

**LARGE-CELL SPLENOMEGALY (GAUCHER'S DISEASE):
A CLINICAL AND PATHOLOGICAL STUDY.**

By N. E. BRILL, M.D.,

ATTENDING PHYSICIAN TO MOUNT SINAI HOSPITAL; PROFESSOR OF CLINICAL MEDICINE,
COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY,

AND

F. S. MANDLEBAUM, M.D.,

PATHOLOGIST TO MOUNT SINAI HOSPITAL, NEW YORK

Owing to the haze which surrounds the conception of medical men in reference to the subject of the Gaucher type of primary splenomegaly, the authors are prompted to make an attempt to show that this specific form of disease has little in common with a promiscuous group of diseases whose chief characteristic is an enlargement of the spleen. The subject has been still further confused by a recent article appearing in *Surgery, Gynecology, and Obstetrics*, March, 1913, by L. B. Wilson, who reports three cases of primary splenomegaly, Gaucher type, for which splenectomy had been performed at St. Mary's Hospital, Rochester, Minnesota. In the literature which he has considered for the preparation of his article, he assumes as authentic cases many of those belonging to the promiscuous group of splenomegalies to which we have just referred, and which writers who have given much time to an intimate study of this disease have justly eliminated. The reasons for their elimination have already been fully considered in the publications of Marchaud, Schlagenhanfer, Risel, and others. We can see no clinical or pathological factors which might have justified Wilson in restoring to the list of proved cases of the Gaucher type those in which the verdict against their genuineness has been so unanimous.

There are varying conditions which are attended by splenomegaly. Some of these are plasmodial infections, syphilis, tuberculosis, amyloid disease, rickets, circulatory disturbances in the portal system, blood diseases (including the leukemias), Hodgkin's disease, and a large group, to which the French have particularly called attention, of associated hepatic cirrhoses of a hypertrophic type, with splenic enlargements. Unfortunately to many of these, and particularly to the group of splenic anemias, the term "primary splenomegaly" has been applied. We deem it desirable, therefore, to isolate from this group one form, whose picture is so distinctive clinically, and whose pathological process is so unique, as to merit an individual name. We would therefore suggest that this affection should be called Gaucher's disease, so as to avoid the use of the term "splenomegaly," which is only one of the features of the

disease, but which has occasioned much of the confusion to which we have alluded above.

DEFINITION. The characteristic features of Gaucher's disease are its incidence in childhood, its frequent presence in other members of the family of the same generation, a progressive increase in the size of the spleen which often reaches colossal dimensions, followed by a similar huge enlargement of the liver, a characteristic brownish-yellow discoloration of the skin, usually restricted to the face, neck, and hands, a peculiar yellowish, wedge-shaped thickening of the conjunctivæ commonly seen on both sides of the cornea, and the prolonged and chronic course of the disease, which does not materially disturb the health of the individual. After the disease has been present for a considerable time there is a definite tendency to hemorrhages, especially appearing as epistaxis, bleeding from the gums, and ecchymoses in the skin following the slightest trauma. The positive finding in the blood, even in the early stage of the disease, is a definite leukopenia. The erythrocytes, however, show no definite change either in number, form, size, or hemoglobin content until the disease has existed for a long time, when an anemia of the chlorotic type makes its appearance. The anemia is rarely pronounced at any stage. The disease is not accompanied by palpable enlargements of the superficial lymph nodes. There is no jaundice and ascites is exceptional. The disease has none of the characteristics of malignancy, and usually is terminated by some intercurrent affection.

The pathological feature of the disease is the presence in the spleen, liver, lymph nodes, and bone-marrow of distinctive large cells, with characteristic cytoplasm and small nuclei. The enlargement of the spleen and liver is due to the presence of these cells in enormous number. In well-established cases all of these organs contain pigment giving the reaction for iron. Whereas the nature and origin of these cells are still moot questions, the histological picture is uniformly characteristic and pertains to no other form of disease.

ANALYSIS OF INDIVIDUAL SYMPTOMS. While there are no individual symptoms which are pathognomonic of this disease, we believe that a definite association of certain symptoms is sufficient to enable one to clinically diagnose its presence. It was this association of symptoms which enabled one of us to make the diagnosis clinically in two cases, which was subsequently confirmed by pathological examination. A detailed analysis of these clinical factors is justified owing to their importance. We shall, however, confine ourselves strictly to such cases as have been proved by histological examination of the tissues obtained either by autopsy or by splenectomy. We purposely shall not consider the cases occurring in brothers and sisters presenting the identical clinical picture as the affected member of the family, because absolute scientific confirmation is lacking.

The cases established under these conditions are: (I) Gaucher,¹ 1882; (II) Collier,² 1895; (III) Picou and Ramond,³ 1896; (IV) Bovaird,⁴ 1900; (V) Brill, Mandlebaum and Libman,⁵ 1904; (VI) Schlagenhauser,⁶ 1907; (VII) von Herczel,⁷ 1907; (VIII) Marchand,⁸ 1907; (IX) Brill, Mandlebaum and Libman,⁹ 1909; (X) De Jong and van Heukelom,¹⁰ 1910; (XI) Mandlebaum,¹¹ 1912; (XII) Wilson,¹² 1913; (XIII) Downes,¹³ 1913; (XIV) Erdmann.¹⁴

ONSET. In the large majority of cases the beginning of the disease cannot be determined, because it starts insidiously and is unattended by any subjective symptoms which might attract the attention either of the parent or the affected individual. After the disease has existed for some time and has given rise to a splenic enlargement, which in some patients may produce symptoms of discomfort or slight pain, it first begins to attract attention; in others, in the course of a physical examination for some other condition, which may have no relation to the disease itself, a splenic hypertrophy is discovered.

AGE. As a rule the disease begins in early life. Among the fourteen proved cases the age at which the disease was detected is as follows: Case I at seven years; Case II at two years; Case III at twenty-eight years; Case IV at three years; Case V at nineteen years; Case VI at five years; Case VII at thirty-three years; Case VIII at twenty-four years; Case IX at twenty-one years; Case X at seven and a half years; Case XI at three and a half years; Case XII at twelve years; Case XIII at thirteen years; Case XIV at one year. From this it may be seen that the disease appeared before the age of twelve years in the majority of cases and in infancy or early childhood in several instances.

SEX. Females are more frequently affected than males. In the fourteen reported cases the disease occurred in males only twice.

¹ De l'épithéliome primitif de la rate, Paris, 1882.

² Trans. Path. Soc. London, 1895, xlv, 148.

³ Bull. Soc. anat. de Paris, 1895, lxx, 531; Archiv. de méd. expér. et d'anat. path., 1896, viii, 168.

⁴ AMER. JOUR. MICRO. SCI., 1900, cxx, 377.

⁵ Proc. New York Path. Soc., 1904, iv, 143; AMER. JOUR. MICRO. SCI., 1905, cxxix, 491.

⁶ Verhandl. d. deutsch. path. Gesellsch., 1907, x, 77; Virchow's Archiv. f. path. Anat., 1907, cixxxvii, 125.

⁷ Wiew. klin. Woch., 1907, xx, 127.

