THE HEREDITARY MECHANISM OF GAUCHER'S DISEASE

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The number of cases of Gaucher's disease that have been described up to the present time is about 250, but it is probable that many more cases have been observed. Collier's case was probably the first in which more than one member of the family was found to be affected. After him, Bovaird, in 1900, described the disease in two sisters. Since then, the familial occurrence of Gaucher's disease has been noted by several observers. About one-third of the published cases have occurred in members of the same family so that a hereditary factor is undoubtedly present. However, the family trees which have been published are quite few, and the exact mechanism by which the disease is inherited is still unknown.

The present author has observed 21 cases of Gaucher's disease. Seventeen were familial and occurred in six different families. Four more cases in these families could not be examined but the available evidence was sufficient to accept them as cases of Gaucher's disease, which brings the total number of familial cases discussed in this report to 25. Four other patients were seen in whom no other members of the family were affected. These were considered to be so-called "sporadic" cases. The clinical features of our patients have been described elsewhere. It is the purpose of this paper to review the scanty data on the heredity of Gaucher's disease from the literature and to present the family trees of the cases which have been observed by the author. In reviewing the literature excellent summaries have been found in the papers by Brill, Mandlebaum and Libman, Hoffmann and Makler, Rowland, Reiss and Kato, De Lange, Atkinson and Thannhauser. Atkinson's admirable review of the cases of Gaucher's disease described in children appeared in 1938 and has been especially valuable.

In considering the familial cases in the literature, one is impressed by the following facts:

1. There have been 64 familial cases reported which occurred in twenty-five families. The inclusion of the cases described in this report would bring the total up to 89 in thirty-one families.

2. In twenty-three of the families in the literature, the disease occurred in a "horizontal" spread only. By this is meant that the disease appeared to be present in the members of one generation only, namely in brothers and sisters or in cousins, but not in parents or grandparents or in the offspring of the patients. This peculiarity in the familial incidence of Gaucher's disease is underlined in a statement by Hoffmann and Makler that "in no series of children has either of the parents suffered from the disease nor has it been transmitted from any adult to a child."

3. In only two families was there a "vertical" occurrence described. In these families the disease was found to be present in two generations; namely, in Rettig's case, in a father and his daughter, and in the case described by Bychowski, in a father and three of his children. Quite recently Morgans published a third
family in which there was suggestive evidence of a vertical spread of Gaucher's disease.

4. In these instances of a "vertical" transmission there was a direct continuity of the disease from one generation to the other. Only one example of "skipping" of a generation has been described in a paper by Anderson. This case is often quoted but the evidence offered does not seem convincing. Anderson observed four sisters with Gaucher's disease. The father and mother of these patients were found to be normal. The grandparents were not examined but "it was reported that the paternal grandmother and two of her sisters had large abdomens and a yellowish brown discoloration of the skin and died of a common cause." The author did not go beyond suggesting the possibility that the grandmother and her sister might have had the disease. It would seem that this evidence is too scanty to warrant the far-reaching conclusions that have been drawn from it by some authors.*

3. The disease does not show a preference for either sex. Atkinson found among 108 cases in children, 50 males and 53 females; the sex of the other 5 cases was not given. Of the author's present series of 25 cases 14 were males and 11 females.

6. Marriage between relatives had not taken place in the ancestry of any of the reported cases of Gaucher's disease.

7. In the families in which Gaucher's disease occurred, there have been a number of normal siblings as well as affected cases.

8. Little is known of the offspring of patients with Gaucher's disease. Many of the cases die before they reach the reproductive age, others do not marry or if married have no children. Furthermore the incidence of abortions and of stillborn babies among the offspring of the reported cases of Gaucher's disease seems to be unusually high.

The survey of the author's cases confirms many of the points mentioned above. In addition it contains some data that may help to answer some of the questions that remained open so far.

DESCRIPTION OF FAMILIES OBSERVED BY THE AUTHOR

FAMILY A

H. U., a Jewish merchant, aged 49, was admitted in February, 1934. He had a typical clinical picture of Gaucher's disease and the diagnosis was established by pathologic examination of a liver biopsy. The patient's father committed suicide. No further information about him was available. His mother had died of old age. The family doctor assured us that he had never found a large liver or spleen in her. Two brothers and two sisters were examined and found to be normal. His wife was normal. She had had no abortions. They had two children; both died shortly after birth.

