Gaucher's Disease: Cases in Five Related Negro Sibships

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GAUCHER'S DISEASE is a relatively uncommon disorder of lipid metabolism characterized by the accumulation of the cerebroside kerasin in the cells of the reticulo-endothelial system. The resulting hyperplasia leads to enlargement of the spleen, liver, bone marrow and lymph nodes. As kerasin cannot be demonstrated in normal blood or in the blood of patients with Gaucher's disease, Thannhauser *et al.* (1939) have suggested that the disease represents an intracellular metabolic defect rather than a storage disease.

The condition is widely distributed in Europe and North America, and has been described in India (Spackman & Mackie, 1925) and Japan (Reiss & Kato, 1932). Several cases have been described in Negroes, and many authors state that the condition is especially prevalent in the Jewish race. The age of onset may vary considerably. In the series of 89 cases tabulated by Hoffman and Makler (1929), 43% occurred in patients under 12 years of age, and 17% began under 1 year of age. The onset has been reported as early as 1 week of age (Siegmund, 1921), and DeLange (1940) and Köhne (1939) described cases beginning in infancy as a special malignant form with brain changes, and suggest that the infantile type should be considered a distinct clinical entity. At the other extreme, Bessie (1937) reports a patient first diagnosed at age 62 years, and states that the spleen was not palpable 7 months earlier.

The clinical course of Gaucher's disease is also subject to variation. Usually the onset is insidious with enlargement of the spleen, which may eventually fill almost the entire abdomen and descend into the pelvis. Enlargement of the liver usually follows splenomegaly. Pigmentation, especially of the skin of the legs and face, may appear later. Pingueculae—wedge-shaped brownish thickenings of the conjunctiva at the corneoscleral junction bilaterally—are also a late sign. Anemia and leukopenia are common, and a tendency to hemorrhage and easy bruising is frequent. Bone pain, which may be either mild or acute and severe, may occur at any time. As acute bone symptoms may be associated with fever, such episodes early in the course of the disease may be confused with acute osteomyelitis. Death is usually by intercurrent infection. The diagnosis may be made with reasonable reliability on clinical grounds alone, but a

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certain diagnosis depends on the demonstration of the typical Gaucher cell in sections obtained from bone marrow, lymph node or other material. An extensive clinical and pathologic description of the disease is given by Thannhauser (1940).

It is the purpose of this report to describe a Negro family in which five cases of Gaucher's disease have occurred in five closely related sibships. Two of these cases have previously been reported by Pachman (1938), and extensive clinical, pathological and biochemical studies were described. A photograph of these same two patients was also published by Snyder (1941).

CASE REPORTS

Case A. Negro female, born 1926. Development was normal until age 5 years when it was noted that the abdomen was becoming progressively enlarged, although general health was good. At age 8 years she began to walk with a limp and some shortening of the right lower extremity was noted. She was admitted to Duke University Hospital, Durham, N. C., on July 7, 1936. The patient was generally emaciated and the abdomen was enormous, with great enlargement of the spleen and liver, and shortening of the right leg. The erythrocyte count was 3,500,000; hemoglobin 6.8 grams; leucocyte count 3,560; platelet count 310,000. X-rays showed decalcification of all bones and a pathologic fracture of the neck of the right femur. Extensive clinical studies of this patient were carried out by Pachman (1938), and photographs, x-rays, and biochemical studies may be found in his paper.

The patient remained in fairly good health for the next two years, but was seen at intervals with edema of the ankles and cramping pains in the legs. Analgesics and a few days of bed rest would relieve these symptoms. Episodes of spontaneous epistaxis were fairly frequent, and blood was present in the stools on several occasions.

On June 30, 1939 (age 13 years) she was seen in acute respiratory distress. The temperature was 104°F, pulse 140/min., and respiratory rate 60/min. Moist rales were heard over the entire chest and she was expectorating blood-tinged sputum. Digitalis and morphine were administered and she seemed to improve and was more comfortable. Several hours later the temperature had fallen to 99°F, pulse 100/min., and respiratory rate 35/min. The leucocyte count was 4,300 with 60% polymorphonuclear cells. Shortly thereafter another episode of acute pulmonary congestion occurred and the patient expired. A gushing hemorrhage from the mouth and nose immediately preceded death. An autopsy was performed and typical findings of Gaucher's disease were demonstrated. The liver and spleen were tremendously enlarged and occupied most of the abdominal cavity. The lungs were congested and there was almost complete consolidation of the right lung and partial consolidation of the left lung. The microscopic sections were characteristic of the disease.