⁸ Münch. med. Woch., 1907, liv, 1102.

⁹ AMER. JOUR. MICRO. SCI., 1909, cxxxvii, 849.

¹⁰ Beitr. s. path. Anat. u. s. allg. Path., 1910, xlviii, 598.

¹¹ Jour. Exp. Med., 1912, xvi, 797.

¹² Surg., Gyn., and Obst., 1913, xvi, 240. An examination of the slides which were kindly sent to us by Dr. Wilson revealed the undisputed existence of the disease in only one of his three reported cases. This conclusion was arrived at after careful and critical study. Our reasons for excluding two of his cases will be referred to later in the article.

¹³ Med. Record, 1913, lxxxiii, 697.

¹⁴ In a recent communication before the New York Surgical Society, J. F. Erdmann presented a spleen which he had removed from a child, aged three years and four months. A portion of the spleen was kindly furnished to us. It shows the presence of the disease in an early stage. An article reporting this case will be published later in the AMER. JOUR. MICRO. SCI.

FAMILIAL OCCURRENCE. The disease often affects more than one child of the family. There seems to be no tendency to hereditary transmission, and in none of the established cases has any parent been affected. If one wishes to include those cases in the family, which from a clinical standpoint have the same symptoms as the individual proved case, then the familial character has been noted seven times. The authors who have mentioned such cases are Collier; Bovaird; Brill, Mandlebaum, and Libman; Schlagenhauser; De Jong and van Heukeloo; Mandlebaum; Erdmann.¹⁵

ENLARGEMENT OF SPLEEN. The splenic hypertrophy is one of the important features of the disease. It is slowly progressive, occurs in every case, and gives rise to a distinct protrusion. The amount of abdominal and thoracic protrusion is in direct proportion to the increase in size of the affected organ. While at first the left side of the trunk is decidedly enlarged, with the subsequent increase in size of the liver, the anomalous one-sided protrusion becomes symmetrical. At the latter stage the trunk is definitely barrel-shaped, the lower part of the thorax joining in a distinct curve with the upper part of the abdomen. The time required for the spleen to reach colossal proportions may be many years. The size of the spleen is greater than that in any other disease, not even excepting leukemia. The upper border may be percussed even as high as the fifth rib in the axillary line, and the lower border not infrequently extends below the iliac crest into the pelvis, so that it cannot be felt by abdominal palpation. Anteriorly the rounded edge may be traced by palpation to the region of the umbilicus, where it often curves to the right, and may thus occupy the greater portion of the abdomen. The posterior border may often be felt in a line continued vertically from the angle of the scapula; occasionally it may even be felt along the vertebral column. At the umbilicus a distinct notch is usually felt, whose depth may admit three fingers. In some cases, however, more than one notch may be felt. The surface is usually smooth, even though a considerable amount of perisplenitis be present.

ENLARGEMENT OF LIVER. This seems to develop only after a considerable increase in size of the spleen has taken place. It gives rise to the uniform thoracic and abdominal protrusion referred to above. Its upper border may reach the fourth rib, and its lower border be felt 3 cm. below the umbilicus. Occasionally the splenic enlargement may so overlap the liver that the lower border of the latter can only be felt in the anterior axillary line and posteriorly. The surface is also uniformly smooth.

SKIN. Early in the disease the skin of the face and neck, as well as the hands, presents a peculiar discoloration. It is usually spoken of as a pigmentation,¹⁶ but we prefer to call it a discoloration,

¹⁵ Personal communication.

¹⁶ No histological examinations of the skin affected by this discoloration have as yet been made.

because it is uniform in distribution and intensity, and is limited to the parts of the body exposed to light. In one case only has this discoloration been noted on the abdomen. The color is a peculiar yellowish-brown (ochre). It frequently assumes a deeper shade across the bridge of the nose and around the eyes, and after the disease has existed for a considerable time the discoloration becomes uniformly more intense. Often the skin presents numerous ecchymoses, varying in size and color, because the superficial vessels are particularly susceptible to injury from the slightest trauma. Furuncles assuming a hemorrhagic character have been noted, which on healing have left definite and permanent skin lesions of a dark pigmented nature.

Some authors describe this specific discoloration as a jaundice or a subicteric tint. Our own analyses show an absence of bile in the blood and urine, with an excess, however, of urobilin in both. A tendency to general sweating associated with sudamina has been noted in a few cases.

EYES. Early in the disease a change in the conjunctiva of both eyes may be noted. This manifests itself in a brownish-yellow, wedge-shaped thickening, affecting first the nasal side of each conjunctiva, its base being limited by the cornea. Later on the temporal side also becomes the seat of a similar thickening. The development and growth of these thickenings are very slow. They seem to originate near the corneal margin and extend in the process of growth to the inner and outer canthus respectively. They resemble in some respects the lesion of the conjunctiva known as pinguecula, and may reach dimensions of 3 mm. along the corneal margin and 5 mm. in length. We have never seen a case of the disease in which this peculiar ocular lesion was absent, and therefore again emphasize its diagnostic significance.

HEMORRHAGES. There seems to be a tendency in all of the cases to bleeding from the mucous surfaces. In most of the cases epistaxis is a frequent occurrence; in some cases this is associated with bleeding from the gums, which are often swollen and spongy. Melena and metrorrhagia have been observed. Attention has been called above to the occurrence of hemorrhagic furuncles and numerous ecchymoses in the skin.

BLOOD. An important positive factor is a leukopenia which appears early in the disease and persists throughout. As few as 500 leukocytes to the cubic millimeter have been noted. The average count of all the reported cases is 4600. The differential count, using the average of all the authentic cases, is as follows: Polynuclears, 66; small lymphocytes, 20; large lymphocytes, 13; eosinophiles, 1. In two cases myelocytes were found, 2 per cent. and 1 per cent. respectively. Mast cells were also noted in two cases, 0.8 per cent. and 0.5 per cent. respectively.

It is remarkable that notwithstanding the fact that the disease

involves the entire hemopoietic system, its effect on the blood-forming organs should be attended by so little demonstrable change in the morphological characters of the blood. The number of erythrocytes is not materially diminished until the disease has existed for some years. The red-cell count for quite a long period is close to normal. Later in the disease a diminution slowly takes place. In the advanced cases the average of all the reported counts is 3,700,000. As high as 6,000,000 red cells have been noted in one case. There seems to be a greater reduction in the hemoglobin content than in the number of the red cells, giving rise to a low color index, and therefore of a mild anemia of the chlorotic type. The appearance of the patient does not even suggest an intense degree of anemia, because the skin of the majority of patients does not show an inordinate amount of pallor, nor do their mucous membranes.

There is little if any change in the contour, shape, or size of the red cells. The color may be slightly paler than normal. In only two of the cases have nucleated forms been observed; in these a solitary normoblast was seen in each. Megaloblasts have never been noted. The large specific type of cell, the so-called "endothelial cell," whose presence in all the hemopoietic organs characterizes the disease, is never found in the peripheral circulation. The hemoglobin shows a reduction before the red cells suffer any marked decrease. Its average in all the cases reported is 65 per cent. As high as 92 per cent. and as low as 35 per cent. have been observed.

