FAMILIAL INCIDENCE OF NON-LIPOID RETICULO-ENDOTHELIOSIS (LETTERER-SIWE DISEASE)

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Letterer (1924) described the case of a child of 6½ months who was admitted to hospital with fever, generalized lymphadenopathy, an enlarged liver and spleen, a petechial rash, and anaemia. The child died four days after admission, and on microscopic examination, Letterer found that the architecture of the spleen and lymph nodes was destroyed and these organs were diffusely infiltrated by large clear histiocytic cells. The liver, bone marrow and skin showed similar changes.

Siwe (1933) recorded the case of a girl of 16 months. He found three other cases of this condition in the literature. In his description of the disease, he stressed that it was neither familial nor hereditary, that it occurred exclusively in early childhood and was invariably fatal.

Abt and Denenholz (1936) reviewed nine cases including one of their own and named the condition 'Letterer-Siwe's Disease.' Several reviews of the literature have appeared since then; the most recent are those of Schafer (1949), MacKelvie and Park (1950), Claireaux and Lewis (1950), and Havard, Rather and Faber (1950). Since these were published Veslot, Duperrat, Browaeys, Garnier, and Pley (1950), and Steele (1950) have both reported one case. None of these authors has found a case with familial incidence. The following is a report of two sisters who both died of the disease in early infancy.

Case Reports

Case 1. M.P., a girl aged 3 months, was admitted to the Victoria Hospital for Children, London, on May 4, 1950. She was delivered normally at full term and her birth weight was 8 lb. 4 oz. She appeared healthy until three weeks before admission when her mother noticed that she was becoming increasingly breathless and pale. Two days before admission, the skin of her face had become yellow and her urine was dark.

The patient's family history showed that both parents were in good health. Their firstborn child, a girl, died of anaemia in July, 1944, at the age of 6 weeks. Notes and material for study were kindly provided by the hospital where she died and the case is described below (Case 2). Their second child, a boy, born in 1946, had always thrived and was in good health. There was no history of similar illness among the relatives of either parent.

On admission, the child was seen to be very pale and jaundiced with some oedema. Her weight was 11 lb. 1 oz. The spleen was easily palpable and firm and the liver was felt two fingers' breadth below the costal margin. Only the left tonsillar lymph node was palpable. The haemoglobin was 25% (Haldane) with 1·6 m. R.B.Cs. per c.mm. The W.B.Cs. were 3,100 per c.mm. with the following differential count:

Myelocytes = 5%
Metamyelocytes = 14%
Mature polymorphonuclears = 9%
Monocytes = 28%
Lymphocytes = 38%
Atypical mononuclears = 6%

Two normoblasts were seen in counting 100 leucocytes. The R.B.Cs. were agglutinated by Rh positive (anti-D) serum and the direct Coombs test, the Wassermann and Kahn reactions were all negative. X-ray examination of the arms and legs revealed no bony abnormality.

Throughout her stay in hospital she had a temperature of between 99 and 103° F. She was treated with repeated small blood transfusions and the haemoglobin on the fifth day was 48%. At this time, the platelet count was 28,000 per c.mm. Eight attempts at marrow puncture from the tibia, iliac crest, and sternum were all unsuccessful.

On the fifth day in hospital petechiae appeared on the skin and she began to bleed from the mouth and nose. This continued and the abdomen became distended. On the seventh day and again on the ninth day she had convulsions. She died on May 13, 1950, nine days after admission.

Necropsy. Jaundice was present and there were scattered petechiae on the skin and mucous membranes of the mouth. The heart was normal in size. The muscle was pale and petechiae were found on the endocardium, especially over the papillary muscles. Each pleural cavity contained 120 ml. of clear yellow fluid. The lungs were oedematous. There were enlarged lymph nodes at the bifurcation of the trachea. Scattered

petechiae were present over the mucosa and serosa of the whole alimentary tract. There was a mass of lymph nodes adherent to the duodenum and surrounding the common bile duct but not completely occluding it. The glands were firm, discrete, and greyish red on cut section. The liver was moderately enlarged. It gave a faint reaction for iron with acid ferrocyanide solution. The genito-urinary apparatus and endocrine glands appeared normal. The spleen was five times its normal size and was dark in colour. It gave a similar iron reaction to the liver. The femoral marrow was pale pink in colour and was firm and gritty. There were petechiae in the brain and the grey matter was bile-stained.

