reber(40) 1924	F	5	6	7	x	Neck rigidity, laryngeal spasm, hypertonicity
6. Oberling & Woringer(36) 1927	M	5	5	8	-	Opisthotonus, convergent strabismus, choking spells and convulsions, very marked apathy, & sensory loss.
7. Oberling & Woringer(36) 1927	F	1.5	5	11	x	Strabismus, catatonia, apathy, dysphagia, laryngeal spasm, opisthotonus hypertonicity, exagerated deep tendon reflexes, trismus, mental & physical retardation.
8. Oberling & Woringer(36) 1927	F	2	5	12	-	Opisthotonus, laryngeal spasm, hypertonicity, exaggerated deep tendon reflexes, trismus, convergent strabismus, clonic convulsions, dysphagia, sensory loss.

TABLE I
CASES OF ACUTE GAUCHER'S DISEASE WITH NEUROLOGICAL SYMPTOMS REPORTED FROM THE LITERATURE

AUTHOR	SEX	ONSET Mo	1st SEEN Mo	DEATH Mo	AUTOPSY	NEUROLOGICAL SYMPTOMS
9. Oberling & Woringer(36) 1927	M	.8	1	1	x	Apathy, poverty of movement.
10. Dienst & Hamperl(9) 1927	F	2	3	5	x	Opisthotonus, strabismus, hypertonicity, laryngeal spasm.
11. Hoffman & Makler(26) 1929	M	16	17	17.5	-	Neck rigidity, hypertonicity exaggerated deep tendon reflexes, opisthotonus.
12. Stransky (50) 1930	M	4	5	6	-	Opisthotonus, hypertonicity, laryngeal spasm, stupor.
13. Moncrief (35) 1930	M	2	2	4	x	Opisthotonus, exaggerated deep tendon reflexes strabismus.
14. Frick & Friedrich (13) 1930	M	-	-	18	x	Hypertonia.
15. Meyer(33) 1932	F	6	7	9.5	x	Dysphagia, opisthotonus, convergent strabismus, laryngeal spasm, catatonia, poverty of movement
16. Findlay(11) (12) 1931	M	11½	-	13	x	Opisthotonus, nuchal rigidity, hypertonia.
17. Winter (55) 1932	F	3	4	8	x	Unable to look to one side, dysphagia, opisthotonus, hypertonicity.

TABLE I
(Continued)

AUTHOR	SEX	ONSET Mo	1st SEEN Mo	DEATH Mo	AUTOPSY	NEUOLOGICAL SYMPTOMS
18. Meyer(34) & Woringer(56) 1934	F	4	4	75	-	Opisthotonus, nuchal rigidity, poverty of movement, strabismus, catatonia, laryngeal spasms.
19. Dessylla & Robles(8) 1934	M	6	-	7	-	Hypertonia, opisthotonus, increased deep tendon reflexes, trismus, laryngeal spasm, dysphagia.
20. Aballi & Kato (1) 1938	F	1w	3	5	x	Opisthotonus, nuchal rigidity, hypertonicity, strabismus, dysphagia, laryngeal spasms, catatonia.
21. DeLange(7) 1939	F	3	6	6	-	Opisthotonus, clonic convulsions, nuchal rigidity, laryngeal spasm.
22. DeLange(7) 1939	M	3	4	5	x	Opisthotonus, nuchal rigidity, few body movements, apathy, hypertonicity.
23. Kohne (29) 1939	M	4	8	8	x	Laryngeal spasm, hypertonicity, opisthotonus, convergent strabismus, hyperactive reflexes.
24. Donat(10) 1941	F	6	-	8	x	Hypertonia, opisthotonus, hyperactive reflexes, laryngeal spasm.
25. Ulrich (54) 1942	F	6	-	8	x	Hypertonia, opisthotonus, trismus, hyperactive reflexes, dysphagia.

TABLE I
(Continued)

AUTHOR	SEX	ONSET Mo	1st SEEN Mo	DEATH Mo	AUTOPSY	NEUROLOGICAL SYMPTOMS
26. Schairer (46) 1942	M	3	45	8	x	Nuchal rigidity, laryngeal spasms, trismus, dysphagia, stupor.
27. Frisell(14) 1943	F	3	4	7	x	Convergent strabismus, opisthotonus, apathy, laryngeal spasms.
28. Giampalmo (19) 1946	M	16	-	20	x	Hypertonia & trismus.
29. Garrahan, Gabrirassi, Albores & Moran(15) 1945	M	B	7	7	-	Opisthotonus, convergent strabismus, laryngeal spasm, hypotonia of extremities, spasm of central muscles.
30. Landolt, Zollinger, & Eugster (31) 1948	M	4	7	7	x	Tonic convulsions, exaggerated deep tendon reflexes, laryngeal spasms.
31. Schairer (47) 1948	M	6	65	7	x	Opisthotonus, dysphagia, laryngeal spasms.
32. Giampalmo (20) 1949	F	1w	-	6w	x	Hypertonia, opisthotonus convergent strabismus, laryngeal spasms, dysphagia.
33. Debre, Bertrand, Grumbach, & Bargeston(6) 1950	M	1w	5	55	x	Rigidity, laryngeal spasm, strabismus, convulsions, opisthotonus.
34. Strengers (52) 1950	-	-	-	10	x	Strabismus and spasticity, opisthotonus.

TABLE I
(Continued)

AUTHOR	SEX	ONSET Mo	1st SEEN Mo	DEATH Mo	AUTOPSY	NEUROLOGICAL SYMPTOMS
35. Strengers (52) 1950	-	-	-	9½	x	Strabismus, & spasticity opisthotonus.
36. Stengers (52) 1950	-	-	-	10	x	Strabismus, spasticity, opisthotonus.
37. Kaiser(28) 1950	-	-	-	30	x	Hypertonicity, laryngeal spasms.
38. Rodgers & Jackson (42) 1951	F	3½	5	9	x	Dysphagia, trismus, hypotonia, opisthotonus, nuchal rigidity, laryngeal spasms.
39. Geddes(17) 1953	M	3	4	10	x	Dysphagia, opisthotonus, laryngeal spasms, hypertonicity.
40. Boucoumont, Bertrand, & Roujon (2) 1954	F	2	3	4	-	Opisthotonus, nuchal rigidity, exaggerated deep tendon reflexes.
41. Girgensohn, Kellner & Sudhoff (21) 1954	F	B	B	1d	x	------
42. University of Nebr. College of Medicine 1955	M	B	8w	3	x	Opisthotonus, dysphagia, laryngeal spasms, strabismus, hyperactive reflexes.

TABLE I
(Continued)

CASE REPORT:

S.W., an 8 week old white male infant entered the University Hospital on July 9, 1955. With a history of failure to gain weight properly and holding his head in opisthotonus most of the time since birth.

The patient was the first child in the family. He was born at term by a low forceps delivery. The mother was in labor 6 hours. The child was said to have appeared normal at birth, however, a certain amount of difficulty was encountered at the termination of the low forceps delivery (Respiratory difficulty).

Both parents were American born, non-semitic. The mother was in good health. The father gave a vague history of bleeding tendencies and stuttered. No family history of any neurological disease or spenomegally could be obtained.

The infant had gained only 12 ounces since birth, taking 2 ouces of Lactum every 2 to 3 hours and 2 ounces of water daily with 1 or 2 tablespoons of Pablum or vegetables. The child was noted to choke quite frequently while eating. The parents had noted some asymmetry of the child's face. This was most marked on crying.

Physical examination on admission revealed a

small well-shaped, poorly nourished, white male infant appearing somewhat smaller than stated age of 8 weeks. The child held its head in opisthotonus with hyper-extension of the spine. The arms were flexed at the elbows with the hands at chin level. There was marked hypertonia of all musculature. All deep tendon reflexes were exaggerated. A slight strabismus was noted on admission, however the nature and degree of this was somewhat indefinite. The pupils reacted well to light. The lungs were clear to auscultation and percussion. The heart rate was 160 with no murmurs noted. The abdomen was rounded and appeared distended. The liver was palpable 4 cm. below the costal margin. The spleen was palpable to the iliac crest and was very firm and smooth.

The initial impression was possible reticuloendotheliosis or toxoplasmosis.

Laboratory studies on admission were as follows: on 7-1155: Hb. 9.5 grams, RBC 2.8 million, WBC 15,600. Differential count: segs 30, staffl, lymphocytes 64, monocytes 5. The blood serology was negative. Packed cell volume was 28%. Platelet count was 165,000. Urinalysis; ph 5.5, sugar trace, microscopic negative. Blood cholesterol 133 mg %, cholesterol esters 73%. The prothrombin time was normal.