LYMPH NODES. The superficial lymph nodes of the body are not usually palpable. Where careful search is instituted, occasionally a few solitary lymph nodes in the axilla and in the groin may be felt as small, hard, pea-sized bodies.

ABSENCE OF JAUNDICE AND ASCITES. We have already directed attention to the peculiar brownish-yellow discoloration of the skin of those parts of the body which are exposed to light. This discoloration has been called jaundice by some writers. We insist that this is a misnomer, because bile pigment has not been found in the blood or urine. Ascites is almost invariably absent, even though the disease has existed for twenty-five years or more. In only one case has it been reported.

SYMPTOMS OCCASIONALLY MANIFEST. After the spleen and liver have grown to a large size a few patients complain of abdominal pain, chiefly referable to the region of the spleen. This pain is not constant. It may be absent for many months before it is complained of again. During the period of pain, tenderness over parts of the spleen may be elicited. This would seem to be occasioned by the presence of local areas of perisplenitis. Pain and tenderness over the liver are only exceptionally present. The weight of the spleen and liver gives rise in a few patients to a sense of dragging discomfort in the abdomen. It is remarkable that not-

withstanding the colossal size of the spleen and liver, there is very little complaint in the majority of the patients referable to these organs.

Very late in the existence of the disease, only after many years, some patients direct attention to pain in the lower ends of the femur and tibia, and still later to pain and tenderness in the muscles of the thigh and calf. Bone tenderness over the sternum and tibia is absent.

A remarkable feature of this disease, to which we have already drawn attention, is the preservation of the feelings of comparative comfort and well-being which dominate the patient. As a rule, patients do not feel depressed, nor are their mental activities diminished.¹⁷

EMACIATION. Most of the advanced cases present a loss of adiposity. The appearance of the patient, with the tremendously enlarged abdomen and the emaciated frame, makes a striking picture. In one of our cases, a female adult, there was a total body weight of 89 pounds.

DURATION AND TERMINATION. The disease is essentially chronic; its course is slow and progressive. Schlagenhauser's patient lived for thirty-six years after the disease was detected. The average duration of all the authentic reported cases where death has not resulted from splenectomy is 19.3 years. The disease is usually terminated by some intercurrent affection. A few of the reported causes of death are tuberculosis, pleurisy, and pericarditis. Operative procedure (splenectomy) has occasioned three deaths. Another case died as the result of an accident causing a fracture of the skull and laceration of the brain.

PATHOGENESIS. Much speculation has been indulged in to explain the nature and origin of this disease. When first described by Gaucher its nature gave rise to considerable discussion, and it was considered by some to be a form of malignant disease. Later writers, taking into consideration its clinical course, its long duration, as well as its histological features, have justly disproved this assumption. Various theories have been offered, such as the influence of an endogenous toxin, of an enzyme manufactured by the spleen, infection by protozoa, tubercle bacilli, and the like. No evidence has ever been presented which might substantiate any of these as causative factors. While it is true that a tropical form of splenomegaly, known as kala-azar, exists

¹⁷ One of the patients now under observation, in whom the disease is known to have existed for at least twenty-four years, presenting a gigantic spleen and liver, which together almost completely occupy the entire abdominal cavity, is still able to attend to her household duties and social functions, and though forty-four years of age, still indulges in the summer in sea-baths, swimming, and tennis. This is one of a family in which four cases have occurred. The existence of the disease in two of these cases was confirmed by autopsy. We have purposely added this case in a footnote, so as to adhere to the plan expressed above, to include in our paper only the cases which have been proved histologically.

in which protozoa have been found, a thorough search for similar organisms has always failed. In the present state of our knowledge the confession must be made that we know nothing definite of the pathogenesis of this disease.

DIAGNOSIS. While the diagnosis of the disease in its early stage is well-nigh impossible, owing to the absence of associative symptoms, the fact that more than one member of the family may be afflicted with varying degrees of combined splenic and hepatic enlargements ought to suggest the possibility of its existence. When the disease has sufficiently developed, so as to give rise to a distinctly large spleen, even though but one member of a family be affected, the diagnosis, while difficult, may possibly be made. The factors which might enable one at this stage to determine the existence of the disease are the large spleen, a beginning hepatic enlargement, the conjunctival lesion, and the absence of anemia, jaundice, and ascites. Blood examinations must always be made, so as to exclude the possibility of a leukemia.

When the disease is fully developed the diagnosis ought to be possible in the majority of cases. The enormous enlargement of the spleen and liver; the brownish-yellow discoloration (non-icteric) of the skin; the conjunctival thickening; the long duration of the disease; its predilection for females; its familial occurrence; the feeling of comfort and ease, notwithstanding the tremendous protrusion of the lower thorax and abdomen; the tendency to hemorrhage, manifested by epistaxis and bleeding from the gums; the ecchymoses in the skin; the persistent leukopenia; the mild degree of chlorotic anemia without changes in the red cells; the absence of jaundice and ascites; the absence of palpable lymph nodes, make a symptom complex which differentiates this disease from the groups called splenic anemia and Baati's disease, with which groups it is most likely to be confounded.

While it is true that splenic anemia and Gaucher's disease have much in common, yet we believe, contrary to Hutchison,¹⁸ that they are distinct and can readily be separated. The features common to both are the splenic enlargement, the chronicity of the affection, the hemorrhagic tendency, the absence of leukocytosis, and the anemia of the chlorotic type. The differential factors are the relatively shorter duration of the disease in splenic anemia; the pallor of the skin, which toward the end becomes distinctly jaundiced; the more pronounced type of the anemia, which occurs early and is a prominent factor in the disease; the feeling of distress and illness; the tendency to hemorrhages of a more generalized type, as expressed by frequent attacks of hematemesis as well as melena; the relatively smaller size of the spleen; the markedly smaller size of the liver; the absence of the conjunctival

¹⁸ A System of Medicine, Abbutt and Rolleston, 1909, v, 759.

lesion, and the presence of ascites. These factors are so distinctive that in a large majority of cases the differential diagnosis between Gaucher's disease and splenic anemia may be established.

It was the recognition of these differential factors which enabled one of us (Brill),¹⁹ De Jong and van Henkelom, and Renben²⁰ to diagnosticate the presence of Gaucher's disease during life, which diagnosis was subsequently confirmed by histological examination in each instance.

The disease may be confounded with chronic splenomegalic acholuric jaundice, which likewise is a familial form of disease, and occurs in infancy and early childhood, sometimes hereditary, and is associated with anemia, with considerable enlargement of the spleen, and a moderate enlargement of the liver. The distinctive blood changes, such as fragility of the red blood cells, normoblastic and megaloblastic crises, and leukocytosis, would differentiate this from Gaucher's disease.

Hanot's disease is likewise characterized by its chronic course as well as by a large liver and spleen. Jaundice in this disease is an early symptom, and exists continuously in varying degrees of intensity. At any time during the course of the disease an icterus gravis may occur. The urine usually contains bile. Its course is generally attended by fever, which is rarely or ever present in Gaucher's disease. The hepatic and splenic enlargements are moderate as compared with the hypertrophy of these organs in Gaucher's disease. Leukocytosis is usually a prominent feature.