Case B. Negro male, born February, 1929. This patient is a half-brother of Case A. Development was normal for the first two years. During the third year he began to have "spells" described as a drawing backward of the head, stiffening of the neck, and jerking of the extremities and body. A physician made a diagnosis of intestinal parasites, treatment was given, and unidentified worms were expelled. At this time it was noted that the abdomen was enlarged and the physician is said to have palpated a mass in the left upper quadrant. The abdomen continued to enlarge gradually, but the general health was rather good.

At age 7 years some transient edema of the ankles appeared, and shortly thereafter (July 7, 1936) he was admitted to Duke Hospital. Positive physical findings at this time

included generalized lymphadenopathy, slight yellowish thickenings of the conjunctiva at the corneoscleral margins of the right eye, recent conjunctival hemorrhage of the left eye, extremely protuberant abdomen, spleen enlarged with lower pole at symphysis pubis and notch at umbilicus, and liver enlarged to 9 cm. below costal margin. The erythrocyte count was 3,600,000; hemoglobin 7.2 gm.; leucocyte count 4,000, with a relative lymphocytosis; platelet count 192,000. Biopsy of an axillary lymph node revealed typical Gaucher cells. X-rays of the long bones showed diffuse calcification with small areas of destruction in the necks of both femurs. Studies on fat metabolism were carried out by Pachman (1938), and his paper includes an extensive clinical description, photographs, X-rays of long bones, and pathological and biochemical findings.

Two years later (September, 1939, age 10 years), the patient was found to be poorly nourished, with a height of 47 inches (119 cm.) and a weight of 64 pounds (29 Kg.). The abdomen was extremely protuberant and pendulous (see photograph, fig. 1). The head was smaller than average for this age. The wedge-shaped conjunctival thickenings had become larger and were bilateral. The chest was funnel-shaped, and there was respiratory embarrassment and upward displacement of the heart. The apex impulse was palpated in the 3rd and 4th interspaces 1 cm. lateral to the left mid-clavicular line; the right border of dullness extended 3 cm. lateral to the right sternal margin. The cardiac rhythm was regular and a soft systolic murmur was heard at the mitral area. The blood pressure was 96/74. The circumference of the abdomen at the level of the pelvic crest was 35½ inches. The spleen and liver were tremendously enlarged and the lymph nodes were generally palpable but not tender. The patient became progressively weaker and expired on February 1, 1940. An autopsy was performed, and typical findings of Gaucher's disease were demonstrated.

Case C. Negro male born August 15, 1936. Development was normal during the first year except that he is said to have had rickets at age 8 or 9 months. After the child began walking, it was noted by the parents that the abdomen was pendulous, but a physician was not consulted. After age 2 there were several spontaneous hemorrhages from the nose and mouth.

When examined at age 3 years (July 8, 1939), the patient was small for his age. His weight was 27 pounds, and the following measurements were recorded: height, 33 inches; head circumference, 19½ inches; chest circumference at nipple line, 20½ inches; abdominal circumference at pelvic crest, 24½ inches. There were no pingueculae and the chest was normal except for a soft systolic cardiac murmur. The spleen was easily palpable, smooth, firm and non-tender, and extended to the midline below the umbilicus. The liver was also enlarged and reached almost to the border of the spleen in the left upper quadrant and 4 cm. below the costal margin in the right flank (see photograph, fig. 1). The cervical, axillary and inguinal lymph nodes were enlarged but non-tender. The patient ran a progressive down-hill course and expired on January 8, 1940. An autopsy was performed, and the typical changes of Gaucher's disease were demonstrated.

Case D. Negro male born 1939. Enlargement of the abdomen was noted by the parents prior to the child's first birthday, and progressively increased. When examined at age 2 years (March 4, 1941) he was poorly developed for his age with little subcutaneous fat and a protuberant abdomen. The spleen was enlarged, extending to the midline, and the splenic notch was palpated just above the umbilicus. The liver was palpable 5 cm. below the costal margin. The patient subsequently had several episodes of epistaxis and the course was rapidly progressive. He expired at age 2 years on June 6, 1941 and autopsy revealed typical findings of Gaucher's disease.