The child was admitted to the hospital and dianostic studies were undertaken. On 7-13-55 a 75 cc. blood transfusion was given. The speen remained palpable to the iliac crest and some increase in strabismus was noted. The infant took feedings very poorly. On 7-17-55 he choked with his feeding. On 7-14-55 a lumbar puncture was performed. The cerebral spinal fluid showed: 4 cells; 49mg% protein; 50mg sugar.

On 7-19-55 a tibial bone marrow aspiration was done with the report as follows:

Crush preparation; Moderate to marked hypercellularity with relative erythroid hyperplasia scattered diffusely. Throughout the crush preparation are histiocytes having a resemblance to megakariocytes. Occasional cells of the histiocyte type contain fibrillary strands within the cytoplasm. Most, however, are granular, Megakariocytes are adequate.

Section of paraffin preparation of the aspirated material, formalin and Zenker fixed, stained by hematoxin and eosin techniques as well as aniline-blue-orange, also show accumulations of histiocytes. The nuclei are relatively small and eccentric. Many of the histiocytes are granular. Discrete vacuolization is not observed. Occasional cells have fibrillary strands

within the cytoplasm. Although the greatest number of these histiocytes are non-descript in character; the occasional cells having striated or fibrillary character are characteristic of Gaucher's disease.
Diagnosis: Gaucher's cells in tibial bone marrow.

X-ray studies on 7-19-55 were reported: Chest; normal with splenomegally noted. Skull; normal.

On 7-27-55, the patient regurgitated and aspirated formula and became cyanotic, required suction and oxygen and appeared very dusky. At this time the infant was started on cortisone 10 mg. q.i.d. Color was much improved the next day. Choking persisted with ingestion of food. Opisthotonus became more marked throughout the hospital stay. The child was kept in oxygen intermittantly until 7-27-55, for the remainder of the hospitalization was used continuously. The lungs were clear to auscultation, however. The child's respiratory and cardiovascular condition continued down hill. On 8-19-55, the patient suffered considerable respiratory and circulatory distress and was placed on digitoxin. This was given intermittently, as it was very difficult to establish a maintainence dose. After 8-17-55, no further attempts were made to feed the child except through a nasogastric tube, because of the repeated aspirations of

formula. The child's general condition gradually deteriorated and he expired on 9-9-55 following an episode of marked respiratory distress and cyanosis.

Sternal bone marrow aspirations were done on both parents in an attempt to show the carrier state. No Gaucher cells could be found in either aspiration from the parents.

AUTOPSY FINDINGS

Gross:

Heart: no abnormalities were noted.

Lungs: The right lung weighed 63.5 grams, the left weighed 59 grams. The surface of the lungs was glistening. They were mottled in character. Some areas were dark purple, others were pink, while some areas had a yellow discoloration. On cut section nodular areas measuring up to 1 cm. were observed in all lobes. These were most prominent in the upper lobes. The bronchi contained considerable amounts of frothy fluid.

Liver: The liver weighed 400 grams, The capsular surface is smooth and glistening. It was considerably paler than usual. On serial section the liver had a yellowish pink mottled pattern.

Pancreas: No abnormalities.

Adrenals: Somewhat smaller than normal.

Kidneys: No abnormalities noted.

Urinary bladder: No abnormalities noted.

Gastrointestinal tract: Some distention of the bowel was noted. Otherwise, no abnormalities.

Lymph nodes: Numerous shotty lymph nodes were identified throughout the body.

Microscopic:

Heart: Normal except for some increase in the epicardial connective tissue.

Lungs: Scattered throughout the sections of lung are large and small nodular collections of typical Gaucher's cells, which generally are within the alveoli but frequently are fused into masses which appear to destroy the normal archectecture of the lungs in these areas. In some areas only few cells are see within the alveoli. Many alveoli contain moderate numbers of lipoid filled macrophages as well. Also noted in the lung are rather large numbers of plasma cells which are within the alveolar walls, and also, withing the alveoli. Occasional alveolar spaces are lined with or contain lumps of fibrin material which is somewhat hyalinized in appearance. Throughout the lung there are many areas showing large amounts of amorphous pinkish material filling the alveolar spaces. Still other areas show numerous polymorphonuclear leukocytes, superimposed with lipoid filled macrophages. The Gaucher's cells are usually single, andshow the typical, faintly straited eosinophilic cytoplasm with a small nucleus. The latter generally is ovoid to somewhat irregular with condensed shromotin. Occasional cells show vesicular nuclei. Only rare multi nucleated cells are noted.

Liver: The sections show the presence of numerous Gaucher's cells located within sinusoids, for the most part. These tend to occur about the central veins and radiate from the central veins. In general, the infiltration tends to avoid the portal areas. It is interesting to note that fat stains reveal fatty metamorphosis in the form of small cysts in the region of the portal veins, which are not involved in the Gaucher's cell infiltration. There are focal areas in the liver in which the collection of Gaucher's cells in sufficiently intense to have caused considerable atrophy of the liver cells.

Spleen: The spleen shows extensive replacement by masses of Gaucher's cells, which appear to occupy the sinusoids and the red pulp. In some areas the sinusoids are not visible, while in other areas they are present as slit-like spaces, lined by rather prominent endothelial cells. The Gaucher's cells appear to be entirely in the pulp and not within the sinusoids. The Malpigian bodies are rather infrequent and frequently are partially replaced by Gaucher's cells Masses of Gaucher's cells are noted within the adventitial tissue of the arterioles of the spleen.

Pancreas: The pancreas in common with the connective tissue of the submucosa of the bowel and the capsule of

the thymus shows thickening of the connective tissue. This appears as a widening of the connective tissue bands within which numerous fibrils are seen. This is accompanied by an eosinophilic ground substance. The presence of the ground substance throughout the tissue appears to preclude the possibility of simple edema as a cause for connective tissue thickening. No Gaucher's cells were seen in pancreas. A single lymph node in the capsule of the pancreas is heavily infiltrated with Gaucher's cells.

Gastrointestinal tract: Sections from stomach, small bowel, colon and appendix show no Gaucher's cells within the lymphoid components.

Adrenals: The adrenal glands show a rather prominent zone of Gaucher's cells in the zona reticularis but none elsewhere. There is some evidence of hemorrhage in the central portion of both adrenals.

Kidneys: Sections of the kidney appear normal for a child of this age. No Gaucher's cells were seen.

Thymus: The thymus shows approximately 90% replacement by Gaucher's cells. The Hassel's corpuscles are degenerated and consist larely of cystic spaces witha thin wall containing some amorphous debris. The capsule of the thymus is quite thickened as previously mentioned.

Testes: The testes appear normal except for thickening of the connective tissue capsule.

Brain: The entire brain shows a diffuse atrophic change. The pyramidal cells show shrinking and some mummification. Some areas of gliosis were noted. Throughout the cortical regions occassional large cells were noted which bear a resemblance to the Gaucher cell's, under phase Microscopy (Figure II). These were most prominent in theoccipital cortex. A final report of the brain pathology is unavailable at this time.

Microscopic Diagnosis:

Broncho pneumonia

Lipoid pneumonia

Infiltration of lung by Gaucher's cells.

Pulmonary edema

Infiltration of liver by Gaucher's cells

Fatty metamorphosis of liver

Severe infiltration ofspleen by Gaucher's cells

Thickening of connective tissue

Capsules of the thymus, pancreas and testes with thickening of the submucosae connective tissue of the G. I. tract.

Severe infiltration of the thymus by Gaucher's cells.