It would appear unnecessary to mention in this connection the possibility of mistaking leukemia, Hodgkin's disease, and pernicious anemia for Gaucher's disease. The characteristic blood picture and the enlargement of the lymph nodes in leukemia would immediately differentiate it, although the possibility of a stage of remission in leukemia with an approximately normal blood-count might be met with, when a differential diagnosis would be established with greater difficulty. Even under such conditions the marked pallor of the skin, the enlarged superficial lymph nodes, and the absence of leukopenia would suggest some other condition than Gaucher's disease.

The only form of Hodgkin's disease which would admit of the possibility of error in diagnosis is the splenomegalic form without enlargement of the lymph nodes. Such a form, however, is still a moot subject of discussion. The usual form of Hodgkin's disease, while it may present some enlargement of the spleen, is commonly associated with periods of fever and with greatly enlarged lymph nodes. A combined splenic and hepatic enlargement of colossal size does not occur in Hodgkin's disease.

¹⁹ AMER. JOUR. MED. SCI., 1901, cxvii, 377.

²⁰ Amer. Jour. Dis. Child., 1912, iii, 28.

The characteristic high color index, the definite changes in size and shape of the red-blood cells, together with the nucleated forms, the extreme degree of anemia, the color of the skin, the preservation of the adiposity, are sufficient factors in establishing the diagnosis of pernicious anemia, even though a moderate degree of splenic enlargement be present.

French authors, particularly Chauffard, Lerehoullet, Gilbert and Fournier, and Gilbert, have described under the terms metasplénomégalic hypertrophic hilar cirrhosis, presplénomégalic hypertrophic hilar cirrhosis, hypersplénomégalic hypertrophic hilar cirrhosis, and a special juvenile type with great splenic enlargement, a medley of diseases whose existence has seldom been met with in any other country than France. The clinical history and pathological features of these forms are so involved, both in obscurity and chaos, and the characters which would entitle them to clinical entities are so meager and ill-defined, that it is possible some of these forms may have been examples of unrecognized Banti's disease or Gaucher's disease.

PATHOLOGY. The description of the pathology herewith presented is based upon the investigation and study of the material obtained post mortem in three cases, and upon the spleens obtained after splenectomy in two other cases, representing in stage of development, the early, the intermediate, and the late periods of the disease.²¹

The organs involved in Gaucher's disease are the spleen, liver, lymph nodes, and bone-marrow, all of which show the presence of peculiar large cells and a variable amount of iron-containing pigment. The large cells are characteristic and present the following features. They are usually round or oval in shape, but when seen in large compressed masses may assume a polygonal outline. The average measurement is from 20μ to 40μ in diameter, and a cell may contain from one to four or more nuclei of relatively small size. When smears are made from the freshly cut organ (Fig. 1), cells of high size may frequently be found.²² The cytoplasm stains faintly with acid dyes and often presents a streaked and wrinkled appearance, but with high magnification a granular character may be noted. Some of the cells show vacuoles, probably the result of phagocytosis. Degenerative forms are not present excepting in cases of long duration, but in the liver the cells may be so fused that their individual outlines are not easily recognized. The nuclei are small, round, deeply staining, or, occasionally, somewhat larger irregular bodies. Rarely do the nuclei show atypical mitotic changes. Whereas the cells are quite unlike any found in other

²¹ The ages of the patients from whom this material was obtained were three years, four and a half years, twenty-eight years, thirty-four years, and thirty-seven years.

²² A cell of this type from the spleen measured 71.7μ by 100μ , and contained thirteen nuclei.

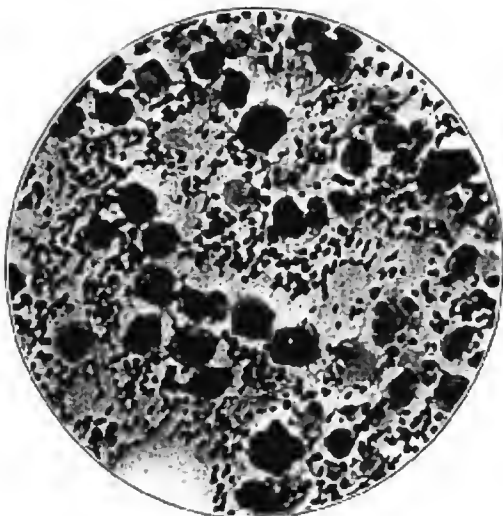


FIG. 1.—Smear from fresh surface of spleen. The size of the large cells as compared with the red-blood cells is readily appreciated. $\times 300$

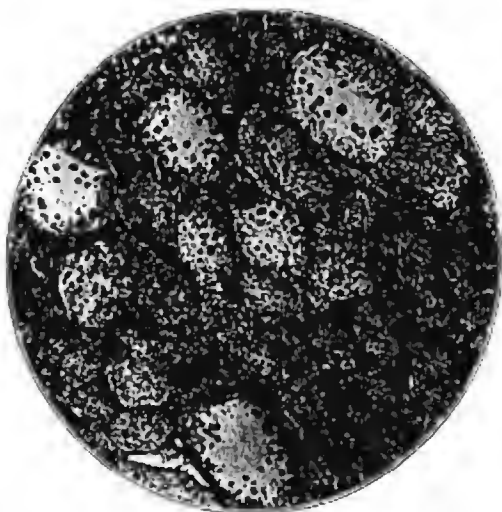


FIG. 2.—Section of spleen showing dilated venous sinuses filled with blood cells (not visible with low power) and large cells. Remainder of field composed of alveoli completely filled with large cells and separated by normal pulp cells. $\times 80$.

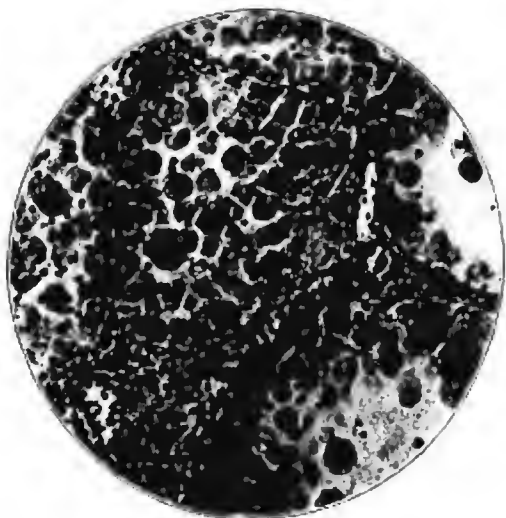


FIG. 3.—Section of spleen. On the right are segments of two sinusoids containing large cells and red-blood cells. Connective-tissue septa between the alveoli are seen above and on the left. $\times 300$.



FIG. 4.—Section of liver showing the large amount of interlobular connective tissue. The large cells cannot be differentiated with this power. $\times 80$.



FIG. 5.—Section of liver showing large cells in the mesher of the connective tissue and in the sinusoids. The large cells are compressed and their outlines somewhat obscure. $\times 300$.



