

FAMILIAL SPLENOMEGALY

A CLINICAL STUDY *

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During the last year we had the opportunity to observe at least two cases which presented the clinical picture of splenomegaly of Gaucher's type. The family history runs as follows:

CASE 1.—The first child of the family, a boy, 2 years of age, was taken into the hospital in 1901; death soon occurred. To our regret, no clinical history was at our disposal, but the diagnosis, "hepatitis," made at that time, gives us reason to believe that the child had an enlarged liver.

CASE 2.—The second child, a brunette, 11 years of age, was admitted to the hospital for the first time in 1912. The skin, slightly yellow tinted, did not show any signs of marked jaundice. The spleen, distinctly enlarged, was hard and smooth, not painful on palpation; the liver was enlarged, especially the left lobe felt remarkably firm; no ascites; the urine contained small traces of urobilin. The white cell formula was normal. Both the reactions of Wassermann and von Pirquet were negative; no visible glandular enlargement; temperature practically normal.

A year later the same child was admitted for the second time. Although she had had no special complaints during the course of the year, she did not look as well as before. The size of spleen and liver had increased. The spleen extended to the navel; the left hepatic lobe was felt 5 inches below the ensiform cartilage of the sternum; no ascites, no jaundice. The urine contained no bile pigment, but showed a marked urobilin reaction; hemoglobin 70 per cent. (Sahli); blood count, 5,200,000 red cells, 6,800 white cells. Differential count: 64 per cent. neutrophils, 13 per cent. eosinophils, 0.3 per cent. basophils, 16.6 per cent. lymphocytes, 5.3 per cent. transitional cells. (The average blood count of a girl 12 years of age is 80 per cent. hemoglobin, 5,196,450 red cells, 8,555 white cells, polynuclear neutrophils, 53.79 per cent., eosinophils, 3.57 per cent., lymphocytes, 33.25 per cent., transitional cells 9.39 per cent.) There were slight anisocytosis and poikilocytosis. Both Wassermann and von Pirquet reactions were negative. There was no glandular swelling. The temperature was normal. Five weeks later sudden death occurred within a few hours after a serious hematemesis.

CASE 3.—Seventeen days after birth the third child died from an umbilical infection.

* Submitted for publication Dec. 21, 1917.

* The authors are greatly obliged to Dr. P. J. L. de Bloeme, director of the Sanatorium Hoog-Laren, formerly assistant physician at Loomis Sanatorium, New York State, for his kindness in translating their paper.

CASE 4.—The fourth child, a boy, aged 11 years, dark blonde, looked healthy. The spleen was palpable beneath the costal margin; the urine showed a trace of albumin and urobilin.

Blood examination: hemoglobin (Sahli) 85 per cent.; red cells 4,280,000; white cells 8,850; differential count: polynuclear neutrophils 43 per cent.; eosinophils 8.7 per cent.; basophils 1.3 per cent.; lymphocytes 44 per cent.; transitional cells 3.6 per cent.; Türk's cells 1 per cent. Von Pirquet's test (human tuberculin), slightly positive; with bovine tuberculin, strongly positive.

CASE 5.—The fifth child was a girl, blonde, 9 years of age. Liver and spleen were not palpable; urine normal. Blood count: hemoglobin 87 per cent.; red cells 5,700,000; white cells 8,825; polynuclear neutrophils 40.5 per cent.; eosinophils 7 per cent.; basophils 0.7 per cent.; lymphocytes 48.5 per cent.; transitional cells 3 per cent.; Türk's cells 0.2 per cent. Von Pirquet's test was negative.

CASE 6.—The sixth child, taken into the hospital in May, 1916, a girl, 7½ years of age, brunette, did not look well. The abdomen was distended, with dilated veins; circumference on the line of the navel, 60 cm.; linea alba pigmented; no cutaneous hemorrhages; no bleeding from the gums; micropolyadenia; knee reflex and cubital reflex somewhat increased; bones not painful on percussion; second pulmonary sound somewhat accentuated; no pulmonary changes.