Infiltration of bone marrow by Gaucher's cells

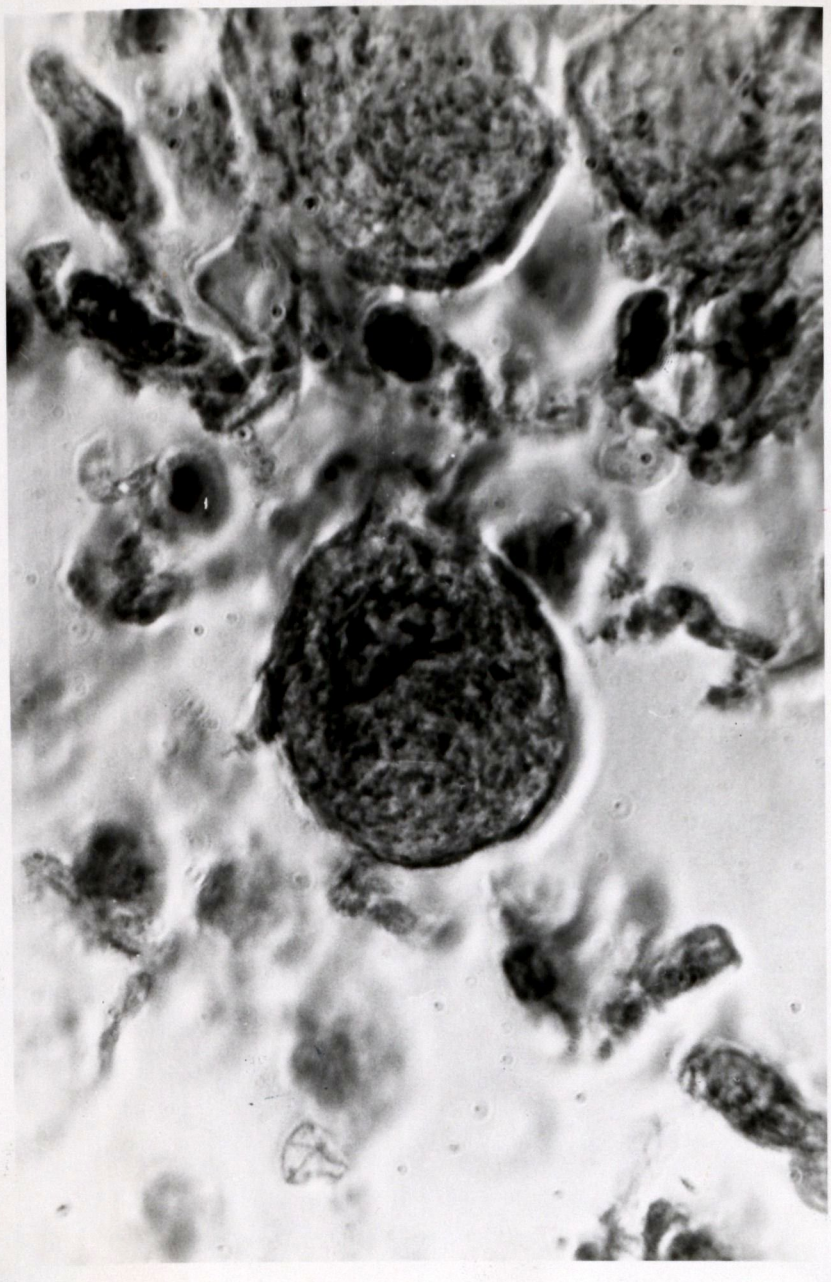

Figure I: Gaucher's cell in spleen; Hemotoxylin-eosin stain; Phase contrast microscopy; Magnification 1360x; Large cell measures 178 micra by 152 micra.

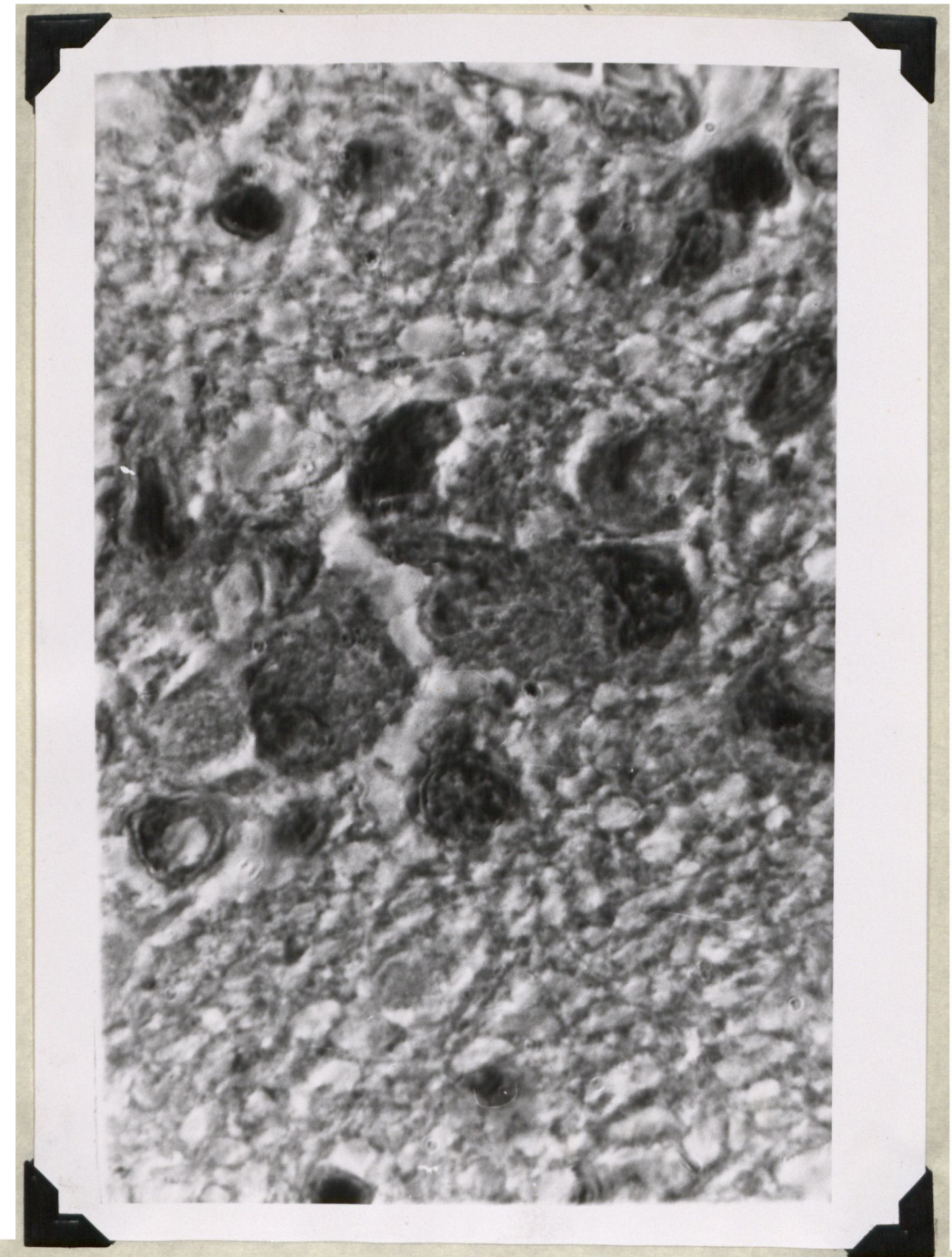

Figure II: Cell in the occipital cortex of the brain, which resembles the Gaucher's cell in Fig. I. Hemotoxylin-eosin stain; Phase contrast microscopy; Magnification 1360x; Large cell measures 152 micra by 114 micra.