He is an example of a "sporadic" case, the only one of five siblings, originating from what appeared to be normal parents, who had Gaucher's disease. The fact that both his children died shortly after birth is probably significant.

FAMILY B. (FIG. 1)

No medical information was available concerning the grandfather (Ia) of this family. He had been married twice. His first wife was reported to have died of apoplexy. Nothing was known about his second wife.

* In the paper by Bloem, Groen and Postma, it was said that Anderson's family suggested that the inheritance of Gaucher's disease might be of recessive character. Bloem and Postma now agree with the author that this statement should not have been made.
He had three children by his first marriage (II 1-3).

II 1. Female, unmarried, died in 1932, aged 75, of degenerative heart disease. She had been repeatedly hospitalized and no signs of Gaucher’s disease were found on any occasion.

II 2. Female, still alive, 75 years of age when we examined her. She was found to suffer from gallstones and chronic cystitis but there was no evidence of Gaucher’s disease. Her daughter (III 8) and two grand-daughters (IV 14-15) were examined and found to be normal.

II 3. Male, died in 1922, aged 62, of pulmonary embolism, after prostatectomy. He had once been told by a doctor that he had a big liver but the surgeon who operated on him had found nothing abnormal on an (admittedly superficial) examination of the abdomen. He had had no abnormal tendency to bleed. His wife had a mild diabetes but otherwise she was found to be normal. They had eight children (only seven of whom are represented in figure 1).

II 4. Female, 53 years old, was found to have a chronic cystitis but was otherwise normal, as were her three children (IV 1-3).

III 1. Female, was known to her doctor to have a very large spleen and leukopenia. She suffered from nosebleeds. She died at the age of 36 from a severe postpartum hemorrhage on giving birth to her fifth child. This fifth child died of unknown cause one day after birth. The other four children were found to be normal. We feel that she very likely had Gaucher’s disease.

III 2. Male, had frequent nosebleeds and hemorrhages after tooth extraction. No clinical signs of Gaucher’s disease were found. Both his sons were normal.

III 3. Female, a typical case of Gaucher’s disease, with a very large spleen and liver, symmetrical pigmentation of the legs, bone lesions and typical blood findings. She is unmarried.

III 4. Male, was found to have a slight glycosuria. He was otherwise normal, as were his two children.

III 5. Male, was found to be normal. He was married but had no children.

III 6. Male, married, was found to be normal, as was his only child, a daughter.

Not included in figure 1 is one other female, who was found to be normal, as was her only child, a son.

From the second marriage of II 2, also sprang three children.

III 7. Female, had five children. None of these could be personally examined but information obtained from family doctors and from hospital records revealed no evidence of Gaucher’s disease in any of them.

III 8. Male, died suddenly at the age of 50, probably of coronary occlusion. Up till then he had always been a healthy man. His wife had had hypertension; she died of apoplexy. They had eleven children (III 14-24).

III 9. Male, unmarried, was found to be normal.

III 10. Female, found to have a very enlarged spleen and liver; this was confirmed by the surgeon when
she was operated on for gall stones. She had a tendency to bleed. In 1937 she died of subdural hematoma after an insignificant trauma of the head. Although we were not able to examine her personally, she very probably had Gaucher’s disease. She was married but had no children.

III 20. Female; in 1936 she was reported by Bloem, Groen and Postma as having gall stones but being otherwise normal. Since then the patient has withdrawn her former refusal to be examined. The present author has had an opportunity to examine here. She had a definitely enlarged spleen but refused laboratory examinations. She suffers from nose bleeds. She has two children (IV 16-17). It was not possible to examine them but they are reported as being normal.

III 21-22. Were either abortions or dead children. This could not be ascertained with certainty.

III 23. Male, was found to have an enlarged spleen and liver, myopia and malar flushes, leukopenia and thrombopenia. He refused sternal puncture. We regard him as very likely a case of Gaucher’s disease. He was unmarried.

III 24. Male, died at the age of 13, after splenectomy. The diagnosis of Gaucher’s disease was made by pathologic examination of the spleen after operation.

II 6. Female, was normal, as were her six children (III 25-30). None of them had attained the marrying age.