The spleen was distinctly enlarged; had a smooth surface; felt firm. The incisure was easily felt. The lower border of the spleen was felt 1½ inches above the anterior superior iliac spine; the right border was 2½ inches removed from the median line. The enlargement of the liver was located chiefly in the left lobe, firm on palpation, extending 3 inches below the costal margin, reaching almost to the spleen. The edge of the left hepatic lobe was sharp, of the right lobe dull; the right lobe felt soft. The incisure for the gallbladder was easily palpable; no ascites, no jaundice. The urine contained no albumin, no sugar, not more than physiologic traces of urobilin; the diazo test was negative; no bile pigment. Microscopically, there were a few chromocytes and leukocytes. The urobilin test was made quite frequently, with the result as stated, before the operation took place. The Wassermann test was negative; von Pirquet positive (strongly positive with bovine tuberculin, slightly positive with human tuberculin). The temperature was sometimes slightly elevated. The blood count always showed a leukopenia, varying from 3,000 to 6,200 leukocytes. Notwithstanding the leukopenia the number of mononuclear lymphocytes remained, on some days, normal or only slightly subnormal; no marked anemia. The amount of hemoglobin and the number of erythrocytes were practically normal (Table 1). Spleen and liver became slightly enlarged during the two months which the patient spent in the hospital before the operation; splenectomy was performed on July 18.

CASE 7.—The seventh child was admitted to the hospital in May, 1916. The patient was a girl, 5½ years of age, looking well, well nourished, of the brunette type, but not so dark as her little sister. The injection of the mucous membranes was satisfactory. There was pigmentation of the linea alba and a few pigmented small spots on the skin of the abdomen, but no jaundice. The reflexes were not increased; a slight micropolyadenia existed; no heart murmurs; at the base of the left lung there was slightly impaired resonance on percussion, an inch wide, without auscultatory changes. The circumference of the abdomen on the line of the navel was 53 cm.; dilated veins were slightly visible; no free fluid in the abdominal cavity.

The spleen was hard; its surface smooth, not painful on palpation; the incisure was not clearly felt. The spleen extended 1 inch above the superior anterior iliac spine; the right edge was 2½ inches removed from the navel. Splenic dullness was heard in the axillary line at the ninth rib. The hepatic enlargement was chiefly located in the left lobe, although not so marked as in

the previous case. The surface was smooth, not painful on palpation. The lower border of the liver was felt in the median line, 4 inches below the ensiform cartilage. The hepatic incisure was distinctly palpable. In the anterior axillary line the hepatic border was felt 2 inches below the costal margin. The urine contained no albumin, no sugar, no bile pigment. The repeated urobilin test showed only once a slightly increased amount of urobilin. Wassermann's test was negative; von Pirquet's test was positive (more marked when using bovine tuberculin). The temperature showed sometimes slight elevations. The blood examination showed, (1) a leukopenia varying from 4,200 to 8,500 leukocytes; (2) a large amount of hemoglobin, a high count of erythrocytes (Table 2).

The spleen became slightly enlarged during the two months of residence at the hospital. Splenectomy was performed July 5, 1916.

TABLE 1.—BLOOD EXAMINATIONS BEFORE AND AFTER SPLENECTOMY
IN CASE 6

Date	Hb., per Cent.	Red Blood Cells	White Blood Cells	Neu- tro- phils, per Cent.	Eo- sino- phils, per Cent.	Baso- phils, per Cent.	Lym- pho- cytes, per Cent.	Transi- tion- als, per Cent.	Türk, per Cent.	Total Lympho- cytes
5/10/16	81	4,540,000	5,000	38.7	2.2	0.7	55.0	3.2	2,750
5/17/16	75	5,020,000	4,600	41.2	4.7	0.2	52.2	1.5	2,400
6/ 6/16	46.2	3.5	45.2	5.0		
6/17/16	6,200							
6/26/16	4,400							
6/30/16	5,050							
7/ 8/16	4,250							
7/ 7/16	80	4,645,000	3,550	45.3	1.6	0.6	49.0	4.0	1,740
Operation, July 18										
7/20/16	76	5,750,000	23,150	72.4	22.6	3.8	0.2	5,230
7/22/16	81	6,510,000	20,000	62.6	1.4	0.6	32.0	3.8	6,400
7/24/16	81	6,360,000	19,975	45.0	6.5	45.0	2.7	0.7	9,000
7/31/16	83	6,370,000	17,625	56.7	39.2	4.0	6,900
8/ 7/16	85	4,360,000	14,175	25.0	8.5	60.5	2.7	3.2	8,575
8/ 8/16	..	4,570,000								
8/14/16	84	6,260,000	17,225	29.7	3.7	63.5	2.5	0.5	10,930
10/ 7/16	85	4,600,000	19,650	22.8	6.0	66.4	3.4	0.4	13,050
10/26/16	86	4,315,000	21,000	33.0	14.0	1.25	51.7	3.7	10,860
Normal at age of 7-8 years.....	78	5,042,860	8,353	60.18	3.69	27.98	7.75	2,337