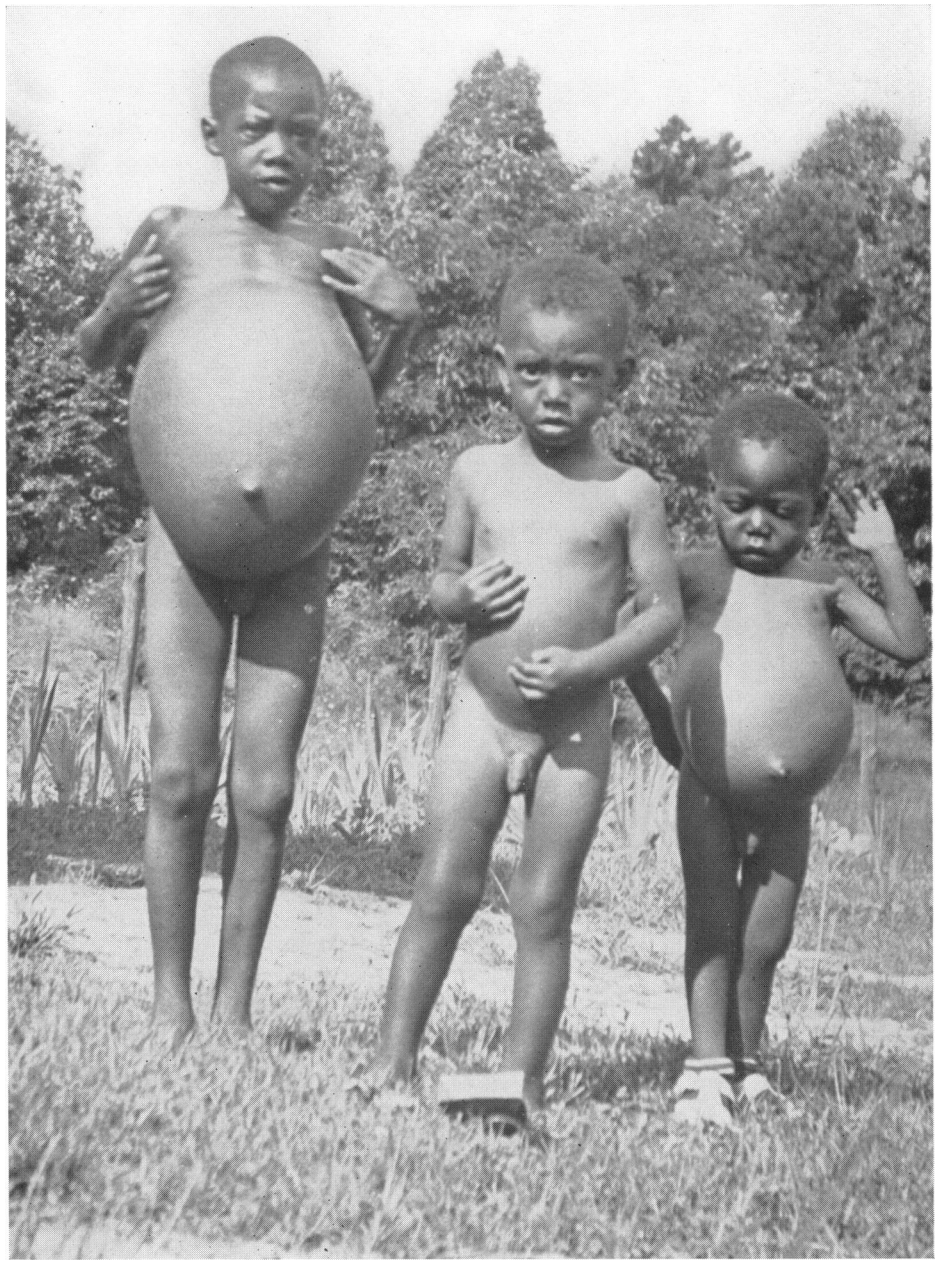

FIG. 1. Gaucher's Disease: *left*, case B; *right*, case C. A normal cousin of the same age as case C is also shown to indicate the general retardation of growth in the affected children.

Case E. Negro male born November 28, 1944. This child also developed enlargement of the abdomen at about age 1 year. Later spontaneous hemorrhages from the nose and

mouth were frequent. The spleen, liver and lymph nodes were enlarged as in the earlier cases. He had frequent episodes of diarrhea. He apparently had an unusual appetite for gritty substances, and red clay is said to have been a favorite item of diet. He expired on April 10, 1948 (age 3½ years), but an autopsy was not obtained.