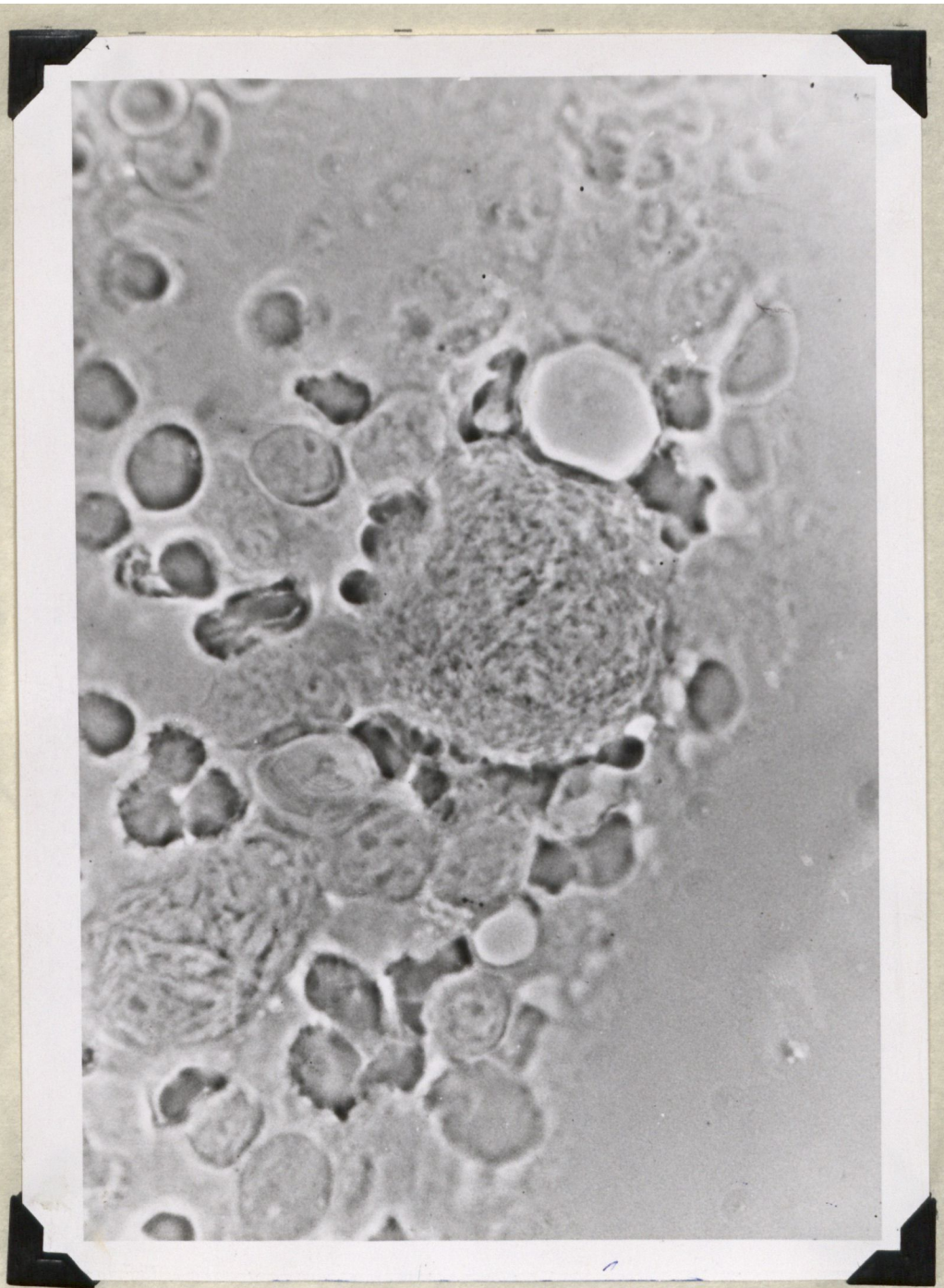

Figure III: Gaucher's cell in bone marrow; Unstained; Dark phase microscopy. Magnification 1360x. Large cell measures 167 micra by 167 micra.

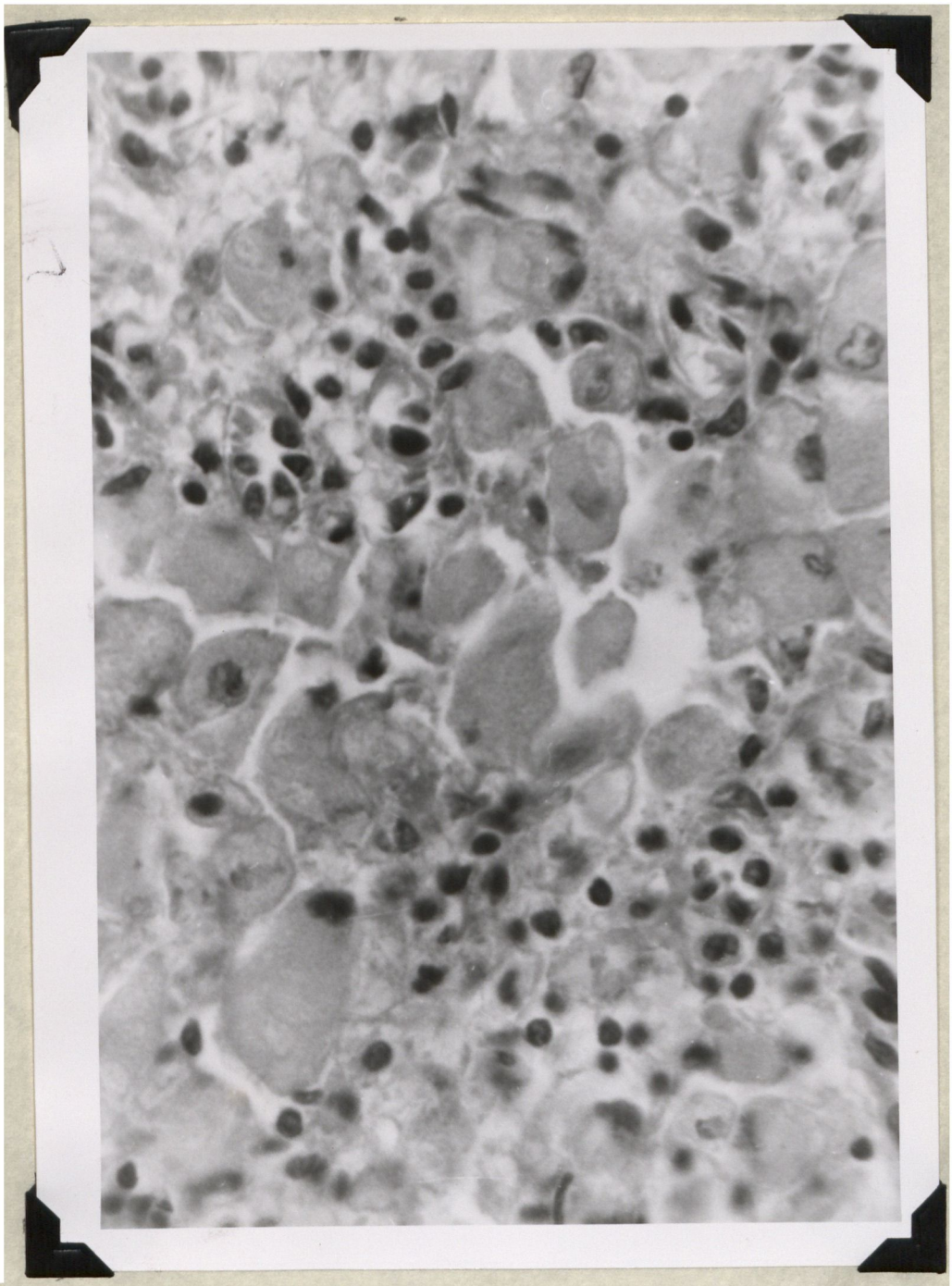

Figure IV: Gaucher's cells in liver; Hemotoxylin and eosin stain. Magnification 940 x.

INCIDENCE

Gaucher's disease is a rare condition even in its chronic form with less than 300 cases reported in the literature, as stated by Gordon and Kaufman (22) in 1950.

There are probably many more people with Gaucher's cells distributed in their body who are entirely asymptomatic. These cases are considered to be sub-clinical Gaucher's disease and some have been proved to be carriers.

Groen (23) in 1948, was able to deteet Gauchers cells in the bone marrow of apparently healthy persons, the offspring of whom had manifest Gaucher's desease. Stransky and Dauis-Lawas (51) were also able to do this.

In the review of the literature, 42 cases of the acute form with neurological manifestations were found. This may not be all of the reported cases, however, I hope by far the greatest percentage. Numerous cases have undoubtedly gone undiagnosed,as can be seen by noting that many of the cases recorded in the literature were diagnosed at autopsy. Still, the disease remains a rare affliction of children.

The sex distribution of the cases reviewed was, male 20, female 18, with 4 cases in which the sex was not noted in the abstract reviewed. The sex incidence is about equal.

ETIOLOGY

The true etiology of Gaucher's disease remains obscure. From the very beginning numerous etiological causes have been postulated. Along with most diseases of obscure origin, tuberculosis and syphilis have been regarded by some as etiologically related to Gaucher's disease. The majority of the cases on record, however, have manifested no evidence of acid-fast infection and tuberculin and Wasserman tests have usually been negative. (state Aballi and Kato(1).

The familial occurence of the disease has long been recognized. Collier (5), in 1895, was the first to note the occurence in more than one member of a family. Bovaird (3) in 1900, described the case in two sisters. Pick (38) stated that there was a family history in more than one-third of the cases reported up to 1933.

This familial occurence of the disease has led to numerous investigations of the hereditary mechanism. Groen (23) in 1948 was the first to really show hereditary mechanism. He was able to furnish proof by detecting Gaucher cells in thebone marrow of apparently healthy persons, the offspring of whom had manifest disease. Because of these findings Groen (23) stressed the fact that:

"The disease tended to become more severe in every

succeeding generation until after two or three generations it became clinically manifest in the affected individual early in life. In the next generation it would then establish itself during fetal life so as to give rise to abortions, stillbirth or early death of the affected infant."

Green (23) further states that, Gaucher's disease is a mutation which, once established, is transmitted as a simple dominant hereditary trait. The severity of the disease may vary considerably. It can be present in such a slight degree that the amountof kerasin accumulated during life is too small to give rise to clinical manifestions. In other cases the progresssion may be so slow that the disease becomes manifest only in old age, provided the affected individual lives long enough. These individuals with sub-clinical Gaucher's disease suffer from Gaucher's trait rather than from the actual disease. However, they can transmit the disease to 50 percent of their offspring.