The mother said that the enlargement of liver and spleen was already noticed in the sixth child when 4 years old; in the seventh child when 2 years old. There is every reason to believe that the disease in question is congenital in origin.

The occurrence of the positive Wassermann reaction does not

seem to be constant in those cases. In the case of Patients 6 and 7 the reaction was, in the beginning, slightly positive. On later examination, carried out by another serologist, the test was slightly positive in the case of one girl, negative in that of the other child; on third examination, performed by the same serologist, the reaction proved negative in both instances.

TABLE 2.—BLOOD EXAMINATIONS BEFORE AND AFTER SPLENECTOMY
IN CASE 7

Date	Hb., per Cent.	Red Blood Cells	White Blood Cells	Neu- tro- phils, per Cent.	Eo- sino- phils, per Cent.	Baso- phils, per Cent.	Lym- pho- cytes, per Cent.	Trans- luc- als, per Cent.	Türk, per Cent.	Total Lympho- cytes
5/19/16	79	4,140,000	4,250	58.2	4.6	0.3	34.6	1.6	1,470
5/27/16	82	5,460,000	4,600	45.5	7.0	46.2	1.2	2,125
6/14/16	85	5,200,000	6,950	45.7	3.2	47.7	3.2	3,315
6/15/16	8,500							
6/16/16	5,900							
6/19/16	6,650							
6/23/16	6,350							
6/27/16	7,250							
7/ 1/16	83	5,750,000	4,375	54.0	3.0	0.5	36.0	6.5	1,575
7/ 5/16	80	5,600,000	4,200	48.5	3.5	46.5	1.5	1,953
Operation, July 5										
7/ 7/16	86	5,600,000	18,250	78.8	0.2	0.2	11.6	8.4	0.4	2,117
7/ 9/16	85	5,680,000	18,750	63.0	7.0	22.7	7.2	0.2	4,153
7/12/16	..	6,200,000	13,500	54.0	8.2	1.0	33.5	4.8	0.4	4,522
7/17/16	84	5,200,000	14,300	55.8	9.6	1.2	30.2	7.0	4,318
7/20/16	81	4,900,000	9,200	50.8	3.6	1.2	40.8	5.6	0.2	3,753
7/26/16	12,325	41.5	4.4	0.2	46.3	6.6	0.9	5,716
8/16/16	92	5,720,000	13,600	38.5	12.3	46.0	2.2	6,256
10/ 5/16	88	4,915,000	12,450	44.0	2.0	1.0	50.0	4.0	6,225
10/28/16	84	4,625,000	17,950	38.25	8.5	0.7	47.2	6.0	8,472
Normal at age of 5-6 years.....										
	77	5,189,000	9,813	55.39	6.22	31.04	7.35	3,042

While we collected the foregoing data about the children, we also examined the parents and three of the living grandparents.

The father, 45 years of age, was a dark, thin, strong man, always feeling well. He had never heard of any illness in his family; no enlargement of spleen or liver demonstrable on percussion or palpation; urine normal; no bile pigment present; urobilin test showed nothing abnormal; blood examination was performed three times. The normal figures are given first, Table 3.

The first examination shows a slight leukopenia; the second and third show figures which are practically normal, although somewhat low; a relative lymphocytosis was always present. We want to emphasize this point, although we do not venture to state that the origin of the disease in the children can be traced back to the father. We get the distinct impression, however, that in such cases an examination of the family ought to be carried out as carefully as possible.