FIG. 6.—Section of retroperitoneal lymph node. The large cells form distinct cellular masses, between which are seen strands of normal lymphoid cells. $\times 80$.

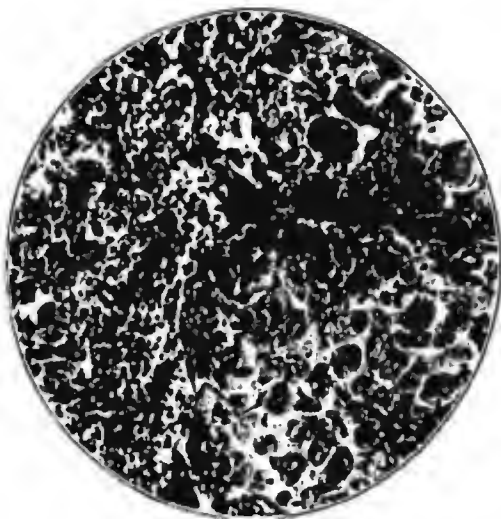


FIG. 7.—Section of spleen node, showing lymph sinuses filled with large cells whose outlines are clearly distinguished. $\times 300$.



FIG. 8.—Section of bone-marrow from the tibia, showing compressed and distorted large cells. On the left and below are small groups of normal marrow cells. $\times 300$.

pathological processes, one might compare them with atypical, swollen, and desquamated endothelial cells.

SPLEEN. This organ always retains the shape and general appearance of a spleen. The surface is perfectly smooth excepting in cases of long duration, when the capsule may be markedly thickened and rough, and show scattered areas of perisplenitis, as well as localized depressions due to infarctions. The color varies from brownish pink to brownish red. The cut surface is usually brownish red and often mottled with white or grayish streaks. The Malpighian bodies are not visible, nor can the trabeculae be recognized. Minute hemorrhagic dots are frequently seen, and the infarcts when present are often surrounded by hemorrhagic zones. The splenic vein in adult cases may show slight sclerosis; it is frequently of bugh size.

The spleen varies in size and weight according to the duration of the disease. In one of our cases it measured 45 x 25 x 13 cm. and weighed 7400 grams (14 pounds 13 ounces), one-sixth of the entire body weight. The average weight in thirteen authentic cases (including the one of only 490 grams obtained from a child) was 3600 grams (7.2 pounds).

Microscopic examination shows that the normal splenic structure is replaced by large, round, or irregularly shaped, alveolar spaces, whose walls are formed by delicate connective-tissue fibres, distinctly lined by endothelium. These spaces represent the greatly dilated venous sinuses of the organ (Fig. 2). In all these spaces the characteristic large cells are seen, some lying free, others attached to the endothelium. Many of the sinuses also contain red blood cells. Sinuses are also seen, presenting the same general appearance and filled with large cells, but without definite endothelium (Fig. 3). A few normal pulp cells are usually found between the sinuses, also capillaries of normal appearance. Reticulum fibres cannot be detected within the sinuses. In most cases the follicles are few in number, and with the exception of a slight thickening of the walls of the central artery in long-standing cases, show no changes. In early cases, however, the follicles may be of enormous size. Scattered throughout the pulp are isolated groups of the typical large cells, and some of these large cells are usually seen between the lymphoid cells at the peripheral portions of the follicles. The germinal centres of the follicles in early cases show atypical lymphoid cells without mitotic changes, also large nucleated cells (phagocytes) containing Flemming bodies. Early cases may also show large cells resembling megakaryocytes, containing fused masses of deeply staining nuclear matter. Large hemorrhagic areas are not uncommon in long-standing cases, and pigment is invariably present. This is seen between the connective-tissue fibers of the trabeculae, within the endothelial cells of the capillaries, and in many of the typical large cells. The pigment

granules are brown or brownish yellow in color, and show the usual iron reaction. The early cases, however, show little or no pigment. In cases of long duration areas of degeneration may be found, but the contours of the large cells may still be recognized, as a rule. In two cases, Schlagenhanfer's and Erdmann's, areas of tuberculosis were observed. These we believe are only incidental and have no bearing or relationship to the diseased process.²³

LIVER. In young individuals the surface is smooth and glistening; its color is a light yellowish pink. On section the same color is noted and the lobules are but faintly indicated. In the older cases the surface may be slightly uneven, owing to localized areas of perihepatitis with irregular thickening of the capsule. The color in these cases assumes a darker hue of brownish red. On section the parenchyma swells above the cut surface; its color varies from a brownish pink to a brownish red. A few grayish streaks and markings are often noted, but they bear no relation to the usual lobular outlines. Occasionally fine hemorrhagic points are seen. The size of the liver is invariably increased, and is in direct proportion to the duration of the disease. In one of our cases the weight of the liver was 4800 grams (10 pounds). The average in all adult cases where the weight of the liver was noted (five in number) was 3450 grams (7.2 pounds).

The noteworthy feature of the liver, microscopically, is the enormous amount of interlobular connective tissue, which gives the usual picture of a fibrosis when examined with the low power (Fig. 4). A more critical examination, however, shows that a great number of cells, identical in type with those found in the spleen, are situated in the meshes of the connective tissue. Many of these cells have lost the typical appearance, and individual cells cannot always be differentiated. They frequently appear as flattened or compressed and fused masses (Fig. 5). In the sinusoids, however, isolated large cells are found. These cells usually are well-preserved, but they are not directly connected with the reticulum fibrils which form a delicate net-work between the columns of liver cells. In the advanced cases most of the large cells in the sinusoids are situated near the peripheral portions of the lobules.

²³ At the 1912 meeting of the German Pathological Society, W. H. Schultze reported a case of diabetes, with marked lipoidemia, in a man aged twenty-seven years. The spleen, which was only slightly hypertrophied, contained large cells, in which Schultze found a distinct lipid substance. No large cells were found, however, in any of the other organs. On account of the similarity of the cells to those found in Gaucher's disease, he calls attention to the possible occurrence of a lipid substance in the latter. No fresh material being available, our observations to establish this fact could only be made on a portion of spleen fixed in formalin. We succeeded in obtaining a faint stain with Nile blue, but the results with the Fischler, Smith-Dietrich, and Cissocio methods were not corroborative. A final decision as to the presence of a lipid in the cells in Gaucher's disease should not be made until the various methods have been employed on frozen sections of fresh unfixed material, for Bell (Anatomical Record, 1910, iv, 199) has shown that formalin solutions often have a solvent action on lipoids, and the staining methods may give negative results in consequence of such fixation.

The individual liver cells are not apparently affected by the presence of the large cells, nor are any changes noted in them as the result of compression by the interlobular connective tissue. Occasionally the liver cells show a somewhat coarsely granular appearance, and in old cases minute fat droplets have been seen. None of the large cells in the liver appear to have phagocytic properties. In the early stages of the disease iron-containing pigment is absent, but in the more advanced stages it is always found, situated in the capsule as well as in the neighborhood of the smaller bloodvessels, but not in the large cells. The bile-ducts are not affected and appear normal, and no changes are present in the intralobular veins or in the branches of the hepatic artery.