The interesting points in this family tree are:

1. Gaucher’s disease appeared among the cousins of two families who were united only by one grandfather who had been married twice. Yet this man, who was the only link between the affected families, was apparently not a sufferer, nor were his two sons, who were half-brothers. However, these men (II 2 and II 5) produced two and four children, respectively, who had the disease in a marked degree.

2. One of the sufferers who married (III 2) had one child that died shortly after birth. Furthermore, no less than 5 cases of early infantile death or stillbirth occurred in the offspring of II 5, although he was not a clinical case but only a “transmitter.”

3. A high proportion of the patients in this family were unmarried, or they were married but had no children. As a result, no cases of Gaucher’s disease occurred in the fourth generation.

4. The normal members of the third generation all had normal children (if they had any). The few Gaucher patients who produced offspring had one stillborn baby and also some normal children.

FAMILY C. (FIG. 2.)

M. S., male, a 65 year old Jewish merchant, was admitted in November of 1934. Twenty years previously he had had a severe hemorrhage after an operation for hernia and subsequently had bleeding of a
marked degree with every wound or dental extraction. At the time of this operation no abnormalities were found on physical examination, but he now had a large spleen and liver, pingueculae, myopia, malar flushes, pigmentation and a typical blood picture of Gaucher's disease. Nothing was known about his father or mother. One brother died in an accident. Two others, aged 79 and 69, were examined and found to be normal. The patient had one daughter, who refused examination, and two sons. The elder son, aged 30 was found to have bronchitis, pigmentation, malar flushes, myopia, pingueculae, and an enlarged spleen. The younger son, aged 27, had the same signs but showed in addition early pigmentation of the legs and a typical blood picture. The elder son was married but had no children. The younger son was unmarried. Neither of them had any complaints at the time of examination.

This family is remarkable because the diagnosis could be established in the father and two sons. The disease manifested itself in the father late in life. At the age of 45 nothing abnormal was found in this man. In his sons, however, the clinical picture was already fully developed at the age of 30 and 27 years, respectively.

FAMILY D
A 40-year old Jewish housewife, who was known for many years to have a swollen abdomen and pigmentation of the face with malar flush. On examination she was found to be a typical case of Gaucher's disease. Her father and mother, aged 61 and 60, respectively, were normal on physical examination. She had one sister who was also normal. She was married but she had no children. This patient was regarded as a so-called 'sporadic' case of Gaucher's disease.

FAMILY E
Male, aged 25, non-Jewish, was admitted in 1934 with a typical picture of Gaucher's disease. Later, he was readmitted and the diagnosis was established by sternal puncture. Nothing was known about his parents, who were both dead. His sister, the only other living member of the family, was found to be normal. He married but he never had any children. He was another example of a 'sporadic' case that produced no offspring.*

FAMILY F
Mrs. E. R. B., a Jewish married woman, born in 1890, had had her spleen removed in 1922. A diagnosis of Gaucher's disease was made on the specimen. She came under our observation in 1938 with a picture of cor pulmonale. The liver was enlarged. Gaucher's cells were found in the bone marrow. The patient's father had died of carcinoma of the rectum; her mother of apoplexy. Both had died in a hospital. No enlargement of the spleen or liver had been found in either of them. The patient had two sisters and one brother, who were all found to be normal. Her husband was also normal as were her two children, 35 and 19 years old, respectively. She had had no abortions. She was considered to be a 'sporadic' case of Gaucher's disease.

FAMILY G. (FIG. 3)
Mr. Fz., a Jewish lawyer, born in 1901, was examined in 1937. He was found to have an enlarged spleen and liver, pigmentation and areas of destruction in the bones. Gaucher's cells were found in the bone marrow. Curiously enough, this patient had also harbored another rare disease, namely, an islet cell tumor of the pancreas. The patient's father had died of arteriosclerosis; his mother of 'kidney trouble.' One sister has gall stones. She showed no evidence of Gaucher's disease on clinical examination. One brother is suffering from Gaucher's disease. The diagnosis was established on clinical grounds and verified by sternal puncture elsewhere. A second brother is reported as suffering from 'a slightly enlarged spleen and a moderate secondary anemia.' A third brother died when 5 months old. The patient was unmarried.

This patient further told us that a cousin on the maternal side had had his spleen removed; a diagnosis of Gaucher's disease had been established by pathologic examination of the specimen. We have not been able to verify this statement.