DESCRIPTION OF PEDIGREE

The five patients described above were all closely related, their relationships being indicated in the pedigree (fig. 2). The two couples indicated in the first generation are the earliest ancestors concerning whom definite information is available. A daughter (*II-5*), age 87, of the first couple was interviewed, and also a daughter-in-law (*II-9*) of the second couple. The daughter-in-law claimed to be 100 years old, and on examination seemed to be of about this age. Both of these informants thought that there was some kinship between the two first generation couples, but were unable to furnish exact data. All that is known definitely is that these two couples lived on adjoining farms in Davidson County, North Carolina, before the Civil War. Most of their descendants remained in the same rural community, and intermarriage among these descendants was frequent.

As the result of these intermarriages, most of the individuals in the fourth and fifth generations are related, and many of the fourth generation married cousins. Over a period of about 10 years, five patients with Gaucher's disease were recognized in five sibships in the fifth generation. As may be seen from the pedigree, the parents of four of these patients were related, in each case being second cousins. Of these four cousin marriages, the parents of three of the affected children (cases A, B, and E) have the first couple in generation *I* as common ancestors. The fathers of these cases are also descended from the second couple of generation *I*. The parents of case D are second cousins with the second couple in generation *I* as common ancestors, but the father is also descended from the first couple. The parents of case C are not known to be kin, but the father is descended from the first couple and the mother from the second couple of generation *I*.

The relationships between the five patients are rather complex, and are most easily visualized by means of a path diagram of the kind more familiar to animal geneticists (fig. 3). Each possible pair of patients is related by at least six pedigree paths, while there are no less than 10 paths connecting cases B and E. Cases B and D, for example, are connected by 9 paths, being half first cousins, as well as full second cousins and full third cousins in three different ways. The degrees of kinship are more readily expressed as *coefficients of relationship* (Wright, 1922), and these are of some interest as the patients are actually more closely related than would appear at first sight. The coefficients of relationship (r) are listed in fig. 3. Thus, the closest relationship, between cases A and E, is nearer that of full sibs ($r = .50$) than that of half-