On microscopical examination it was observed that the organs were infiltrated with large reticulum cells. These were large round or oval cells with faintly eosinophilic cytoplasm. Most of the nuclei were oval or indented and pale-staining with fine scattered chromatin. Some were rounded and darker. Mitoses were infrequent. The cells were not forming reticulin and no fat was seen in frozen sections stained with Sudan III and IV. Many cells showed active phagocytosis. Some lymphocytes, polymorphonuclears, and plasma cells were present among them.

The sinuses of the spleen were filled with a large number of these cells which were ingesting red blood cells. Often six or eight erythrocytes were present in a single cell (Fig. 1). The Malpighian bodies were small and there were some scattered foci of erythropoiesis. Some free iron was present. The lymph nodes around the pancreas and common bile duct and in the porta hepatis were similarly infiltrated. The follicles were inconspicuous and the lymphatic sinuses contained reticulum cells ingesting lymphocytes and polymorphonuclear cells. In the liver, the infiltration was much less in extent and confined to the portal tracts. There were small foci of erythropoiesis and some free iron. The bone marrow contained large numbers of reticulum cells with greatly reduced haemopoietic tissue. The epiphyses of the vertebral bodies were normal. There was slight infiltration with reticulum cells in the lung, pancreas, and heart muscle.

Case 2. P.P., a girl aged 1 month, was admitted to hospital on July 5, 1944, with pallor and failure to gain weight. She had been born at full term weighing 8 lb. 2 oz. She had been jaundiced for three days in the first week of life and had been discharged after 15 days weighing 8 lb. 1 oz. Four days later, she had been again lightly jaundiced but this had only lasted two days. Since then, her weight had gradually diminished.

On examination she weighed 7 lb. 3½ oz. She was very pale and the liver, spleen, and inguinal glands were palpable. The haemoglobin was 20% with 1·2 m. R.B.Cs. per c.mm. The W.B.Cs. were 5,800 per c.mm. with the following differential count:

Polymorphonuclear cells=8%
Myelocytes=1%
Lymphocytes=79%
Monocytes=9%
Basophils=1%
Nucleated R.B.Cs.=2%

A tibial marrow puncture was attempted but a small amount of blood only was withdrawn. She was treated by blood transfusion but died five days after admission. Her temperature was between 101 and 103° F. until the day before her death when it fell below normal.

Necropsy. The body was very jaundiced. The lungs showed patches of bronchopneumonia. The liver weighed 270 g. and was firm and greenish. The spleen was large. The brain showed no abnormality but there was bile staining of the cerebrospinal fluid. No information was given on the size of the lymph nodes.

Microscopic examination was made on sections of the spleen (Fig. 2), bone marrow, liver, and lung. All the sections showed changes similar to those in Case 1.

Discussion

The sisters whose cases we have reported both died in early infancy with almost identical clinical histories and post-mortem findings. They both appeared to be healthy at birth. The disease began as a rapidly progressive anaemia with hepato-splenomegaly, petechial haemorrhages, and fever. In both, the leucocyte count was low with scanty granulocytes. Large numbers of pale histiocytes were present in the organs, especially the spleen, lymph nodes, and bone marrow. The cells did not contain fat and eosinophils were not present among them.

Erythroblastosis foetalis can be excluded as the disease was not present from birth, the mother was Rh positive, and in Case 1 the direct Coombs test was negative. Dr. R. R. Race has kindly grouped the blood of the father, mother and their surviving child and found them as follows:

Father: O, MsNs, R_2r, Le(a+), Lu(a−), Fy(a+), K−, P+.
Mother: A_1B, MsMs, R_2r, Le(a−), Lu(a+), Fy(a+), K−, P+.
Brother: B, MsMs, R_2r, Le(a−) Lu(a+), Fy(a+), K−, P+.