* The cases described so far are the same as those in the publication by Bloem, Groen and Postma.
FAMILY H

A 30 year old Jewish business man, born in 1908, was examined in 1938. He was a typical case of Gaucher’s disease, with enlargement of the liver and spleen, hemorrhagic diathesis, and involvement of the bones. Gaucher’s cells were found in the sternal marrow. His mother was examined and found to be normal. His father had died from a heart attack. He was the only child. He was married to a normal wife. He had one child, a boy, 3 years old, who was found to be normal. This man was regarded as a “sporadic” case of Gaucher’s disease.

FAMILY 1. (FIG. 4)

I 1. A retired Jewish butcher who died aged 82, had a chronic bronchitis and inguinal hernia. No signs of Gaucher’s disease were found in him during his life. His wife had died of carcinoma of the uterus. An internist who had examined her several times told us that he had never found a large spleen or any other abnormalities which could have indicated the presence of Gaucher’s disease. They had 12 children.

II 1. Male, 55 years old, was found to be normal, as were his two children, 19 and 17 years old, respectively.

II 2. Male, 8 years old, died of carcinoma of the colon. No evidence of Gaucher’s disease had been observed in this man by the surgeon who operated on him. His only child, a son, was examined and found to be normal.

III 1. Female, died in 1927, 28 years old, after an operation for carcinoma of the ovary. No evidence of Gaucher’s disease was found, but the family had noticed that she had the same malar flushes as the
lings II 5, II 8 and II 9. She was myopic. She died on the day of operation, possibly of an internal hemorrhage. No further evidence could be obtained and the presence of Gaucher’s disease in her case must be regarded as suspicious. She was married but had no children.

II 5. Female, unmarried, was not on speaking terms with any other member of the family. She could not be traced for examination.

II 6. Male. He emigrated from Holland to the U.S.A. at an early age. He could not be examined. He was said to suffer from nose bleeds, and he had the same peculiar malar flushes as the affected siblings. His wife was apparently normal. Their first baby was stillborn. After this his wife had two abortions. We cannot go beyond suspecting Gaucher’s disease in this case.

II 7. A boy, died at the age of 2 years.

II 8. Female, was first seen by us in 1938. She complained of severe sciatica. She was found to have an enlarged spleen and liver, and lesions in the lumbar vertebrae, the sacral and the iliac bones. She had malar flushes, myopia and a tendency to bleed. Blood picture showed leukopenia, hypochromic anemia and thrombopenia. Typical Gaucher’s cells were found in the sternal marrow. In addition, she was found to have gall stones. Later she developed pulmonary tuberculosis. She was unmarried.

II 9. Male, who had never been examined previously. On examination he was found to have pingueculae, pigmentation of the skin, malar flushes, myopia and an enlarged liver and spleen. One year before examination he had suffered from sciatica but this had disappeared without treatment. Gaucher’s cells were found in the sternal marrow. His two children (III 8–9) were found to be normal.

II 10. A boy, died at the age of 6 months.

II 11. Female, was found to be normal, as was her only child.

II 12. Male, had vague abdominal complaints; no clinical signs of Gaucher’s disease were found. His wife had had two abortions. There were no children.

This family presented “horizontal spread.” In the second generation there were two proven cases of Gaucher’s disease and two individuals who could not be examined but in whom there was a justified suspicion of the disease. Neither of the parents of these cases had shown clinical evidence of Gaucher’s disease. All but one of the normal members of the second generation, who had produced children, had a normal offspring. This one exception was an apparently normal man (II 12) whose wife had two abortions. One of the cases of Gaucher’s disease in this family had normal children. One of the suspected individuals had produced no live children but one stillborn baby and two abortions. The “reproduction balance” in this family was: From 8 normal individuals in the second generation sprang 5 normal children and 2 abortions; from 2 patients plus 2 suspected cases sprang 2 normal children, one stillborn baby and two abortions, so that in the third generation there was no case of Gaucher’s disease left.

FAMILY J. (Fig. 5)

Two Jewish girls, sisters (A.X. and E.X.) born in 1923 and 1927, respectively, were examined in 1939. A.X. had an enlarged spleen and liver, malar flushes, hypochromic anemia, leukopenia, thrombopenia, hemorrhagic diathesis, bone involvement, and typical pigmentation. Typical Gaucher’s cells were found in the marrow.