In Schlagenhauser's case numerous miliary tubercles were found in both lobes of the liver. We do not believe that they have any direct relationship to the disease.

LYMPH NODES. In noteworthy contrast to the usual absence of enlarged superficial lymph nodes, those in the thorax and abdomen are always increased in size. The mesenteric, retroperitoneal, and iliac lymph nodes, also the nodes at the hilus of the liver and the spleen, and those in the region of the pancreas, are enlarged in early cases. They measure from 0.5 cm. to 2. cm. in diameter, and are usually soft and friable. The color is brownish gray or reddish gray or a bright red, or the surface may be pale and the central parts deep red. The bronchial lymph nodes are also enlarged and present a similar color.

In advanced cases the abdominal and thoracic lymph nodes are also increased in size, but to a relatively less degree than in children. In our own cases none of the nodes exceeded 2 cm. in diameter. The color varies from yellow or ochre to dark red, and in very advanced cases the nodes may be brownish black. The yellowish nodes may show hemorrhagic markings on section.

Microscopic examination in the advanced cases shows the presence of the typical large cells, extensive fibrous changes, a large amount of pigment, and a diminution or entire absence of lymph-adenoid tissue. The large cells are frequently present in such enormous numbers that the picture of a glandular organ is commonly absent. The connective-tissue framework is intact, however, and an occasional follicle or a small remnant of lymphoid tissue may still be preserved here and there (Fig. 6). Notwithstanding the presence of large cells in such abundance, the individual cell bodies are clearly and distinctly outlined, and fusion of cells is rarely seen in the lymph nodes. The large cells are found also in the lymph sinuses (Fig. 7). The capsule is often greatly thickened and the trabeculae very prominent, giving the appearance of a fibrosis. The large cells appear to have a definite relationship to the reticulum and to the endothelium of the lymph sinuses. The pigment is dark brown in color, crystalline or amorphous in char-

acter, and always gives the reaction for iron. It is distributed throughout the node, but is most abundant in the sinuses under the capsule and along the trabeculae. Pigment crystals are often found in the large cells, giving evidence of their phagocytic properties.

The lymph nodes in the early cases show variations in the degree of involvement. Some groups present an involvement which may be as far advanced as in the adult cases; other nodes may show the lesion in an earlier stage. In our last case, a boy, aged four and a half years, the iliac, mesenteric, retroperitoneal nodes, and those at the hilus of the liver, presented an older type of lesion than the bronchial and pancreatic nodes or the nodes near the splenic vein. The general picture in the advanced lesion in children is identical with that described in adult cases, but the capsule and trabeculae are less prominent, and pigment is absent. The follicles may show great hypertrophy of the germinal centres with much cellular activity, as evidenced by active mitosis in the lymphocytes. Eosinophilic myelocytes may be found in these nodes in considerable number.

The nodes presenting an early type of lesion may appear quite normal with low magnification. The typical large cells are seen, however, if a more critical examination be made, and they can be found in the lymph sinuses and here and there between the pulp cells. The follicles are quite prominent, and in the germinal centres phagocytic cells containing remnants of red-blood cells and pigment may be noted. In our case a small amount of pigment was found in all of the nodes showing the early type lesion, but in the nodes about the splenic vein it was very prominent. It appeared as rounded granules of yellow or brownish color and was always situated in large cells which bore a striking resemblance to the typical large cells of the disease. Remnants of red-blood cells were also present in these phagocytic cells, side by side with the pigment granules. A close relation of reticulum and large cells could be seen in these nodes. Eosinophilic and neutrophilic myelocytes were present, also a few polymorphonuclear cells with eosin granulations.

BONE-MARROW. The lesion in the bone-marrow was first noted by us in 1904, twenty-two years after Gaucher's first description of the disease. The color of the bone-marrow is always red, and small white or yellowish areas may be present. The consistency, as a rule, is soft. The typical large cells are found either singly or in groups, and no characteristic variation in the degree of involvement between early and advanced cases is apparent. At times the large cells may be seen in extensive groups, and in such situations considerable distortion of the cells may result from compression (Fig. 8). Reticulum fibers are present between the cells, and a close relationship between the two exists. Some of the large cells show vacuoles, but no distinct phagocytes are seen. Pigment

is present in small amount, but only in cases of many years' duration, and is found in the vicinity of the larger bloodvessels. Small areas of normal lymphoid tissue may be discovered in the early cases. Those portions of the marrow not involved show normal cells, including myelocytes of all types, eosinophile and neutrophile leukocytes, normoblasts and megakaryocytes.

OTHER ORGANS. In many of the cases a considerable degree of hypertrophy has been found in the lymph-adenoid tissue of the lower ileum and cecum, also marked pigmentation in the muscle fibers of the intestine. In Schlagenhauser's case fine pigment granules of a yellow color were seen in the muscular tissue of the uterus, and marked perivascular pigmentation was noted in several normal organs, including the salivary glands. The thigh muscles in Marehand's case were the seat of hemorrhages and pigmentation, with an active new formation of striated fibers.

Although the large cells typical of the disease are found only in the hemopoietic system, it is noteworthy to mention that Risel²⁴ reports finding some of these cells in a connective-tissue septum of the thyroid gland in Marehand's case. Inasmuch as a small collection of lymphoid cells was seen nearby, one may reasonably assume that the latter represented misplaced lymph-adenoid tissue in which the large cells had their origin.

TREATMENT. This paper would be incomplete if no reference were made to the treatment of the disease. Before splenectomy came into vogue as a remedial measure, attempts at cure had been made by drugs, chief among which was arsenic in its various forms administered by mouth and hypodermically, and local injections into the spleen of methylene blue and pyoktanin. None of these agents seemed to have any influence upon the progress of the disease, nor did they produce any amelioration in the condition of the patient. The only effect of the x-rays applied to spleen and bones was to temporarily reduce somewhat the size of the spleen without arresting the disease.

It is too early to give judgment upon the value of splenectomy. While the blood seems to regain some of its normal elements, such as the increase in the number of red and white cells and the amount of hemoglobin, we cannot say how permanent this change may be. Of the 8 splenectomies performed among these 14 cases, 3 died as a result of the operation. Of the remaining 5, no report has been made, so far as we know, by Picou and Ramond or by von Herezel in reference to the subsequent history of their cases. In De Jong and van Heukelom's case, however, the liver continued to enlarge. The cases of Downes and Erdmann have so recently been operated that the signs of improvement which at present are manifest may be only temporary. It would seem to us that a disease which is

not confined to the spleen, but involves all the organs of the hemopoietic system, could not be materially stayed in its progress by the removal of but one member of this system. However the future must decide. Inasmuch as more improvement has resulted from splenectomy than from any other measure it is our duty to recommend this operation and to insist that it be performed as soon as the disease is suspected.

DISCUSSION. Were it not for the fact that an extensive literature pertaining to the subject of Gaucher's disease has been steadily accumulating, containing reports of alleged cases based on meager observation, insufficient symptomatology, and uncorroborated by histological examination of any tissue, the authors would have deemed their work concluded without further discussion. But many of these cases which have found a position in this literature ought to be, once and for all, removed. While the original reporters of some of these have not diagnosed their individual cases as belonging to the Gaucher type, subsequent commentators have included them in the list, chiefly because they were of familial type and had large spleens and anemia.