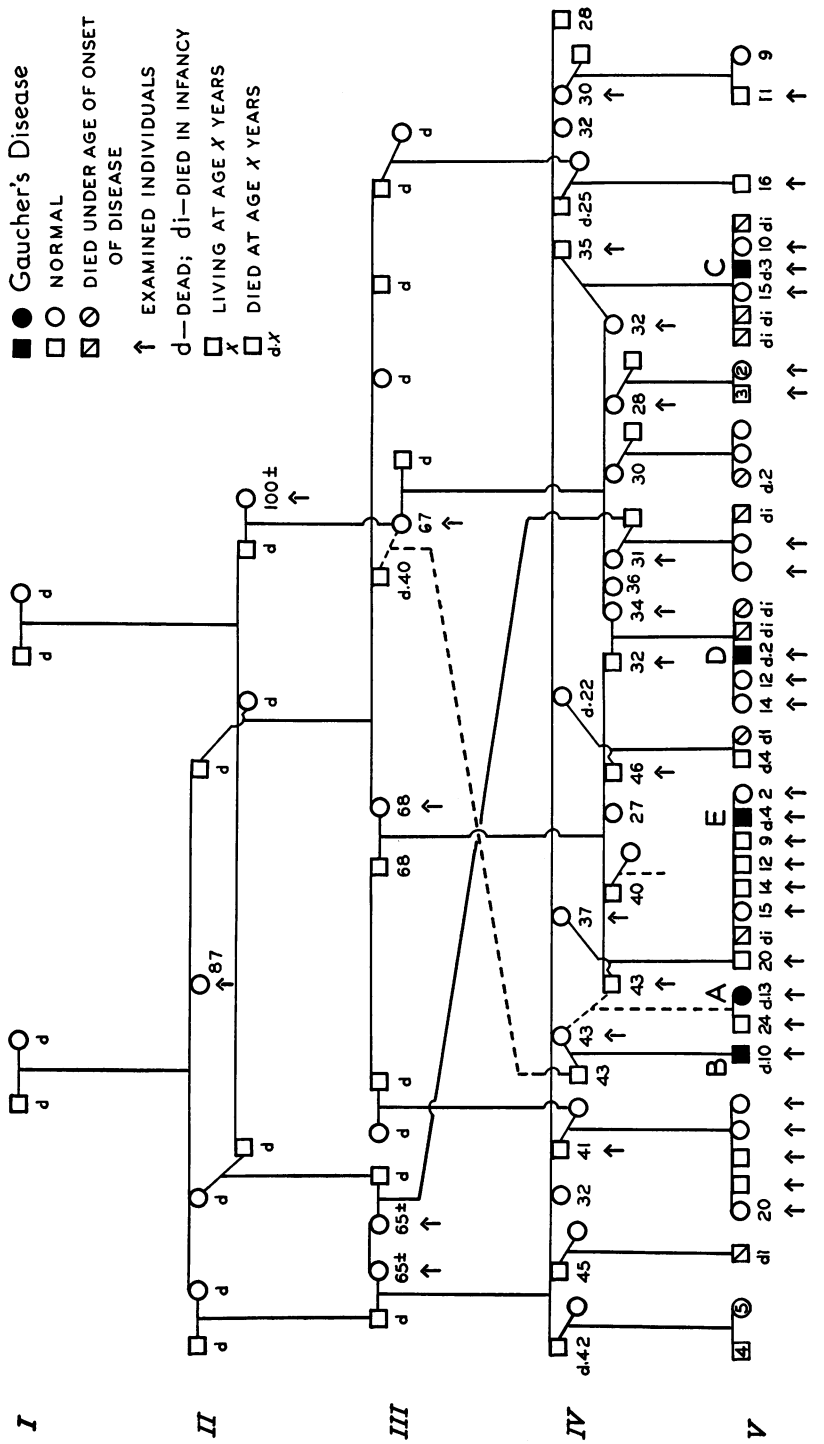

FIG. 2. Pedigree of five Negro patients with Gaucher's Disease

sibs ($r = .25$), while the most distant relationship is slightly less than that of full first cousins ($r = .125$). Also, it will be seen that all of the 10 relationships are *bilineal* in the sense defined by Cotterman (1941), i. e., between every pair of patients there are at least two paths which are completely independent, having no links in common. For example, the path connecting E and A through their father is independent of the paths connecting them through their mothers. Such relatives are commonly expected to both show a rare recessive trait.

In addition to the matings producing abnormal children, three other cousin marriages occurred among descendants of the two couples of the first generation and are indicated in figure 2. These three marriages gave rise to 6 children, of whom two died in infancy of unknown causes, one died at age 4 years of an un-

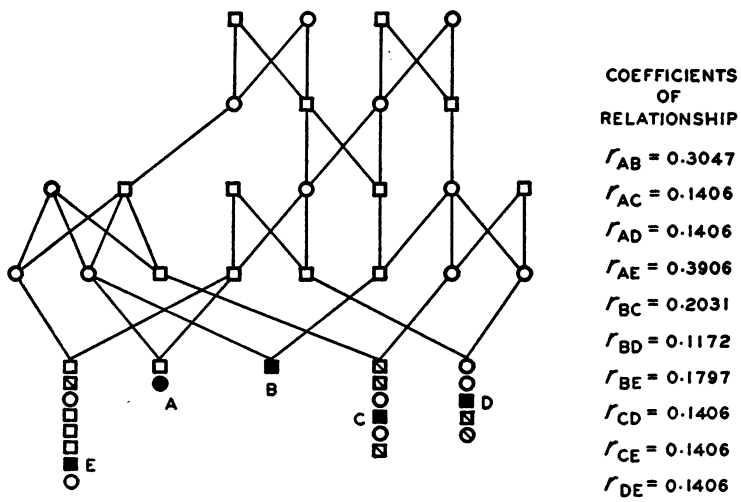

FIG. 3. Path diagram showing relationships between 5 cases of Gaucher's Disease

related disease, and three were examined and found healthy. To avoid undue complication of the pedigree, two additional cousin marriages that were without issue are not indicated on the diagram.

As the pedigree indicates, the five patients with Gaucher's disease collectively had 17 siblings, 10 male and 7 female. Of these, six (5 male, 1 female) died in infancy. Two of these died during the first 48 hours of life of unknown causes. Two died during their first summer of "colitis." The only female in this group died at age 3 months of bronchopneumonia. All of the mothers denied the occurrence of any stillborn infants or miscarriages. The youngest brother of case C died at age 6 months of bronchopneumonia, but the parents report that this child had an enlarged abdomen prior to the final acute illness, and the parents thought that he was developing the family affliction. This child was seen a few hours prior to death by a physician having no previous knowledge

of the family, and there are no records available bearing on the question of diagnosis of early Gaucher's disease. Of the eleven siblings of the patients who survived the first year of life, all were examined at ages ranging from 2 years to 24 years, and had no signs suggestive of the disease.