E. X. underwent splenectomy in 1930. Gaucher’s cells were identified in the spleen and kerasin was isolated from the specimen. She had swelling of the liver, transient pigmentation, malar flushes, bone involvement, anemia, thrombopenia, but no leukopenia. Gaucher’s cells were present in the bone marrow.

The mother of these girls (I 1) was found to be normal on clinical examination. Her sternal marrow was normal. The father (I 2) had bilateral pingueculae and a few scattered gray spots on the skin of the legs. His liver and spleen were not enlarged. The blood picture was also normal. In the sternal marrow,
a few abnormal cells were found that might have been called reticulum cells or stem cells but the faintly-stained protoplasm was nonhomogeneous in character, and resembled in its structure compressed tissue paper. It was felt that these were actually small Gaucher cells and a diagnosis of subclinical Gaucher's disease was established. No other case was found in the family, although three brothers of the patients were examined clinically and by sternal puncture.

This then was a family in which, what seemed to be at first the sporadic occurrence of Gaucher's disease in two sisters could be explained by unmasking the father as a subclinical case or an almost normal "carrier." It seems significant that whereas this man had no clinical evidence of the disease at the age of 39, both his daughters were already affected as children and showed signs of steady progress of the disease.*

\[ \text{FIG. 5. Family J} \]

\begin{center}
\begin{tikzpicture}
\node[circle,fill=black,inner sep=2pt] (1) at (0,0) {1};
\node[circle,fill=black,inner sep=2pt] (2) at (0,1) {2};
\node[circle,fill=black,inner sep=2pt] (3) at (1,0) {3};
\node[circle,fill=black,inner sep=2pt] (4) at (2,0) {4};
\node[circle,fill=black,inner sep=2pt] (5) at (3,0) {5};
\node[circle,fill=black,inner sep=2pt] (6) at (0,-1) {1};
\node[circle,fill=black,inner sep=2pt] (7) at (1,-1) {2};
\node[circle,fill=black,inner sep=2pt] (8) at (2,-1) {3};
\node[circle,fill=black,inner sep=2pt] (9) at (3,-1) {4};
\node[circle,fill=black,inner sep=2pt] (10) at (4,-1) {5};
\draw (1) -- (2);
\draw (3) -- (4);
\draw (5) -- (6);
\draw (7) -- (8);
\draw (9) -- (10);
\end{tikzpicture}
\end{center}

\textbf{DISCUSSION}

The familial occurrence of Gaucher's disease without clear-cut transmission in a vertical line from parents to children has puzzled many observers. It has given rise to peculiar theories which challenge the established laws of heredity. Rowland,\textsuperscript{16} for instance, writes: "As Gaucher's disease is a constitutional anomaly, that is, a mutation in the human species that follows Mendelian law, it is sometimes inherited recessively and sometimes shows dominant characteristics."

The concept of Gaucher's disease as a mutation is founded on its being a congenital anomaly of a sudden occurrence. However, a mutation, once it has established itself, would be expected to be transmitted as a constant entity from parents to offspring. Actually, very few instances have been observed in which a patient with Gaucher's disease has transmitted the disease to his offspring. This is, in the first place, due to the fact that many cases of Gaucher's disease occur in children who die before they reach the reproductive age. Among the cases that reach maturity, a number remain unmarried and among the married patients there is a remarkably high incidence of abortion, stillbirth, and of children who die shortly after birth. For the rest, a certain number of normal children have been observed among the offspring of patients with Gaucher's disease. This, however, cannot be an argument against the hereditary character since, even if a disease is dominant, it will affect only 50 per cent of the offspring. All these points, evident from the literature, were confirmed by the genetic data here presented.

* The cases belonging to the families F to J have been described by Garrer and Groen.\textsuperscript{9}
Obviously, Gaucher's disease has a tendency to extinguish itself. If the disease is present at birth, death seems to result within a year. If it begins in childhood, death occurs in the first or second decade. In young adults the disease can be compatible with life for many years, but the affected offspring die before or shortly after birth and only the unaffected children survive. The only cases, therefore, which are left to study the transmission of Gaucher's disease from a parent to his children are those in whom the disease manifests itself late in life.