The serum of the mother tested against the father and the child gave no reaction by the Coombs test, and Dr. Race did not think it likely that the known blood groups could have played a part in the aetiology of the disease.

Repeated Wassermann and Kahn tests on the serum of both parents were all negative. These tests were also negative in Case 1. The diagnoses of leukaemia, Hodgkin's disease, reticulosarcoma, or lipoid reticuloses were excluded by the appearances of the blood and of the tissues at necropsy. Of the nine cases reviewed by Abt and Denenholz (1936) only four had localized bone lesions. Thus the absence of these lesions by no means rules out the diagnosis of Letterer-Siwe disease.

Orchard (1950) described a case in which a

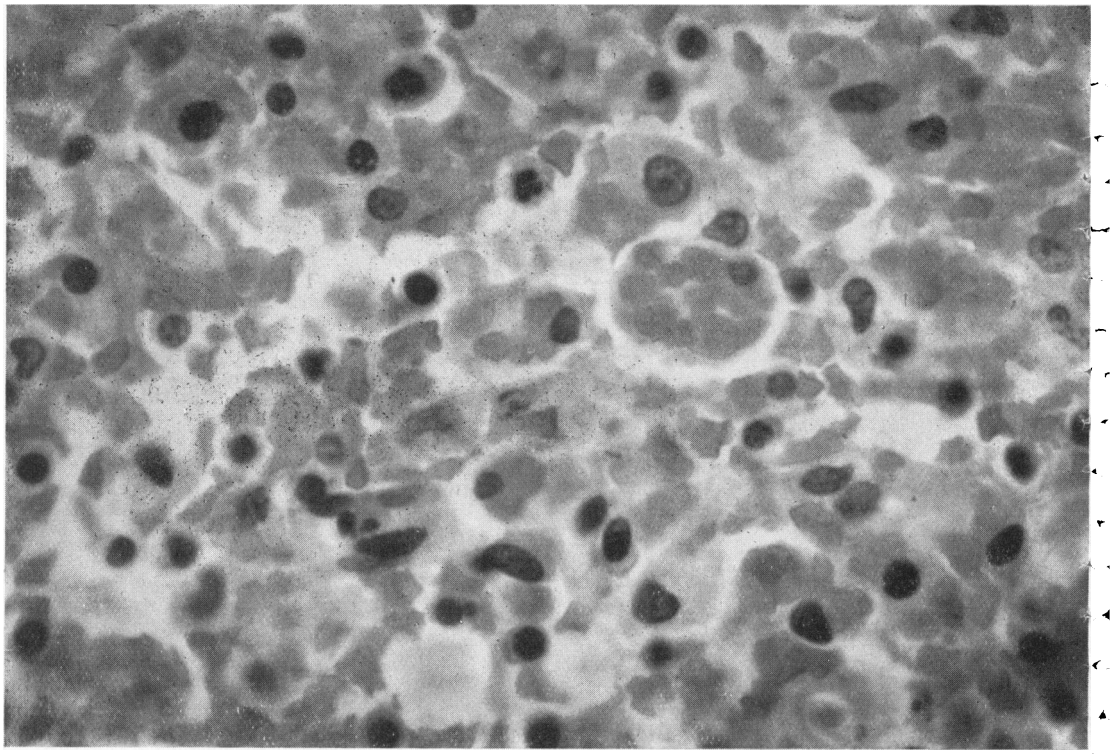

FIG. 1.—Spleen of Case 1 × 800. Stained haemalum, phloxine-tartrazine. Note the erythrophagocytosis.