Among those most frequently cited are the following: Weichselbaum,²⁵ Harris and Herzog,²⁶ Rolleston,²⁷ Borissowa,²⁸ Springthorpe and Stirling,²⁹ Stengel,³⁰ Umber,³¹ O'Malley and O'Malley,³² Cowan,³³ Rettig,³⁴ and Plehn.³⁵ In their original contributions, Borissowa, Stengel, Rettig, and Plehn described their cases as belonging to the category of Gaucher's disease.

Borissowa's case has occasioned considerable study and discussion, and has been analyzed by Marchand, Askanazy, Schlagenhauser, Risel, and De Jong and von Heukelom. These authors are not unanimous in their opinions as to the exact nature of her case, but they are agreed that it does not belong to the Gaucher type. The cells are much smaller, the cytoplasm has entirely different characteristics, and the nuclei are much larger than in Gaucher's disease. Naegeli,³⁶ who examined the blood, called attention to the presence of megalocytes, megaloblasts, and the high color index, as well as marked leukocytosis and 3 per cent. of myelocytes.

Through the kindness of Dr. Stengel we had the opportunity in 1905 of studying the sections in his case, and concluded that they

²⁵ Virchow's Arch. f. path. Anat., 1881, lxxv, 502.

²⁶ Ann. Surg., 1901, xxiv, 111.

²⁷ Clin. Jour., 1902, xix, 401.

²⁸ Virchow's Arch. f. path. Anat., 1903, clxxii, 108.

²⁹ Lancet, London, 1904, ii, 1013.

³⁰ AMER. JOUR. MED. SCI., 1904, cxxviii, 497.

³¹ Zeitsch. f. klin. Med., 1904, lv, 259.

³² AMER. JOUR. MED. SCI., 1905, cxxix, 996.

³³ Quart. Jour. Med., 1908, l, 11.

³⁴ Berlin. klin. Woch., 1909, xvi, 2046.

³⁵ Deutsch. med. Woch., 1909, xxxv, 1749.

³⁶ Blutkrankheiten und Blutdiagnostik, 1908, 401.

presented no histological evidences in common with our own. This conclusion was also reached by Ledingham,³⁷ who says that Stengel's case cannot be included "in the category either of Banti's disease or the Gaucher type of splenomegaly."

Rettig's one case (the daughter) showed, in addition to a moderate enlargement of the spleen and liver, and a discoloration of the skin, the presence of enlarged cervical, axillary, and inguinal lymph nodes, and a decided leukocytosis, the latter features being uncommon to Gaucher's disease. His other case (the father) presented a similar picture, though the lymph nodes were not enlarged. Plehn's cases represent a disease occurring in two generations, father, son, and daughter. Both Rettig's and Plehn's cases have been diagnosed on purely clinical grounds. They have many points of similarity with the clinical picture of the disease, and we shall await with interest subsequent communications which may substantiate their diagnoses.

Weichselbaum's case lacks all clinical data, and its histology is very meager. If a conclusion could be reached from his facts, one might suspect that his case represented an endothelial sarcoma, an opinion which Risel also entertains.

Harris and Herzog's first case was subjected to a splenectomy. From the histological examination one is not justified in including it in this group. Marehand, Schlagenhauser, and Risel, independently, have expressed doubts as to its genuineness.

Rolleston at no time intimated that his case was one of Gaucher's disease. In his clinical lecture on splenic anemia he incidentally discusses the subject of Gaucher's disease, without even hinting that either of the two cases therein presented were anything else than splenic anemia.

Springthorpe and Stirling's cases belong to one family and appear in two generations. On account of the familial occurrence alone, some authors have included them under the group of Gaucher's disease. Their clinical data are insufficient for this conclusion. Splenectomy was performed upon two of them, but the reports of the histological examination are lacking in detail and insufficient to justify the diagnosis.

In the case reported by O'Malley and O'Malley the spleen diminished 10 cm. in size while under observation, the liver also became reduced in size, ascites was present, and a moderate grade of leukocytosis was noted. The patient died after splenectomy. The liver showed atrophic cirrhosis without "unusual endothelial proliferation;" the spleen had none of the characteristics of Gaucher's disease.

Umber stated positively that his first case was one representing an early stage of Banti's disease. On this account we cannot

³⁷ A System of Medicine, Allbutt and Rolleston, 1909, v, 773.

understand how any writer could have included it under Gaucher's disease. Having read his clinical history and the report of the histological findings in the spleen and liver, we can find no evidence to disprove Umher's own diagnosis of Banti's disease. Umher's second case, a seventeen-year-old boy, who had sixty-four liters of ascitic fluid removed during a period of four months, finally recovered. Umher states in his paper that his original diagnosis of Banti's disease was incorrect, and that the disease was probably a thrombotic process in the branches of the portal vein following scarlet fever.

Cowan was unable to classify his cases, stating that they resembled cases of splenic anemia in infancy. A perusal of his communication does not support in our minds the conclusion of other writers who have placed them in the group of Gaucher's disease.

We regret to see that Wilson, who is one of the latest contributors to the subject of Gaucher's disease, has included in his three cases two which admit of the most serious doubt. The author himself asserts in his article that one of his cases is quite identical with Stengel's case. He describes in the third a colloid degeneration as a later process of the disease. Wilson's first case (No. 8869) is a typical example of Gaucher's disease. The second case (No. 9315), like Stengel's, shows an enormous amount of connective tissue, mostly arranged in bands encircling the venous sinuses. The large cells seen in the sinuses show branching forms lacking the more or less rounded contours seen in other cases, and the nuclei appear relatively large, though we admit that this appearance may be due to shrinkage. Giant cells resembling the Langhans type are present in large numbers. These are seen in the sinuses and also between the lymphoid cells. The resemblance to a tuberculous lesion is most striking, even though distinct tubercles are not seen. In none of the other cases have giant cells of this variety been encountered in the sinuses. In a few of the cases isolated multinuclear cells described as "giant cells" have been observed, but there is no recorded case excepting that of Stengel in which giant cells of the Langhans type have been found in such profusion. For these reasons we do not believe this case to belong to the category of Gaucher's disease. Wilson's third case (No. 58,571) has no resemblance whatever to any lesion described as characteristic of Gaucher's disease. The sections show enormous spaces (sinuses) filled with a homogeneous, faintly granular material, giving the impression of a circulatory disturbance with stasis and resulting exudation. It is true that in a few situations, particularly in small sinuses under the capsule, large desquamated endothelial cells are found, but this is not uncommon in many forms of splenic hypertrophy due to various causes.

Having given an exposition of the constituent factors of Gaucher's disease, there still remains the consideration of the views of various

authors as to the origin of the characteristic large cells and the nature of the pathological process. Briefly summarized these are as follows: Gaucher believed that the disease represented a primary epithelioma of the spleen. Collier concluded it to be an endothelioma. The Morbid Growths Committee who examined his slides decided the sarcomatous nature of the process. Picou and Ramond thought the disease represented a primary epithelioma, non-malignant at the beginning, which was converted later into a malignant process, which subsequently involved the lymph nodes. Cornil, who discussed this case, expressed the opinion that it was a primary hypertrophy of the spleen with proliferation of the reticulum.