DISCUSSION

The genetic mechanism responsible for Gaucher's disease in this family may be deduced with reasonable reliability directly from the pedigree. The occurrence of multiple cousin marriages would be highly effective in bringing a rare recessive gene into homozygous condition. As is seen from figure 3, the 5 cases of Gaucher's disease collectively possess only 8 parents, 7 grandparents, not more than 12 great-grandparents, and not more than 20 great-great-grandparents. On the hypothesis of recessive inheritance, it is of course certain that all 8 parents were heterozygous for the gene, and that at least 3, but probably not more than 4, of the 7 grandparents carried it. The demonstrated relationships among the grandparents further allow us to assume that all defective genes in the pedigree may have been derived from one member of each of the two couples in generation *I*. Finally, on the basis of the alleged relationship of these two couples, it is possible that all 10 genes present in the 5 affected children in generation *V* may have descended from a single heterozygous ancestor shared by the two members of generation *I*. This is certainly a very likely possibility, although there are other possibilities which are perhaps not much less probable. Since the *coefficient of inbreeding* (Wright, 1922) for the 4 children arising from second cousin unions is only 1/64, it is probably not many times greater than the frequency of the recessive gene in the general population. Hence it seems not unlikely that at least one of the demonstrated inbreeding paths did not actually represent the path of descent, and that instead a second (independent) gene may be present. This second gene might be independent of the first in the sense of separate origin by mutation in a different ancestor. Or, it might be independent only from the point of view of the known pedigree. For example, a second gene, introduced through one of the 3 unrelated grandparents (generation *III*) might actually be of same descent as the first through relationship paths which are unknown. In either case, the multiple bilineal relationships among the patients offer innumerable opportunities for two such genes to explain the observed events.

If the children who died in infancy are removed from consideration, the ratio of normal to affected children in the affected sibships is 11:5, which is not significantly different from the expected ratio of 12:4. The total sex ratio of the affected sibships is normal, being 9 males to 7 females; even when the children dying in infancy are included, the sex ratio (14:8) cannot be regarded as a significant departure from the normal. Also, the deviation from expected

equal numbers of affected males and females is not significant, as a deviation from equality as great or greater than 4:1 would be expected in 3 out of 8 sibships of 5 by chance alone. The evidence supplied by the pedigree thus appears to be compatible in all respects with the hypothesis that Gaucher's disease is due to an autosomal recessive gene in the homozygous state.

The possibility that other genetic mechanisms might satisfy the conditions of this pedigree may be summarized briefly:

1. *Dominant.* The possibility that a dominant gene with reduced penetrance might account for the facts is extremely remote. With a ratio of normal to affected of 11:5 in the affected sibships, it would be assumed that the penetrance of the postulated gene must be at least 25 to 30 per cent, but all 8 parents and 7 grandparents of the affected individuals are normal, and no cases are known in earlier generations.

2. *Sex-linked Recessive.* This hypothesis could be satisfied only by assuming that heterozygous females occasionally show the disease, and that case A represents such an event. It would also be necessary to assume that the same rare gene entered the pedigree through two unrelated individuals, *II-9* and *III-2*. Furthermore, the ratio of normal to affected males among the offspring of known heterozygous females would be 12:4, a probably significant (chi-square = 4.0) deviation from the 1:1 ratio which would be expected on the hypothesis of a sex-linked gene.

3. *Partially Sex-linked Recessive.* The suggestion of an excess of males among the affected children raises the possibility of this mechanism, for, although partial sex-linkage is not expected to produce unequal numbers of affected males and females in a series of unrelated sibships, it would do so in a single large sibship, and indeed, the 5 sibships containing affected children in this kindred are so closely interrelated that they approach the equivalent of one large sibship.