The mother, 44 years of age, was a dark, healthy, well built woman; spleen and liver not enlarged; the left kidney, floating, was easily palpable. The blood count showed the following figures: hemoglobin 92 per cent. (Sahli); erythrocytes 5,350,000; white cells 6,070; differential count: polynuclear neutrophils 55.9 per cent.; eosinophils 4 per cent.; lymphocytes 35.3 per cent.; transitional cells 5.3 per cent.; Wassermann test negative.

Paternal grandmother, 71 years of age, of dark complexion (both Children 6 and 7 bear a marked resemblance to her). She had been married twice; had twelve children; five died in infancy; once she had twins; once a premature

TABLE 3.—RESULTS OF BLOOD EXAMINATION OF FATHER OF CHILDREN

	Hb., per Cent.	Red Cells	White Cells	Neutro- phils, per Cent.	Eosino- phils, per Cent.	Baso- phils, per Cent.	Lympho- cytes, per Cent.	Transi- tionals, per Cent.
Normal	..	5,137,000	6,800	60.7	2.4	0.5	20.25	3.5
5/25/15	88	5,340,000	5,200	32.2	2.4	1.4	61.8	4.8
6/ 8/16	6,875	45.7	3.8	0.2	46.2	0.2
11/ 1/16	6,425	42.0	1.6	2.0	50.3	4.0

birth. The other children were well; their offspring were also in good health. She never heard of any disease in her family like that of her grandchildren. Neither liver nor spleen was palpable; Wassermann test negative. Blood examination: hemoglobin (Sahli) 81 per cent.; red cells 4,918,000; white cells 9,100; differential count: polynuclear neutrophils 54.3 per cent., eosinophils 1.6 per cent.; lymphocytes 40.6 per cent.; transitional cells 3.1 per cent.

Maternal grandfather, 74 years of age, never had been ill; blonde complexion; no abnormal findings on examination. Blood count: hemoglobin (Sahli) 90 per cent.; red cells 4,950,000; white cells 8,250; polynuclear neutrophils 48.5 per cent.; eosinophils 1 per cent.; basophils 2 per cent.; lymphocytes 43.6 per cent.; transitional cells 5 per cent.; Wassermann test negative.

Maternal grandmother, 73 years of age, had always been well; had nine children, of whom three died (whooping cough, pneumonia, debility). She had never heard of any special disease in her family. Liver and spleen not enlarged. Blood examination: hemoglobin (Sahli) 87 per cent.; red cells 4,135,000; white cells 5,820; differential count: polynuclear neutrophils 49.3 per cent.; eosinophils 0.6 per cent.; basophils 0.6 per cent.; lymphocytes 45 per cent.; transitionals 5 per cent.

Based on the foregoing data no other clinical diagnosis but splenomegaly of Gaucher seemed to us possible. We will not consider in detail the differential diagnosis.

What is the prognosis in cases suffering from this disease? A

number of cases seem to take a very slow course. Observations are known where the patients died at the age between 30 and 50 from intercurrent diseases, but we also know of cases in which the disease was the cause of death on account of hemorrhages. In the foregoing cases the disease was decidedly progressive. One child, and probably two children, had fallen a victim to the disease. The oldest of the two girls, taken into the hospital, had begun to show signs of cachexia. We considered ourselves justified in proposing surgical interference. Both cases were successfully operated on by Dr. J. Ph. Backer, consulting surgeon of the hospital.

The operation on the younger child (Case 7) was performed first. No adhesions were found, no noticeable hemorrhage took place. After splenectomy the liver was entirely accessible to palpation, its surface smooth; the left hepatic lobe was firmer than the right.