Bovaird regarded the disease as "a hyperplasia of the spleen, characterized by an unusual development of endothelial cells and the transformation of a considerable part of the organ into dense connective tissue." He likewise considered the lesion in the lymph nodes and liver to be an endothelial hyperplasia, confined in the liver to the lymph spaces in the perilobular connective tissue. He suggests the likelihood of "the action of some systemic poison affecting several members of a family."

Brill, Mandlebaum and Libman thought that the large cells arose from endothelium or normal reticulum in the hemopoietic apparatus, and suggested a peculiar susceptibility of these structures to some unknown toxic agent. They stated that tuberculosis, when found in these cases, must be considered as a superimposed process.

Schlagenhauser stated that the large cells could be readily differentiated from the endothelial cells and did not arise from them. He considered the process to be a systemic disease of the lymphatic-hemopoietic apparatus, with proliferation of the reticular structures, affecting the spleen primarily, then the regional and other lymph nodes, and finally the liver and bone-marrow. For a time he thought that the tuberculous lesions were secondary, but finally decided that some toxin, probably of a tuberculous nature, but without other manifestations of true tuberculosis, was the most likely etiological factor.

Von Herczel considered the spleen to be the seat of an inflammatory process or a new growth. The histological examination was made by Krompecher, who confessed his inability to explain the complicated picture. Risel subsequently examined the slides and found the typical picture of Gaucher's disease. This diagnosis was accepted by Krompecher.

Marchand was of the opinion that the cells might have their origin either from reticulum or endothelium, and that they contained some unknown substance of a peculiar homogeneous, amyloid nature, with the properties of some form of semi-solid hyaline material. Risel, after a more detailed study of the material in Marchand's case, concludes that while there is no positive proof that

the cells arise from reticulum, and no transitional stages between reticulum and cells can be observed, nevertheless he believes the reticulum must be their seat of origin. He also states it is his belief that in the lymph nodes the cells may arise from the endothelium of the lymph sinuses, late in the course of the disease, as well as from the reticulum within the follicles. He admits that the presence of the cells in the venous sinuses of the spleen is difficult of explanation, assuming that they originate in the reticulum. He concedes that the cells are carried to the capillaries of the liver through the portal vein, but he acknowledges his inability to explain their presence in the connective-tissue spaces of Glisson's capsule.

De Jong and van Heukelom concluded that the cells arise from proliferated reticulum, but could not deny the possibility of an endothelial origin. They believe that the cells have the power of multiplying, because they found peculiar cells undergoing direct cell division in the spleen, and because the liver continued to enlarge after splenectomy in their case.

Mandlebaum thought that the large cells might be derived from large lymphocytes or reticulum cells in the germinal centres of the follicles, and described the phagocytic cells found there. The large cells are carried through the portal vein to the liver, and he believes that their destruction in this organ causes an irritation leading to the production of the connective-tissue process.

Downes calls attention to the extensive, uniform, diffuse, endothelial hyperplasia, and says that the cells "resemble those seen in the so-called 'large-celled hyperplasia' of lymph sinus endothelium."

Wilson considers the process to be a "primary endothelial proliferation with a secondary proliferation of fibrous connective tissue, and ultimately a degeneration of the endothelium with contraction of the connective tissue." He concludes that the large cells are "much more likely to have arisen from the endothelium than from the reticulum."

From the above opinions it may be seen that while all are agreed as to the histological features of the lesion, the source and nature of the cells are still wrapped in mystery. We recognize the fact that neither an origin from reticulum alone nor endothelium alone will explain the pathological features in all the organs. Neither will the theory of an origin from large lymphocytes or reticulum cells in the germinal centres of the follicles explain all of the lesions. It has been shown by Rössle and Yoshida³³ that no differentiation between reticulum and endothelium, especially in lymph nodes, can be made. Therefore it is possible that in the lymph nodes at least the large cells may arise from both of these structures.³⁹

³³ Beitr. z. path. Anat. u. z. allg. Path., 1909, xiv, 110.

³⁹ A full discussion of the various factors concerned in the attempted explanation of the pathogenesis of this disease is to be found in the original articles of Schillinghauser, Risel, De Jong and van Heukelom, and Mandlebaum.

We believe that the disease starts simultaneously in the spleen, bone-marrow, and lymph nodes. In the last, however, it may appear somewhat later or be slower in development, an assumption which finds its support in the fact that we have found in a very early case, a child aged four and one-half years, the process in some of the nodes to be far less advanced than in the spleen and marrow.

If in this communication we have succeeded in giving a place in nosology to what appears to us to be a distinctive clinical and pathological entity we shall be satisfied. This satisfaction would be the more complete and our object more fully accomplished, could we hope that in the future all the cases which lack the distinctive features of the disease would be excluded from the literature.

NOTE.—Since the above was written, with the kind permission of Wilson, the slides of his three cases were submitted to Marchand for an opinion. Marchand writes that Wilson's first case is a typical spleenomegaly of the Gaucher type. He agrees that the second case is one of tuberculosis, even though tubercle bacilli could not be demonstrated in the sections or by animal inoculation. The third case, he says, looks like a lymphangioma, although small collections of cells, seen under the capsule, resemble somewhat those found in Gaucher's disease. A study of these cells in the fresh state would be necessary, however, before giving a final opinion as to the nature of the lesion.

ADDENDUM.—An opportunity to examine fresh unfixed material for the presence of lipid substance has been afforded since this paper has gone to press. Through the courtesy of Dr. E. P. Bernstein we have just obtained from the pathological laboratory of the Lebanon Hospital a piece of spleen removed at operation from a case of Gaucher's disease. Tests with the polariscope, as well as examination of frozen sections stained with Nile blue and Sudan III are negative, thus indicating the entire absence of neutral fat, cholesterol, and cholesterol esters from the large cells in this disease. Chemical studies for the purpose of extracting lipids from the spleen are now in progress.

METALLIC POISONS AND THE NERVOUS SYSTEM.¹

BY GEORGE A. MOLEEN, M.D.,

NEUROLOGIST TO HOSPITAL OF THE CITY AND COUNTY OF DENVER, MERCY, AND ST. JOSEPH'S HOSPITALS, ETC., DENVER, COLORADO.

THIS subject is presented not so much because of being anything especially out of the ordinary, for many of the things which will be mentioned may have been known to some, but one fact that I feel sure is, as is well stated by Gowen, the commonplace of all knowledge, that which we can least afford to despise or to disregard.

In a recent number of *Everybody's Magazine* appears a popular (if not also somewhat exaggerated) article entitled "The Lead Menace," by Gordon T. Bayer, in which the author endeavors to show the importance of the passage of the Occupational Disease Bill, introduced in several State legislatures at the instance of the

¹ Read before the Medical Society of the City and County of Denver, Colorado, April 1, 1913.