An exact test for recessive partial sex-linkage would be very difficult, owing to the complexity of the pedigree. However, it may be shown that, even under a set of assumptions most favorable to the hypothesis, significant evidence for partial sex-linkage seems to be lacking. We assume first that the abnormal gene was introduced through 3, or possibly all 4, of the related grandparents, but not through any of the 3 remaining grandparents. Haldane's (1936) "direct method" for testing recessive partial sex-linkage can then be applied with some modification. Three of the patients, A, D, and E, have their fathers related to their mothers through their common paternal grandmother, but not (in any known way, at least) through their paternal grandfather. It may therefore be assumed that these three fathers received the abnormal gene (g) on their X-chromosome (gx)(Gy). Denoting the cross-over frequency by χ, the probabilities and observed frequencies in the four classes of children are:

Children:	normal ♀♀	affected ♀♀	normal ♂♂	affected ♂♂
Probability:	$\frac{1}{4}(1 + \chi)$	$\frac{1}{4}(1 - \chi)$	$\frac{1}{4}(2 - \chi)$	$\frac{1}{4}\chi$
Observed:	$a = 4$	$b = 1$	$c = 5$	$d = 2$

Case B's father is known to be related to B's mother through B's father's father, but not through B's father's mother. Nevertheless, it appears on other evidence at least equally probable that B's father received his defective gene from his mother. Similarly, the situation for C's sibship is ambiguous. C's father's father is very probably $(gx)(Gy)$, and on this assumption C's father could be $(gx)(Gy)$ with probability $1 - \chi$, or $(Gx)(gy)$ with probability χ. Assuming, however, that B's father and C's father are both $(Gx)(gy)$, we have a distribution of children most favorable to the hypothesis:

Children:	normal ♂♂	affected ♂♂	normal ♀♀	affected ♀♀
Probability:	$\frac{1}{4}(1 + \chi)$	$\frac{1}{4}(1 - \chi)$	$\frac{1}{4}(2 - \chi)$	$\frac{1}{4}\chi$
Observed:	$a = 0$	$b = 2$	$c = 2$	$d = 0$

Since the sibships have been selected because each contains at least one affected child, Haldane computes the cross-over frequency from the totals for the affected and normal children separately. The former give an estimate $\chi = d/(b + d) = 0.4000$, with $(b + d)^3/bd = 20.8333$ units of information, while the latter give $\chi = (2a - c)/(a + c) = 0.0909$, with $(a + c)^3/9ac = 5.2817$ units of information. Now, having considered C's father to be $(Gx)(gy)$, we must then count him as a cross-over, since his father may be assumed to be $(gx)(Gy)$, although the 2 sisters of C's father would then be non-crossovers. We have thus a third estimate $\chi = 0.3333$, with $(1 + 2)^3/2 \cdot 1 = 13.5000$ units of information.

Combining the three sources of information, we obtain a weighted estimate $\chi = 0.336$, with information 39.6150, or standard error $(39.615)^{-\frac{1}{2}} = 0.159$. The deviation from random assortment ($\chi = 0.5$) is in the direction favoring linkage, but cannot be considered significant. Furthermore, in this calculation we have made a number of assumptions most favorable to the linkage supposition; in a more exact treatment, we would have to consider the alternatives, assigning probability weights to each set of assumptions. Consequently, as stated above, the pedigree does not appear to contain significant evidence for partial sex-linkage, and we may conclude that the gene for Gaucher's disease is more likely on one of the autosomes.

The conclusion that an autosomal recessive gene is responsible for this condition is in accord with previous reports. Snyder (1941) suggests that the condition is recessive. Gaucher's disease has long been regarded as "familial" and there have been numerous reports of cases in siblings, the first of these being given by Collier (1895). As many as five cases have been described in one

sibship (Woringer, 1934), and about one-third of the 89 cases collected by Hoffman and Makler (1929) has an affected sibling. The only report of cases in cousins known to the writers is that of Bloem, Groen and Postma (1936), who reported cases in half-first cousins; possible consanguinity of the parents was not mentioned. Cases in the first and third generations of a family are described by Anderson (1933). We are unable to find any reports in the literature suggesting the action of dominant or sex-linked genes.

SUMMARY

1. Five closely related cases of Gaucher's disease are described in a Negro kindred, the diagnosis being proved by autopsy in four cases. Two of these cases were previously reported by Pachman (1938).

2. The pedigree of this family is presented, showing the five cases to be in five separate but closely related sibships, with the parents of four of the affected children being second cousins.

3. It is concluded that Gaucher's disease is due to the action of an autosomal recessive gene which in the homozygous state causes an intracellular metabolic defect resulting in the deposit of kerasin in the cells of the reticulo-endothelial system. A brief review of the literature indicates that evidence presented in other reports is compatible with this conclusion.

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