In 1949, Stransky and Dauis-Lawas (51) were the first to actually show the hereditary mechanism in the infantile form.

Herndon and Bender(25), in 1950, after a study of the disease in five related sibships concluded that Gaucher's disease is due to the action of an autosomal

recessive gene. In the homozygous state this causes an intracellular metabolic defect, resulting in the deposit of kerasin in the cells of the reticulo-endothelial system.

PATHOGENESIS

In 1882 Gaucher (16) described as "primary epithelioma of the spleen" the disease which today bears his name. In his case he found the splenic pulp entirely replace by large cells, and he attributed this condition to tumorous growth, epithelioma of the spleen. Collier (5) in 1895, and Picou and Ramond (34) in 1896, also regarded the condition as neoplastic. Bovaird (3) in 1900, reporting the first case in the U.S. called attention to the simultaneous appearance of these large cells in the liver and lymph nodes. In contrast to the previously mentioned view, he believed that an unknown toxin caused the hyperplasia ofspeen, liver and lymph nodes. Brill, Mondelbaum and Libman (4), in 1909, were the first to point out the skeletal infiltration with the cells. They, also suggested the name Gaucher's disease. Schlagenhaufer (48), in 1906, considered that the condition was a systemic disease of lymphohemapoetic tissue. Lieb (32) in 1927, isolated the substance which characterized the Gaucher's cells and identified it as a cerebroside, named kerasin.

Pick)38) assumed that kerasin originated as the result of a general disturbance of intermediary lipid metabolism, accumulated in the blood and was secondarily deposited and stored in the reticulum cells of the involved organs.

In contrast to this Ottenstein, Schmidt, and Thannhauser (37) in 1948, demonstrated that normal serum and the serum of patients with Gaucher's disease did not contain appreciable amounts of cerebroside. Thannhauser thus concluded that cerebrosides do not originate as a result of a general disturbance of the intermediary lipid metabolism, but are synthesized and stored in the cells where they are found. Thus an imbalance of the intracellular enzymes concerned with cerebroside formation and disintegration, is assumed to be the fundamental defect in Gauchers disease.

SYMPTOMS AND COURSE

Infants affected with this acute form of the disease are usually normal at birth, however we have recorded here several cases with symptoms at birth. One case reported by Girgensohn, Kellner and Sudoff (21) died 16 hours after birth with erythroblastosis foetalis complicating the picture. The diagnosis of Gaucher's disease was made at autopsy. We only include this case because of its very early onset in utero.

These infants usually develop normally for the first few months, and there show cerebral manifestations which dominate the disease picture.

In most cases, the parents first noted dyspeptic manifestations and failure to gain weight. The spleen is usually moderately enlarged at this stage, preceding hepatomegally. The neurologic manifestations usually appear after the onset of the splenic enlargement. It is one of these neurologic symptoms which usually bring the infant to the physician. Although the presenting complaint was quite variable in the cases reviewed, it was usually of a neurologic nature. The most common being: opisthotonus, with strabismus, neck rigidity or stridor.

Thannhauser (53) gives a very good description of the sequence of symptoms in his book. Lipidosis

which we will quote here:

"In most cases the parents first perceive a lack of gaiety and vivacity in the infant. These signs are followed by retarded physical and intellectual development. The child becomes thin. Its abdomen enlarges, and on palpation one finds an enlarged spleen. Subsequently the liver enlarges. Opisthotonus develops. The head is thrown back. The arms, which are elevated to the shoulder level, are flexed at the elbow and held more or less tightly against the body. The legs are flexed and rigid. The spasmodic rigidity makes movement difficult, and the infant becomes "stiff as a wooden figure" (Oberling and Woringer, 36). Dysphagia as well as trismus early make the child unable to take regular feedings. Laryngeal spasms, accompanied by cries and spells of cyanosis, occur frequently. The infant neither sees nor hears. He becomes increasingly mentally debilitated until fever develops mostly with signs of pulmonary involvement. The infant dies during a spell of cyanosis. The tendon reflexes are exaggerated. Progressive and rapid cachexia accompany the neuromuscular syndrome."

In reviewing the literature it was found that the earliest onset, as previously stated was at birth and the latest at 16.5 months. This last case, was reported by Hoffman and Makler (26). It seems that the later the onset, the less severe are the neurological symptoms.

The neurologic syndrome may be quite variable, as can be seen from the review. The most constant findings were opisthotonus, strabismus, hypertonia, laryngeal spasm, and dysphagia in thatorder of frequency. Other neurologic manifestations noted were nuchal rigidity, hyperactive deep tendon reflexes, apathy, trismus, convulsions, both tonic and clonic, mental retardation, poverty of movement, hypotonia, sensory loss, and catatonia.

Delange (7) in his report states that convulsions are not a part of the disease picture, but as noted in the review there are 5 cases with convulsions as a part of the neurologic symptoms. This evaluation of neurologic manifestationsis not meant to be complete, in view of the marked difference in the manner and completeness with which these cases have been reported. This only shows the wide variation with which the central nervous system involvement may present itself.

Meyer(33) states that Gaucher's disease is characterized by a pseudobulbar syndrome, which permitted him to make a diagnosis even before puncture of the spleen was done.

The course in these cases is quite rapid, all cases terminating with death of the patient. The time lapsing from the onset of symptoms until death in

the cases reviewed, varied from 2 weeks (Oberling and Woringer,36) to 10 months (Oberling andWoringer, 36). The average survival period after symptoms were first noted was 4.3 months. Four cases were noted with onset at birth. (Kohne(29), Garrahan et al(15), Girgensohn et al (21), and University of Nebraska College of Medicine). Three cases with onset at 1 week of age (Debre et al (6), Aballi and Kato (1), and Giampalmo (20). This shows the acuteness of the disease with very early termination, following the onset of symptoms.

The time lapsing after onset until seen for the first time by those reporting the case (not necessarily the first time seen by a physician) was variable, ranging from immediate consultation to a lapse of nine months. The average length of time lapsing after onset was two months.

Giamplamo (20) states that convergent strabismus is a very characteristic symptom of the disease. He states that when it first appears it is of short duration but becomes more persistent as the disease progresses. He also revelaed in his review that the most common immediate cause of death was bronchopneumonia.

GENERAL PATHOLOGY

Gross:

The autopsy findings are quite similar to those found in the chronic form of the disease, namely massive splenomegaly, hepatomegaly and lymphadenopathy. In the infantile form the infiltration is not confined to these organs, but Gaudher's cells may be found in the thymus, lungs, adrenals, tonsils, and lymphoid tissue of the intestine.

The central nervous system pathology is a matter of great dispute, and this portion of the pathological change has been considered under a separate heading later in the paper.

Probably the outstanding feature in all types of Gaucher's disease is the Massive splenomegaly. Gordon and Kaufman(22) state that in this country only Gaucher's disease, amyloidosis, and leukemia give splenic enlargement of such magnitude. They describe the spleen as firm in consistency. The cut surface reveals white islands on a reddish background. These islands consist of and accumulation of Gaucher's cells.

Rowland, in Brennemann's Practice of Pediatrics, (44) gives a good description of the gross changes. His observations are summarized as follows: The general cont_ of the spleen is preserved and the surface is smooth with

a firm consistency. The color is dark purple or brownish red. On cut section it shows a mottled coloration. as a result of scattered semitranslucent areas about one mm. in diameter. In the more advanced stages these traslucent areas fuse to form a grayish white network. The malpighian corpuscles become widely separated and obscure. A cluster of enlarged lymphatic glands usually is found at the hilus and along the splenic vein.

Although the liver is generally increased in size, the enlargement is not nearly so great proportionately as that in the spleen. Its consistency is firm and the surface is smooth and glistening. It has a light yellowish brown collor. The connective tissue may be increasedin the advanced stages. At times hemorrhagic points are noted.

The lymph nodes in the thorax and abdomen are almost always enlarged. They measure from .5 to 2 cm in diameter and are usually soft. The mesenteric and retroperitoneal nodes, mostly the hemolymph type are relatively larger than the onther abdominal nodes. The tracheobronchial and the esophageal nodes are increased in size. The enlargement of the superficial nodes is seen commonly in the acute form. The nodes appear dark red, yellowish red or brownish black with grayish white dots even in the glands which are not especially enlarged.

Histopathology:

The microscopic picture is characterized by the presence of so-called "Gaucher cells" in all involved. organs. These are the cells of the reticulo-endothelial system that are enlarged because of their content of kerasin. In appearance they are strikingly uniform, being of large size(20 to 80 microns), with comparatively small nucleus and large cell body. Occasionally cells with two nuclei are seen, but cell division is not observed. The cells are pale and polygonal in shape. The cytoplasm is relatively homogeneous and opaque. With Mallory's stain a delicate network of dark blue wavy or straight striations can be observed, accentuating the wrinkled appearance of the cells. These fascicle-like structures that are found in no other condition. This gives the cell the so-called tissue paper or spider web appearance. (Aballi and Kato (1).