The spleen weighed 170 gm. (about four times the normal weight). Its dimensions were, length, 12.5 cm.; breadth, 6.5 cm.; thickness, 3.5 cm. The shape

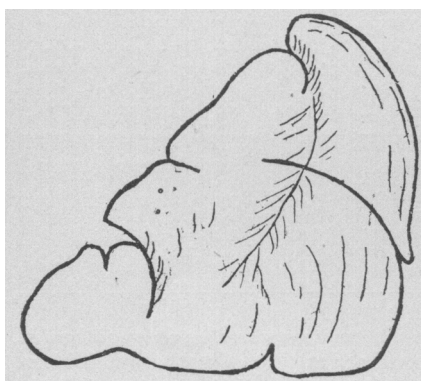


Figure 1

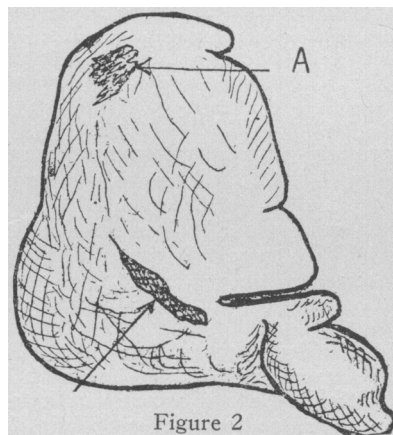


Figure 2

Figs. 1 and 2.—Spleen in Case 7, showing the outline and place of adhesions to the stomach at A.

was normal, but a deep incisure was present running from the center behind to the right upper part. The consistency was firm, the color grayish-red. The surface was slightly nodular, the nodules somewhat more brownish red than the deeper spots between. On further examination of the interior the color was found grayish red, the capsule was not thickened, the connective tissue somewhat more noticeable than usual. The follicles were remarkably distinct and large, more or less transparent. The organ was not very hyperemic; its tissues were firm; the pulp was not easily removed. An accessory spleen the size of a pea and two lymph nodes were removed. The microscopic examination gave in both cases the same findings, which we will discuss later. No special incidents were to be noted after the operation.

Blood examination showed an increase of leukocytes to 18,000. Temporarily, a slight albuminuria occurred; there was no increase of urobilin. The liver decreased somewhat in size after the operation; since then its size has remained stationary (three months *post operationem*).

The operation on the second child was more difficult. The spleen proved to be adherent to the stomach and the head of the pancreas; adhesions were broken

up carefully; no hemorrhage (Figs. 1 and 2). The spleen weighed 470 gm. (eight times the normal weight). The shape was somewhat disfigured. Large incisures were seen; at the right lower margin a very marked incisure was noticed, almost separating one lobe from the remaining body. Its dimensions were: length, 14 cm.; breadth, 13 cm.; thickness, 5.5 cm. Its surface showed a number of small nodules, varying in size. The color of the surface was purple-gray; small yellow patches could be distinguished. The organ was hyperemic; felt firm; at the hilus blue-red lymph nodes were present; during the operation similar nodes were seen on the pancreas. On further examination the capsule was found not thickened; there was much connective tissue; follicles clearly visible, more or less transparent; pulp not easily removable; hemorrhages at different places. Fourteen lymph nodes were removed from the hilus.

This child also stood the operation satisfactorily. There occurred a leukocytosis of 23,000 white cells. After the operation a marked urobilinuria occurred intermittently. The liver increased, first slightly, and returned later to its size preceding the operation (three months *post operationem*). In the summer of 1917 we found the children in good health.

Microscopic Examination of the Spleen, Accessory Spleen and Lymph Nodes.—Immediately after the operation samples were taken from the pulp and stained after the panoptic method of Pappenheim (May Grünwald and Giemsa). Scrapings were examined in normal saline solution. Some sections were frozen and cut. Some small pieces were put in alcohol *au tiers* of Ranvier and studied a few hours later. No large cells, which have been described in such cases, were found. From ten different places of each spleen, sections were made and hardened in absolute alcohol, formaldehyd and solutions of Orth, Flemming and Müller. We stained with hematoxylineosin; Leishmann's and Pappenheim's solution, after van Gieson, Mallory, Bielschowsky and with sudan III and hematoxylin. Large cells were not seen. Accessory spleen and lymph nodes were examined likewise.