An example of this situation is furnished by Family C. The father was a very mild case. When he was 43, he apparently had no clinical evidence of Gaucher's disease and the abnormality was discovered only when he was 63 years old. In his case, the disease had been so mild that it had not interfered with his reaching an advanced age and it had apparently permitted transmission to two children who survived. The transmission in this family was of a simple dominant type. It is significant that whereas the father developed clinical manifestations of the disease at the age of 63, both sons had already showed a marked enlargement of the spleen at the ages of 30 and 17, respectively. Apparently the disease became more serious in the second generation.* This suggests that the frequent occurrence of abortion and stillbirth in the offspring of patients with Gaucher's disease may be due to the fact that the disease makes its appearance in the affected children at an age so early that it has a lethal effect, either during the intrauterine development or shortly thereafter.

Family B shows another interesting aspect of the hereditary mechanism. Here the disease was present in a number of cousins of the same generation. It seems an inevitable conclusion that the affected members of this family inherited their disease from the only ancestor they had in common. It so happened that they sprang from different grandmothers but from the same grandfather. This grandfather, therefore, must have had the genes abnormality.

We are forced to conclude that he transmitted the disease to his sons, who fathered the affected siblings. It is interesting that neither this grandfather nor his two sons exhibited any sign of Gaucher's disease during life, and as we have just concluded that the disease is dominant, the only explanation left is that Gaucher's disease might be present in a carrier individual in a mild, subclinical form. Furthermore one gets the impression from the data available that after every transmission the disease increases in severity until after two (or possibly more) generations, the anomaly is so severe that it manifests itself clinically. From then onwards, it would depend on the severity already reached whether one more affected individual can be produced which can still survive. In the end, however, the mutation becomes incompatible with reproduction or life, and thereby extinguishes itself. The high number of miscarriages, stillbirths and early deaths among the members of Family B is in harmony with this hypothesis.

* This statement was strikingly demonstrated in the study of a recent case of severe Gaucher's disease in a boy of 16. His parents were apparently in excellent health, but examination of both of them revealed splenomegaly in the mother, both by palpation and by x-ray examination. The blood showed slight leukopenia, and the sternal marrow aspiration showed numerous Gaucher cells. X-rays of the bones were negative. This woman must be defined as a carrier since she had always been well and at the age of 42 appeared to be in excellent physical condition. Editor
A proof for this concept could be found in Family J. Here two girls were affected at an early age. The parents were seemingly normal, but the discovery of early Gaucher's cells in the bone marrow of the father unmasked him as a "subclinical case" who acted as a carrier of Gaucher's disease. In Family J this proof could not be furnished because none of the parents was alive when the family was studied.

Several further points emerge from this hypothesis. It is possible, e.g., that what are commonly regarded as so-called "sporadic" cases of Gaucher's disease may be individuals who acquired the disease straightway in a serious degree as the first mutation. It is also possible however, that many of these only manifest a disturbance which was already present in a subclinical degree in one of their parents who acted as a carrier.

Apart from the peculiarity that the disease tends to increase in severity in succeeding generations, the mechanism of transmission in Gaucher's disease appears to be following the genetic rules for one simple dominant trait. Strictly speaking, one would expect that in that case 50 per cent of the offspring would be affected. Actually, the number of siblings in the families described above is too small to decide this point. The patient in Family A had two children, both of whom died shortly after birth and were presumably affected. Two of the three siblings of the patient in Family C had the disease. In these two families the incidence of Gaucher's disease among the offspring seemed higher than 50 per cent. In Family I about half of the patient's offspring were either abortions or stillborns. In the Families B and J, however, the incidence of affected individuals among the offspring of the patients was less than one-half of the siblings and the patients F. and H. had one child each, neither of whom were affected. The total "reproductive balance" of all the families was about as follows: Of 18 adult patients (including the two suspected cases from Family I) 9 were unmarried and 4 were married but had no children, giving an incidence of infertility of 72 per cent. The remaining 5 patients produced 2 abortions, 4 stillborn babies, 4 individuals with Gaucher's disease and 16 normal individuals. The incidence of affected or "stunted" individuals among the offspring of the Gaucher cases was therefore almost 40 per cent. A theoretic figure of 50 per cent, to be expected if Gaucher's disease were inherited as a simple dominant trait, might be reached if a larger number of families were investigated but in view of the high incidence of infertility it is doubtful if this figure would actually give a true picture of the situation. Among 15 normal members of the same generation as the patients, who reached the reproductive age and of whom we examined the offspring we found only 2 who were unmarried and 2 who were married but had no children. The incidence of infertility among this control group was 26 per cent. The remaining 9 persons produced 2 abortions, no stillborn babies, no cases of Gaucher's disease and 20 normal individuals. The incidence of "stunted" individuals among this group was only 9 per cent.