Rowland's description of the microscopic changes is as follows: In the spleen the picture is unique and characteristic. The pulp is nearly or entirely replaced by irregularly shaped alveolar spaces containing Gaucher cells. Many of these spaces are lined by a single layer of such cells, while others are completely filled with them. This structure may give the impression of a malignant neoplasm, but there is no

evidence of a destructive infiltrative process. A large number of blood corpuscles may be present, and in cases of long standing areas of hemorrhage as well as fibrosis are common.

The microscopic examination of the liver reveals an marked increase in interlobular connective tissue. Large numbers of Gaucher's cells are found in the center of the lobules and surrounding the efferent veins. They sometimes appear in the lumen of the portal vein. The Kupcells usually appear normal.

A condition entirely similar to that observed in the spleen exists in the lymph nodes. The white areas are found to be colonies of large cells. The capsule and Trabeculae are thickened in thelate stages of the disease andhere the close relation of the Gaucher cells to the reticulum is especially noticeable.
Gaucher cells are found in all parts of the bone marrow. They appear in large compact masses or in smaller groups. Isolated cells may, however be seen. The cells are usually not so large as those seen in the other organs and are often spindle shaped or elongated as if compressed.

In addition to the above locations Gaucher cells have been found in lungs, adrenal glands, and in the lymphatic reticulum ofintestine and tonsils. In infants

these cells are less aboundant and more widely scattered than in adults.

Giampalmo(20),in 1949, states that the infantile form differs from the chronic form of the disease in that, the acute form very frequently presents enlargement of superficial lymph nodes. Almost invarialbly there is an absence of the characteristic skin pigmentation and pinguecula. There is usually only a slight degree of anemia and only rarely a hemorrhagic diasthesis.

He lists the following microscopic characteristics of the infantile form:

1. The ubiquity of the Gaucher's cells, which are not confined in accordance with Pick's rule, to the spleen, lymph nodes, bone marrow, and liver, but may be found almost everywhere. They are naturally found in quantity in the blood forming organs. The cells very frequently localized in the lung. This infiltration paves the way for bronchopneumonia.

2. The absence of a hemosiderosis

3. The central nervous system changes.

Aballi and Kato(1) state that in the infant the Gaucher's cells are less abundant and more widely scattered than in the adult.

The case reported here is compatable with most of the above findings. It showed a peculiar increase

in the connective tissue in the capsule of the thymus, the pancreas and the submucosa of the bowel. This case showed a terminal bronchopneumonia, as Giampalmo(20) noted. No pigmentation was seen. The lungs were heavily infiltrated with Gaucher's cells. This undoubtedly played a part in the development of the bronchopneumonia. The repeated aspirations of formula by the child also played an important role.

CENTRAL NERVOUS SYSTEM PATHOLOGY

The central nervous system pathology in cases of acute Gaucher's disease with neurological manifestations has been subjected to much controversy. No constant pathological changes have been noted. The cases with thorough study of the brain at autopsy have been few. Oberling and Woringer(36), in 1927, were the first to study the brain thoroughly and stated that they thought the changes noted were "unique". Of the four cases observed by them, two had complete autopsies. Subsequent findings have varied from, no change noted to findings which have been classified as being unique for acute. Gaucher's disease.

The findings of Oberling and Woringer(36)are the first recorded findings of the central nervous system. These investigators found a "progressive cortical atrophy". The pathology was restricted to the large and small pyramidal cells of the cerebral cortex. Although the lesions are the most extensive in the occipital and parietal regions, they are found also throughout the cortical substance. The pyramidal cells are sharp in outline with ordinary stains. The ganglion cells are so retracted that they appear condensed or "mummified". There contours are irregular. Many of these cells contain vacuoles of

variable sizes, some of which are large enough to distend the cell bodies. This substance was not sudanophilic. They thik that it is not the shrinking of these cells that is specific, but the vacuelization which is quit unlike the vacuolization seen in Niemann-Pick's disease. Typical Gaucher's cells were not found in brain tissue.

Jenny in 1930, reaffirmed these findings and again stated that he believed them to be unique.(27)

Aballi and Kato (1), in 1939, add to the above in their review by stating that, except for scattered gliosis under the ependyma of the third ventricle, the pathology is restricted to the pyramidal cells of the cerebral cortex. In the ganglion cells, with Nissl's stain, in addition to mummification, the cytoplasm is seen to be modified by a conglomeration of the tigroid substance. This substance is noted as a chromophilic mass filling a large portion of the cell body and involving part of the processes. There is no neuronophagia. No pathological changes were noted in the brain stem. Other findings were similar to those of Oberling and Woringer(36). They also believed these findings to be unique for acute Gaucher's disease.

DeLange(7), in 1939, although he was unable to study

the brain in his case, asumes that lipidosis of the brain existed.

Kohne(29), in 1939, was apparently the first worker to examine the brain by serial sections. He describes the changes in the brain as follows: He noted a disturbance in the structure of the cortex, ranging from chronic Nissl celldegeneration to sclerosis of ganglion cellsof the third, fifth, or sixth layers. Here entire areas seem to have been affected. The ganglion cells here were completely atrophic. They appear shrunken and mummified. The cortex of the prietal and occipital areas was the most affected by this sclerotic process. No vacuolization of ganglion cells was found. Proliferation of glial cells and neuronophagia was found. No Gaucher's cells were found anywhere in the central nervous system, although they were especially searched for. He believed these changes to be non-specific. These changes were assumed to be the result of the disturbances of lipid metabolism which occur in Gaucher's disease, but the same changes may occur in connection with any acute or chronic disease.

Schairer(46)(47), in 1942 and 1948, gives a thorough evaluation of the changes in two cases. His first case showed non-specific alterations of the ganglion cells, partially in the sense of shrinkage, and more frequently

in the sense of a severe affection extending to complete destruction of the cells. These alterations were not marked in the cerbral cortex and basal nuclei where they involved only isolated ganglion cells, often with definite neuronophagia. Extensive destruction with proliferation of neuroglia was found particularly in the nuclei of the pons, the olivary and dentate nucleus; in the latter only scanty residue of ganglion cells were encountered. Purkinje's cells showed only miler signs of shrinkage. The spinal cord was free. The preserved ganglion cell in all parts of the brain showed a peculiar protoplasm.with a hyaline aspect. In addition, in the area of the basal nuclei isolated definite storage phenomena were demonstrated in the larger ganglion cells; the nucleus was displace towards the border and often shrunken, the tigroid substance was agglutinated at the periphery of the cells, and larger vacuoles were found particularly at the periphery, causeing loosening and unsharp demarcation of the cells. The centerof these cells contained a granular mass staining like Gaucher's substance andparticularly not showing lipoid staining. The neuroglia cells showed no storage whatsoever. As the storage involved only a few cells chemically, an increase in the Gaucher's substance was not demonstrable chemically in the brain.

The white substance showed no pathologic alterations. All myelin sheathes were intact and well-developed.

In 1948, Schairer(47) reports another case with very thorough study of central nervous system. The entire central nervous system was involved, chiefly the ganglion cells however. The alterations were most intense in the cerebellum, followed by the pons, mesencephalon and diecephalon, medulla oblongata, basal nuclei, cerbellar and cerebral cortex and spinal cord. In the dentate nucleus cellular destruction was most advanced, while in the other areas besides preserved cells the beginning of the affection was demonstrable.

Two types of involvement of ganglion cells were described; namely storage phenomena and non-specific degeneration.

The non-specific degeneration is described as an affection of the protoplasm. The protoplasm if first affected near the nucleus but later extends to the entire protoplasm. This changed protoplasm is described peripherally, later it becomes pyknotic and disappears completely. Finally nothing is left of the ganglion cell except a clump-hyaline formation.

The storage phenomena was described as an accumulation of special substance in the protoplasm. This substance seems to correspond to that found in Gauchers

cells of other organs. Feyrter's stain showing metachromasia supported the view that this was similar to Gaucher's cell storage.

This case differed from findings of first case in that myelin degeneration was noted here in the dentate nucleus and diencephalon. In the previous case no myelin degeneration or deficiency was noted. The other findings seem to be similar.

Landolt, Zollinger and Eugster(31), in 1948, described only a non-specific degeration of the cerbral cortex with secondary degeneration in the medulla oblongata and pons. They were unable to demonstrate any vacuolar degeneration of the ganglion cells or homogenization of the protoplasm.