One lymph node showed a small tuberculous lesion (positive von Pirquet's test). Neither spleen contained treponema (Levaditi's method). On examining macroscopically one of the slides, stained with hematoxylin eosin, the follicles were immediately noticeable because of their abnormal size and germinative center. The size of most of them varied between 0.5 and 1 mm. Microscopically some follicles, especially the smaller kind, showed absence of the large germinative center. Some germinative centers were surrounded by a zone of small lymphocytes, closely arranged together, in their turn surrounded by a zone of more scattered lymphocytes. The marked difference between center and environment was caused by concentric fibers, along which the lymphocytes were located. The cells in the center looked like large lymphocytes, with somewhat more protoplasm and nuclei somewhat less stained than those of the smaller lymphocytes, but the center was more dense and many cells were larger than usual. The cells in the germinative center showed, ordinarily, two or three distinct nucleoli, although some of them had only one nucleus and a pale protoplasm. These cells remind us of those, which were first described by Bizzozero and later more carefully studied by Tatiana Waschewitsch.¹ They are especially found in cases of diphtheria and pyogenetic processes. Probably a few of those cells occur normally in each follicle. Itami² also studied those cells. They apparently originated partly from lymphoblasts or lymphocytes, partly from endothelial cells. We found some of them in the follicular periphery and some in the splenic pulp, which seems to occur also under normal circumstances. Like Waschewitsch we found the nucleoli of those cells red in slides stained after van Gieson's method. Some phagocytes were found in the germinative centers and a varying number of karyokinetic figures in the lymphocytes and "tingible Körper" of Flemming in and outside of the cells.

1. Waschewitsch: Virchows Arch. f. path. Anat., 1900, **159**.

2. Itami: Virchows Arch. f. path. Anat., 1909, **197**.

This number varied, but was larger than usual, both in the spleens, accessory spleen and lymph nodes. Some follicles were noticeable for a thickened vascular wall. In the follicular periphery some polynuclear eosinophil cells were found. The slides stained after Mallory's and Bielschowsky's methods showed no changes of the intrafollicular structure; a few fine fibers between the cells were seen.

The picture of the splenic and lymphnodular follicles of our cases shows a marked resemblance to that which Flemming,³ in his classic study, gives of the secondary follicles in mesenterial bovine lymph



Fig. 3.—Photomicrograph of a section of the spleen in Case 7.

glands. Möbius⁴ saw the same thing in the spleen of full grown rabbits. He mentions having seen also in the pulp a few karyokinetic figures, something which we also noticed. In our slides, made from fifty cases of spleens studied in children, we never saw a greater activity of the germinative centers.

3. Flemming: *Arch. f. mikr. Anat.*, 1885, **24**.

4. Möbius: *Arch. f. mikr. Anat.*, 1885, **24**.

In the case of the oldest child, already referred to, the follicles could hardly be called normal. Besides some cells of Bizzozero-Waschkewitsch's type, we saw in the follicular periphery and in the pulp a few cells resembling large lymphocytes. The connective tissue was increased, both as to the trabeculae and the reticulum. Strips of spindle cells in bundles, containing connective tissue, ran through the pulp. The pulp showed some hemorrhages. The venous sinus was wide. Granulocytes in the pulp were easily seen (Leishmann's stain), the majority of which represent, in the case of the older child, polynuclear eosinophils. The splenic pulp in the younger child showed more myelocytes,