One of the important results of the present investigation is the demonstration of the subclinical or "carrier" state in the father of Family J by examination of the sternal marrow. This makes it imperative to use this technic in every genetic investigation of Gaucher's disease. Unfortunately shortly after this was realized the German invasion of the Netherlands occurred and almost all of the Jewish persons
described in this paper were seized and deported to Poland where they were exterminated. As a result the author was unable to perform sternal punctures on the seemingly normal individuals in these families. It is hoped that others who have an opportunity to carry out similar investigations will complement their clinical studies with marrow puncture. Whether healthy individuals in whom early Gaucher cells are found by this technic should best be named "subclinical cases" or "carriers" is a matter of philosophy.

The substrate of Gaucher’s disease is a disturbance in the metabolism of a special lipoid, kerasin. It is commonly assumed that this lipoid is a product of metabolism somewhere in the body which cannot be destroyed by the lack of some enzyme and is consequently stored in the reticulum cells. Another possibility is that there is an increased production of the substance inside these cells themselves. However this may be, the seriousness of the disease depends on the total excess of kerasin that is present in the body. A small quantity of this substance inside the reticulum cells of spleen, liver, bone marrow, etc. does not result in appreciable harm. It is only when excessive amounts are present that the liver and spleen become enlarged, destruction of bone marrow occurs and a serious condition arises. It seems a likely supposition that Gaucher’s disease is due to a deficiency of some specific enzyme. The seriousness of the disease would depend upon whether the enzyme is only somewhat diminished in quantity or totally lacking. It seems that as the disease is transmitted, the quantity of this hypothetical enzyme diminishes in the next individual. This concept is in harmony with what we see in many other hereditary diseases, where what is merely an innocent trait in a parent becomes an actual disease in the offspring. Gaucher’s disease is also another example indicating that hereditary diseases can occur in varying degrees of severity just as acquired diseases, a concept which many physicians still realize insufficiently.

Finally, attention should be drawn to the frequent occurrence of cholelithiasis and mild diabetes in the families with Gaucher’s disease, both in the affected and in the normal siblings.

Summary

The author reviews the literature of the familial incidence of Gaucher’s disease. Almost all the familial cases which have been described occurred in the members of one generation (siblings or cousins) only. To these cases reported in the literature the author adds 23, of which 4 were "sporadic" cases. The other 21 cases occurred in 6 families. The pedigrees of these families are presented. After an analysis of the available data the author presents the following hypothesis for the hereditary mechanism in these families:

Gaucher’s disease is a mutation which, once established, is transmitted as a simple dominant hereditary trait. In the affected individuals this trait gives rise to a disturbance of lipid metabolism which results in the accumulation of kerasin in the reticulum cells throughout the body. The severity of the disease may vary considerably. It can be present in such a slight degree that the amount of kerasin accumulated during life is too small to give rise to clinical manifestations. In other cases the progression may be so slow that the disease becomes manifest only in
old age, provided the affected individual lives long enough. In these "subclinical cases," a diagnosis of Gaucher's disease can sometimes be made by the detection of "early Gaucher cells" in the sternal marrow. Individuals thus affected suffer from Gaucher's trait rather than from the actual disease. However, they can transmit the disease to 50 per cent of their offspring, and thus function as (almost) normal "carriers." In the family trees presented, it appeared that the disease tended to become more severe in every succeeding generation until after two or three generations it became clinically manifest in the affected individuals early in life. In the next generation it would then establish itself during fetal life so as to give rise to abortion, stillbirth or early death of the affected infant. In this way the mutation extinguishes itself, by permitting only the unaffected offspring of the affected individuals to persist. As a practical conclusion it is urged that a sternal marrow examination be included in every genetic investigation of Gaucher's disease as the best method available at present for the detection of subclinical cases or "carriers."

REFERENCES

THE HEREDITARY MECHANISM OF GAUCHER'S DISEASE
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