In 1948, Hallervarden(24) reported 2 cases of what they called, Histiocytosis of the brain, these cases showed diffuse sclerosis of the brain with marked glial proliferation and large giant cells. The cortex was not affected. The author writes that the giant cells were of mesodermal origin and correspond to the Gaucher's disease. He proposes the possibility that these cases were Gaucher'sdisease withlocalization in the brain and no systemic involvement.

Rowland(43) in Brennemann's Practice of Pediatrics,

in 1948, describes the nervous system changes as follows:

"The large and medium-sized pyramidal cells of the brain, certain types of which are regarded as the reticulo-endothelial cells of the central nervous system, present any appearance suggestive of degenerationin the form of atrophy and special vacuolization. The cell projections appear shrunken and retracted. In the cell body there are many small vacuoles and occasionally a large vacuole which crowds the nucleus. The cytoplasm takes on a wrinkled appearance. In the region of the involved cells there is a proliferation of glial cells. It is notable that most of ganglion cells show necrosis but seem to persist in the mummified state."

He perscribes to thehypothesesis of Oberling and Woringer(36) that these changes are "unique" for acute Gaucher's disease.

In 1949, Giampalmo(20) stated that the changes in the nerve tissue consisted predominantly of nissl cell degeneration of the ganglion cells. It may go as far as sclerosis often with complete decline. In a few cases, individual nerve cells were observed to have vacuoles and granules of a substance which was histochemically similar to that in the Gaucher cells. But there is always a moderate flial reaction with prolif-

eration of the satellite cells. The richness and variety of the nervous system picture corresponds to the extension of the changes throughout the entire brain; this picture has not, as was originally assumed, a pyramidal character only, but undoubtedly also has extraphyramidal features.

Strengers(52), in 1950, reported 3 cases but found no typical changes in cerebral tissue.

Debre, Bertrand, Grumbach and Borgeston(6), in 1950, noted the presence of typical Gaucher's cells in the membranes of the brain. They noted two types of pathologic changes is the brain: a non-specific degeneration of the ganglion cells with diffuse infiltraion of neuroglia and pervascular accumulations of typical Gaucher's cells throughout the brain. They believe the degeneration of the ganglion cells was not at all specific for Gaucher's disease. This is the first case report we were able to find with Gaucher's cells found in the central nervous system.

Kaiser(28) in1951, examined the brain of his case and concluded that some elements of the glial tissue resembled Gaucher's cells.

In 1951, Seitz and Stammler(49) reported the cerebral change as a diffuse non-specific affection of the ganglion cells with moderate glial changes. No Gaucher cells were noted in the brain.

Rodgers and Jackson(42), in 1951, made a careful search of the brain of their case, and none of the changes previously described could be found. They found neither Gaucher's cells nor evidence of any peculiar or characr-eristic changesin the pyramidal cells of the cerebral cortex.

In 1953, Geddes(17) described the changes of CNS in his case. He found that the large and medium sized pyramidal cells of the cerebral cortex seemed to have a densified appearance, the Nissl bodies being huddled together so as partly to obscure the nucleus. This appearance he described as mumification. No vacuoles were seen in the ganglion cells. The pathological changes noted in the case presented here has been only preliminary. The entire brain shows diffuse atrophic changes. The pyramidal cells show shrinking and some mummification. Some areas of fliosis were noted. Throughout the cortical regions, occasional large cells were noted which bear a resemblance to the Gaucher's cells. (Fig I and II). These were most prominent in the occipital cortex. Further study is being done at the present time to confirm this.

PATHOGENESIS OF C.N.S. CHANGES

Numerous theories have been advanced as to the exact nature and cause of these afore mentioned central nervous system changes.

Meyer(34) advanced the theory that the factor determining this atypical pathology is due to the peculiar substratum of the developing infantile cortex. Aballi and Kato (1) subscribe to this theory, and go on to state that it is universally accepted that active development of this portion of the nervous system takes place during the first year of life. They propose that further studies in this field need to be undertaken, with a view to uncovering important information on the relationship of different brain cell groups to the reticulo-endothelial system.

Frisell (14), in 1942, explained the cerebral changes as follows: under physiologic conditions kerasin is formed in the reticulo-endothelial cells and is then transported to the brain. There it is an important building substance for myelin sheath formation. Gaucher's disease develops because, although the kerasin is formed normally, it is not transported to the brain. Lack of this substance results in pathologic brain changes. This theory would lend support to the theory of Meyer(34).

Landolt, Zollinger and Eugster, (31) in 1948, chemically analyzed the lipoid of the Gaucher cells. They found that this substance definitely differed from cerebral kerasin. They state that thetheories of cerebral kerasin deficiency and of secondary fixation of kerasin formed by the nerve cells in the reticulo--endothelial system must be discarded.

Schairer, 46) in 1942, comprehensively reviewed this theory. In the case he studied he could find no diminution ofthe cerbroside content of the brain, which would be expected if this were the cause of the cerebral pathology. He also states that, the spinal cord is the richest in cerebraside of all parts of the central nervous system, and it has been found free of involvement in all cases studied up to that time. This, he thinks, also speaks against a simple deficiency of Gaucher's substance as the causative factor. He also found that the Gaucher substance of the spleen contains glucose and not galactose like the kerasin of the brain and thinks this of significance. He further theorizes that perhaps the age reached by the infant plays a part in the amount of storage noted in the brain as more extensive storage has been noted in older infants.

In 1948, Schairer (47) studied another case in

which he thought there was marked storage of Gaucher's substance in the ganglion cells of the brain. This he states definitely contradicts the theory that a kerasin deficiency is responsible for the cerebral lesions.

Seitz and Stammler (49), in 1951, proposed a theory: The possibility that the metabolic disturbance associated with Gaucher's disease might take different courses in the reticulo-endothelial system and central nervous system, and thus lead to the formation of different metabolic products.

Gordon and Kaufman(22), in 1950, noted the following: "Various theories have been propounded to account for the preponderence or neurological manifestations. Some observers believe it is due to altered phagocytic ability of infants and possible diversion of materials needed for maturation of pyramidal cells to the retilculo-endothelial system. Others emphasize the developmental nature of the nervous system at this age and postulate that the enzyme systems are involved."

In this review the above theory could be found in no other reference. This mention of altered phagocytic ability is mentioned only for completeness.

Giampalmo (20) suspects that the pathogenesis of the nervous changes may be attributable to deficiences in the supply of cerebrosides to the brain.

These cerebrosides are retained in the Gaucher cells on the periphery (the lipoid stockade of Troppo). In Infantile Gaucher's disease the situation would thus seem to be the reverse of the situation in the nervous form of Niemann Picks disease. Where the changes in the nerve cells are due to over-supply of phosphatides.

SUMMARY AND CONCLUSION

The literature reporting cases of acute Gaucher's disease with neurological manifestations has been reviewed. A total of 42 cases have been reported. A new case from the University of Nebraska, College of Medicine is reported.

The central nervous system changes in these cases has led to much dispute. Following this review it has been concluded that these changes are non-specific and may be noted in other conditions. The case reported here, however, revealed some peculiar cells in the cortical regions which bear a definite relationship to Gaucher's cells. No definite statements that these are Gaucher's cells have been made, but further study is being undertaken to determine their similarities.

ACKNOWLEDGEMENTS

My sincere appreciation to:

Dr. D. W. Davis

Dr. H. R. Wilcox

Dr. R. B. Wilson

for their able assistance.

I wish to extend my gratitude to Dr. Dorthy Smith for her capable help as my advisor.

Many thanks to:

Joseph Fliedel-Beck

Robert Osborne

for their aid in translation.

BIBLIOGRAPHY

1. Aballi, A. J. and Keto, K.: Gaucher's Disease in Early Infancy; Review of the Literature and Report of Case with Neurological Symptoms, J. of Ped. 13:364, 1938.

2. Boucomont J., Bertrand, L. and Roujon, J.: Maladie de Gaucher Mortelle a l'Age de Quatre Mois, Archives Fran. Ped. 11:72, 1954.

3. Bovaird, D.: Primary Splenomegally, Endothelial Hyperplasia of the Speen; Two Cases in Children, Am. J. M. Sc. 120:377, 1900.

4. Brill, N. E., Mandelbaum, F. S., and Libman, E.: Primary Splenomegally of the Gaucher Type. A Report of the Second of Four Cases Occurring in a Single Generation of One Family, Am. J. M. Sc., 137:849, 1909.

5. Collier, W. A.: A Case of Enlarged Spleen in a Child Aged Six, Tr. Path. Soc. London, 46:148, 1895.

6. Debre, R., Bertrand I., Grumbach, R., and Bargeston, E.: Maladie de Gaucher du Nourrison, Arch. Franc. Ped., 8:38, 1950.