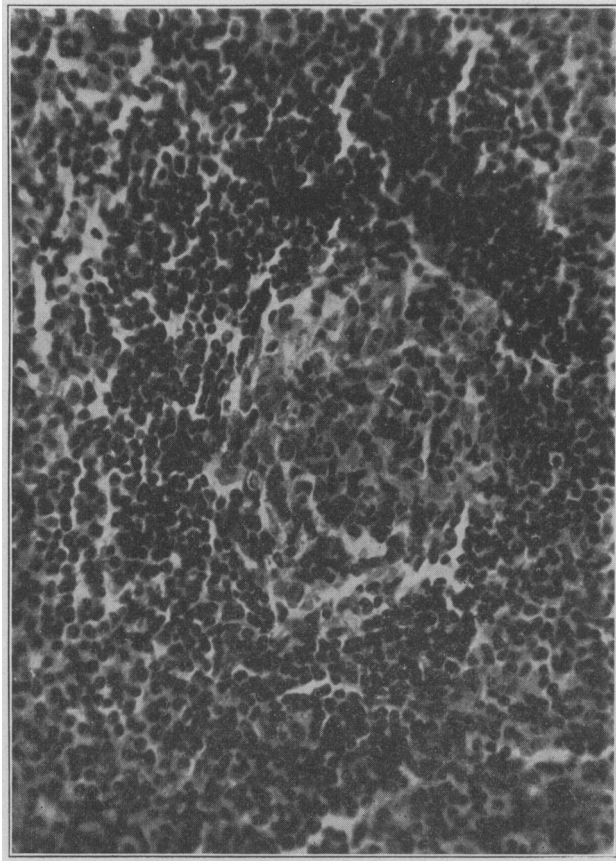


Fig. 4.—Higher magnification of section of spleen shown in Figure 3.

mostly eosinophils, a few neutrophils; some pigment was found in the trabeculae, lying free in the pulp, not in the endothelial capillary cells. Figure 3 represents a photomicrograph of one of our slides (slightly magnified), while Figure 4 shows the same picture greatly magnified.

The accessory spleen gives the same picture as the spleen. Many karyokinetic figures were noted in the follicles. Both lymph nodes showed an unaltered structure. They were hyperemic; nowhere were there large cells, but the follicles resembled the heretofore described splenic follicles. The fourteen lymph nodes of the older child showed varying pictures. They were

all hyperemic; the number of follicles with large, well defined germinative centers was variable; also the degree of karyokinesis. Some glands had follicles with a light center; others had practically none. Nowhere were follicles seen such as those noticed in the spleen, which showed a germinative center surrounded by a darker and a lighter zone.

Finally, we attempted to demonstrate lipoids. In both spleens a number of sudanophil cells were found in and outside of the follicles. As Kusunoki⁵ found those cells regularly in his examination of 132 spleens, we cannot see anything abnormal in their presence. According to Kusunoki, lipid cells are found in the follicles of the spleen of children, whereas in adults they are seen in the pulp. Possibly those cells represent the cells demonstrated by Bizzozero and Waschewitsch. The foregoing microscopic pictures have no resemblance to the pathologic findings in Gaucher's disease. There the normal splenic pulp has disappeared entirely, or almost entirely, and has been substituted by alveola-like sinuses, separated by more or less thick fibrous structure, filled with the well known large endothelium-like cells. The follicles in those instances are underdeveloped.

Originally we thought our cases could be considered as a juvenile type of Gaucher's disease and were supported in our opinion by a case described by Reuben⁷ and Mandlebaum⁸ concerning a boy 4½ years of age. In this case very large follicles, with noticeably active germinative centers, beside the familiar large cells, were found in the spleen and lymphnodes. Mandlebaum⁸ considers that the large cells originate from atypical lymphocytes of the germinative centers. We must acknowledge that no pathologic tissue was found in the examined organs (spleens, accessory spleen and lymph glands). Hypertrophy was the only finding.

Some years ago Dr. R. de Josselin de Jong,⁹ pathologist of the city hospital of Rotterdam, described a case of Gaucher's disease. After examining our specimens he believes that our cases have no connection with the disease mentioned. We have apparently to deal with a congenital *vitium primæ formationis*, on account of which the spleen has developed into a state of "giant growth." Whatever the truth may be, we are dealing in the foregoing cases with a familiar progressive disease of the spleen which produces, sooner or later, an increasing cachexia, and in the course of which a hemorrhagic diathesis occurs *ante mortem*. Our clinical material may show us in the future similar cases, cases which we have not found mentioned before in medical literature.

5. Kusunoki: Ziegler's Beiträge Bnd. 59, 1914.

6. Nederl. Tijdschr. v. geneesk., 1917, No. 12.

7. Reuben, M. S.: AM. JOUR. DIS. CHILD., 1912, **3**, 28, and 1914, **8**, 336.

8. Mandlebaum: Jour. Exper. Med., January, 1914; *Ibid.*, 1912, **16**, 6.

9. De Jong: Nederl. Tijdschr. v. geneesk., 1910, Nos. 8 and 9; Beitr. z. Path. Anat. u. z. allg. Path. (Ziegler's), 1910.