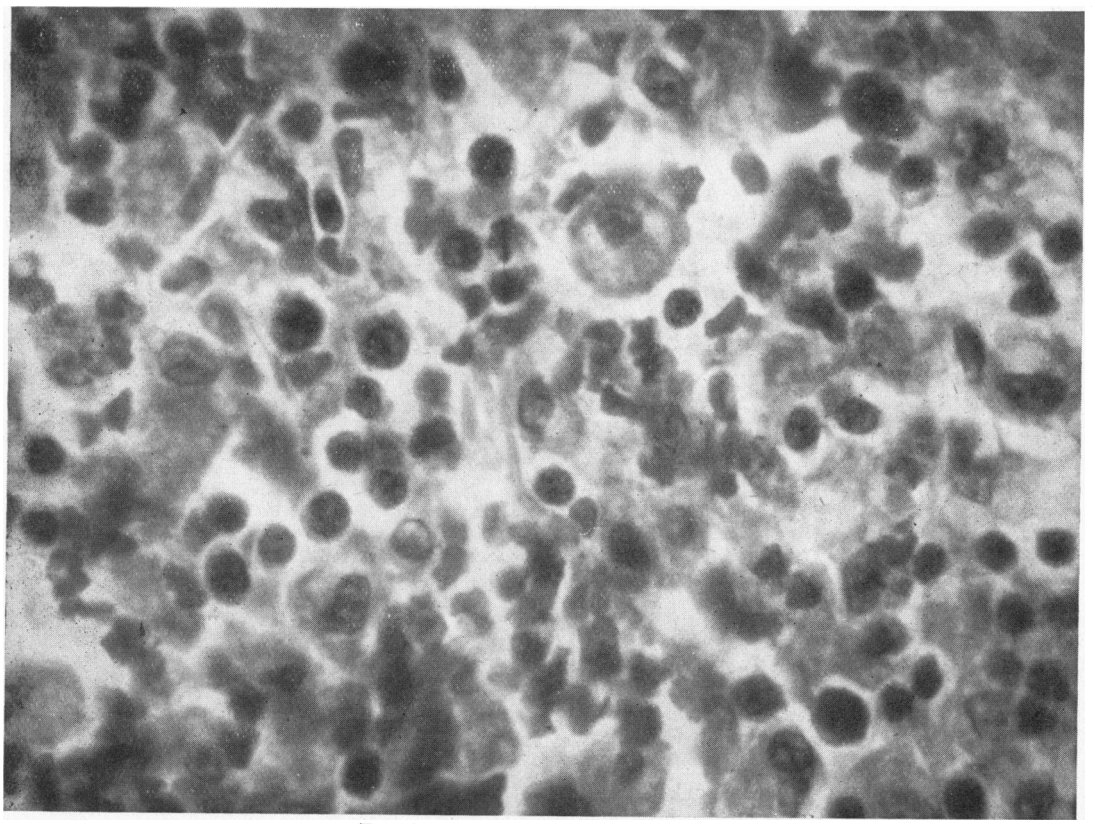

FIG. 2.—Spleen of Case 2 × 800.

number of haemohistiocytes were present in the peripheral blood. It is interesting to note that 6% atypical mononuclear cells were present in the blood of our case 1.

Claireaux and Lewis (1950) reported a case of non-lipoid reticulo-endotheliosis in a child of 14 weeks in which repeated marrow punctures yielded no material. This patient also had enlarged glands in the porta hepatis. In the case records of the Massachusetts General Hospital (1942) appeared the report of a girl aged 23 months with obstructive jaundice which at necropsy was found to be due to enlarged lymph nodes in the porta hepatis. The histology was typical of Letterer-Siwe disease.

Mallory (1942) discussing Letterer-Siwe disease and its possible relationship with Schüller-Christian disease and eosinophil granuloma of bone, stated that the proof of the relationship of these diseases must await the discovery of the aetiological agent. He regarded recent pathological studies as pointing strongly away from a fundamental metabolic disorder and towards a specific infectious agent. Siwe (1949) regarded non-lipoid reticulosis as a distinct disease on the grounds that its onset, course, and prognosis were different from both Schüller-Christian disease and eosinophil granuloma. While some cases of non-lipoid reticulosis appeared to be related to infection, he stressed the need to keep an open mind as to aetiological possibilities.

The cases we have reported favour an inherited rather than an environmental cause.

Summary

The cases of two sisters who died in early infancy with anaemia and hepato-splenomegaly are reported.

The clinical histories and histological appearances are characteristic of Letterer-Siwe disease.

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