7. DeLange, C,: Ueber die Maligne Form der Gauchersche Krankheit, Acta Paediatria, 27:34, 1939.

8. Dessyla, C. and Robles, A.: Boll. Society Ital. Ped., 3:181, 1934, cited by Giampalmo, 1(20) *

9. Dienst, G. and Hamperl, H.: Lipoidzellige Splenomegalie (Typus Niemann), Wien, klin. Wchnschr. 77:1432, 1927.

10. Donat, R.: Die Beteiligung der Lungen beim Morbus Gaucher, Zbl. Allg. Path., 78:273, 1941, cited by Giampalmo (20).

11. Findlay, L.: Gaucher's Disease Verified by Splenic Puncture, Proc. Roy. Soc. Med., 24:848, 1931.

12. Findlay, L.: Microscopic Sections from Case of Gaucher's Disease, Proc. Roy. Soc. Med., 24:1336, 1931.

13. Frick, P. and Friedrich, G.: Morbus Gaucher im fruehen Kindersalter, Arch. f. Kinderheil, 110:1, 1930.

14. Frisell, E.: Gauchersche Krankheit im fruehen Kindesalter, Acta Paediat. 30:470, 1942-1943.

15. Garrahan, J. P., Gamberassi, A. C., Albeores, J. M., and Moran K.: La Enfermedad de Gaucher en el Lacunate (Forma Neurologica), Arch. Argentinos de Pediat. 23:3, 1945.

16. Gaucher, E.: De L'Epitheliome Primitif de la Rate: Hypertrophie Idiopathique de la Rate sans Leudemie, These de Paris, 1882.

17. Geddes, A. K.: Acute (Infantile) Gaucher's Disease; Report of a Case, the Second in a Family, Jour. of.Ped. 43:61, 1953.

18. Gerstl, P.: Rachitisher Zwergwuchs und Splenomegalie Gaucher bei einer Fruggebert, Arch, Kinderheil, 69:356, 1921.

19. Giampalmo, A.: Arch. Maragliano 1:219, 1946.

20. Giampalmo, A.: Uber die Pathologie der Gaucherschen Krankheit im fruehen Kindesalter (mit besonderer Berucksichtigung der neurologischen Form), Acta Paediatrica, 37:6, 1949.

21. Girgensohn, J., Kellner H., and Sudhoff, H.: Angeborener Morbus Gaucher bei Erythroblastose und Gefässverkalkung, Klin. Wschr. 32:57, 1954. cited from Exerpta Med. Ped., 8:641, 1954.

22. Gordon, W. H., and Kaufman, J. M.: Gaucher's Disease, Jour. of Mich. State Med. Soc. 49:785, 1950.

23. Groen, J.: The Hereditary Mechanism of Gaucher's Disease, Blood, 3.2:1238, 1948.

24. Hallervarden, D.: Eine Speicherungshystiozytose des Kinderlichen Gehirns (Gauchersche Krankheit:) Zentralbl. f. allg. Path. U. Path. Anat., 85:101, 1949. Exerpta Medica, Gen. Path. Path. Anat., 3:925, 1950.

25. Herndon, C. N. and Bender, J. R.: Gaucher's Disease in Five Related Negro Sibships, Am. J. Human Gen. 2:49, 1950.

26. Hoffman. S. J. and Makler, M. I.: Gaucher's Disease: Review of Literature andReport of a Case Diagnosed from Section of an Inguinal Lymph Gland, Am. J. Dis. Child. 38:775, 1929.

27. Jenny, E.: Beitrag zur Kenntnis der Varianten der Gaucherschen und Nieman-Pickschen Krankheit, These de Bale, 1930, cited from Thannhauser (53).

28. Kaiser, A.: Morbus Gaucher spezifische Lungen infiltration unter dem Bilde einer miliar-Tbc, Mschr. Kinderheilk 98:252, 1950, cited from Ex. Med. Ped., 5:349, 1951.

29. Kohne, E.: Uber Morbus Gaucher mit Herveranderungen im Sarglingsalter, Bertr, Path. Anat., 102:512, 1939.

30. Kraus, E. J.: Zur Kenntnis der Splenomegalie Gaucher insbesdondere der Histogenese der grosszelligen, Wucherung Ztschr. f. Ang. Anat., 7:186, 1921.

31. Landolt, R. F., Zollinger, H. A. and Eugster, C. H.: Uber die Moligne, Akut verlaufende Form Des Morbus Gaucher, Helvet. Paediat. Acta., 3:319, 1948.

32. Lieb, H.: Cerebrosidspeicherung bei Morbus Gaucher, Ztschr. f. Physiol. Chem., 170:60, 1927.

33. Meyer, R.: Syndrome neurologique et Diagnostic Clinique de la Maladie de Gaucher du Nourrisson Rev., Fr. Pediat., 8:559, 1932.

34. Meyer, R.: Nouveau cas de syndrome pseudo-bulbar du Nourrisson (Maladie de Gaucher du Nourrison) Rev. Neurol., 41:612, 1934.

35. Moncrieff, A.: The Infantile type of Gaucher's disease, Arch. Dis. Child., 5:265, 1930.

36. Oberling, C. and Woringer, P.: La Maladie de Chez le Nourrisson, Rev, Franc, de Pediat., 3:475, 1927.

37. Ottenstein, B., Schmidt, G. and Thannhauser, S. J.: Studies concerning the Pathogenesis of Gaucher's Disease, Blood, 3.2:1250, 1948.

38. Pick, L.: A Classification of the Diseases of Lipid Metabolism and Gaucher's Disease, Am. J. M. Sc., 185:453, 1933.

39. Picou, R. andRamond, F.: Splenomegalie Primitive, Epithelioma Primetif de la Rate., Arch de Med. Exper. et d'Anat. Path., 8:168, 1896.

40. Reber, M.: Zur Splenomegalie Gaucher im Saugling-salter, Jahrb. f. Kinderh., 105:277, 1924.

41. Reuben, M. S.: Gaucher's Disease, Arch. Ped., 41:456, 1924.

42. Rodgers, C. L. and Jackson, S. H.: Acute Infantile Gaucher's disease, Ped. 7:53, 1951.

43. Rowland, R. S.: Brennemann's Practice of Pediatrics, W. F. Prior Co., 1948, Vol. 3 Ch. 23, p. 77.

44. Rowland, R. S.: Xanthomatosis and the Reticulo-endothelial system, Arch. Int. Med., 42:611, 1928.

45. Rusca, L. C.: Sue Morbo del Gaucher Hoematologica, 2:441, 1921.

46. Schairer, E.: Ein Weiterer Fall von Morbus Gaucher beim ,Saugling, Virchows Arch. f. Path. Anat. 309:126, 1942.

47. Schairer, E.: Die Gehernverandderungen beim Morbus Gaucher des Sauglings, Virchows Arch. F. Path. Anat. 315:395, 1948.

48. Schlagenhaufer, F.: Uber Meist Familiar Vorkommende, Histologisch Characteristische Splenomegalien (Typus Gaucher), Virchow's Arch. F. Path. Anat., 87:125, 1906.

49. Seitz, H. and Stammler, H.: Morbus Gaucher beim Saugling, Zbl. Allg. Path. and Path. Anat., 87:336, 1951.

50. Stransky, E.: Ueber Grosszellige Spleno Hepato Megalie, Jahrb. F. Kinderh., 126:204, 1930.

51. Stransky, E. and Dauis-Lawas, D. F.; Heredity in the Infantile type of Gaucher's Disease., Am. J. Dis. Child., 78:694, 1949.

52. Strengers, L.: Kinderafdeling vau zet Zickenhuis van den H. Johannes de te Den Haag. Acute Varm Van de Zickte van Gaucher Bij drie Kinderen vit een Gezin. Maandschrift voor Kinder Geneeskunde, Lcydon, 17:237, 1949, cited from, Excerpta Med. Ped., 4:421, 1950.

53. Thannhauser, S. J.: Lipidosis: Diseases of the Cellular Lipid Metabolism, Edited by H. A. Christian, New York, Oxford University Press, 1940.

54. Ulrich,O.: _____ Kinderarztl Praxis, 13:113, 1942, cited from Giampalmo (20).*

55. Winter, S. J.: Lipid Histiocytosis (Niemann-Pick type) Am. J. Dis. Child., 43:1150, 1932.

56. Woringer, P.: Cinquieme Enfant Atteint de Maladie de Gaucher dans une Meme Famille., Bull. Soc. Ped. Paris, 32:189, 1934.

* The references so marked are not listed in any of the indices. No title could be obtained.