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†Dr. Dennis Cottom was killed in a road accident on 13 August 1971 at the age of 47. His work at St. Thomas' Hospital relating to the newborn, and at Great Ormond Street Hospital, where his interest was mainly renal, have been the subject of a number of papers published in the *Archives* from 1957 onwards.

Familial Haemophagocytic Reticulosis in First Cousins*

Familial haemophagocytic reticulosis is a lethal reticuloendotheliosis with a familial proclivity and characteristic histological manifestations (Varadi, Gordon, and Abbott, 1964). The disease has been described in a number of families (Farquhar, MacGregor, and Richmond, 1958; MacMahon, Bedizel, and Ellis, 1963; Marrian, and Sanerkin, 1963; Miller, 1966; Nelson *et al.*, 1961; Goodall, Guthrie, and Buist, 1965; Neff and Senhauser, 1967; and Bell *et al.*, 1968), but has not been reported in relatives other than sibs. This report documents the occurrence of the disease in two first cousins.

Case Reports

Case 1. This was the second child born to a 20-year-old Caucasian after a normal pregnancy. Her mother and the mother of Case 2 were full sisters. After four months, she developed diarrhoea, vomiting, fever, anaemia, and hepatosplenomegaly which were unresponsive to antibiotics.

The abnormal laboratory studies were: WBC 2500–4150/mm³ (20–30% neutrophils, 6–15% bands, 20–37% lymphocytes, 7–15% monocytes, 20–45% disrupted 'smear' cells), reticulocytes 0.5–8.6%, platelets 60,000–120,000/mm³, Hb 5.0–8.0 g/100 ml, the red cells showed marked anisocytosis and poikilocytosis; serum albumin 2.8 g/100 ml, globulin 1.8 g/100 ml. Bone marrow aspirates showed only very active erythropoiesis and no abnormal cells. Heterophil antibodies, typhoid antibodies, Kahn, PPD, and fungal tests were negative. The chest x-ray and skeletal survey were normal.

During the ten-week admission, there were recurrent

pyrexial episodes during which the haematocrit, white cell, and platelet counts fell and the 'smear' cell count rose. She was treated with blood transfusions and several antibiotics without effect. Splenectomy and liver biopsy were performed but the child died of pneumonia and subdural haematomata consequent to thrombocytopenia two weeks later.

Pathology. Microscopically, the spleen showed hypoplastic lymphoid follicles, and infiltration of the splenic cords and sinusoids by large histiocytes. These cells had oval, band-shaped nuclei and mildly acidophilic, vesicular cytoplasm (Fig). Some of them showed haemophagocytosis, particularly of lymphocytes. The hepatic sinusoids and portal tracts showed similar infiltrates with many of the histiocytes and several Kupffer cells showing active haemophagocytosis. Similar infiltrates were present in the lungs and meninges.

FIG. —Case 1: Imprint of spleen. Two histiocytes containing a mature large lymphocyte, degenerating erythrocytes, vacuoles, and cellular debris. (Wright's $\times 260$.)

Case 2. This was the fifth child born to a 24-year-old Caucasian. Six weeks after birth, he developed fever, diarrhoea, respiratory distress, hepatosplenomegaly, and anaemia which continued despite antibiotics and blood transfusions.

Laboratory studies included: Hb 4.7–8.3 g/100 ml, WBC 1400–7500/mm³ (5–30% neutrophils, 0–5% bands, 0–2% eosinophils, 50–90% lymphocytes and 3–13% monocytes), reticulocytes 0.2–4%, platelets 4000–120,000/mm³. Circulating haemophagocytic histiocytes were never seen. Bone marrow examination showed erythrocytic hyperplasia, but no abnormal cells, nor iron storage. Direct Coombs test, haemantigen

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screening test, heterophil titre, and red cell fragility tests with ouabain on the patient and his parents were normal. Standard cultures including the bone marrow showed no pathogens. PPD, brucellergens and histoplasmin skin tests were negative. A skeletal survey and chest x-ray were normal.

The patient had recurrent episodes of pyrexia and haemolysis, which were unresponsive to antibiotics or steroids. He developed meningeal signs and CSF then contained 40 lymphocytes/mm³. Splenectomy was performed, but there was no improvement and he died of pneumonia and cellulitis around the incision two days later.

Pathology. Microscopically, the spleen showed small lymphoid follicles, with a concomitant increase of the red pulp, widened cords of Billroth, and dilated sinusoids. The tissue and sinusoidal histiocytes were hyperplastic and showed panhaemophagocytosis. The histiocytes were round or oval with lightly acidophilic vesiculated cytoplasm. Their nuclei were mostly oval or indented, with diameters of 10–20 μ . The nucleoplasm contained fine chromatin material and occasionally prominent acidophilic nucleoli. The appearances were the same as in Case 1 (Fig.). There was no mitotic activity and only a small amount of stainable iron.

In the liver, haemophagocytic histiocytes were present within the sinusoids and infiltrated round the portal tracts along with lymphocytes and occasional plasma cells. Some Kupffer cells also showed leucoerythrophagocytosis. Similar infiltrates were present in the lungs, adrenals, kidneys, bone marrow, pancreas, meninges, and perivascularly throughout the brain. No lymphoid nodules were seen in the appendix and Peyer's patches were aplastic; histiocytes were infiltrated through the lamina propria and submucosa. The thymic lymphatic nodules were hypoplastic. The lymph nodes showed follicular hypoplasia but the littoral cells were hyperplastic and some showed haemophagocytosis.

Discussion

These patients both showed the typical clinical features and pathological picture of familial haemophagocytic reticulosis. The clinical features and differential diagnosis have been discussed by Goodall *et al.* (1965).

Familial occurrence of any of the histiocytoses is rare. The fact that this disease can occur in cousins suggests that it is inherited through an autosomal, recessive gene. An extensive pedigree showed no evidence of parental consanguinity and the fathers come from two other unrelated families. The mother of Case 1 has subsequently had 7 abortions and 2 normal children. The families originated from different European countries. During the period of observation, they had lived in the same rural county, but in different villages.

Contact between the families was described as 'occasional'.

The reduction of lymphatic tissue which is a regular feature suggests the possibility of a cellular immune defect in this disease. If this were so, the histiocytes might have crossed the placenta from the mother and caused a 'graft vs. host' reaction. In future cases, this could be checked by HL-A antigen analysis, or, in affected male infants, by chromosomal analyses of reticuloendothelial tissue (Githens *et al.*, 1969).

If the histiocytes are fetal in origin, then the disease may be a recessively inherited malignancy in which the macrophages are sufficiently differentiated to continue phagocytic activity. Alternatively, a defect in the chemokinetic system which controls macrophage activity could possibly result in such a syndrome.

Summary

The occurrence of familial haemophagocytic reticulosis in first cousins is reported. This finding supports the suggestion of an autosomal recessive form of inheritance, but provides no further clues to the aetiology.

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