

## Familial Haemophagocytic Reticulosis

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Familial haemophagocytic reticulosis was described first by Farquhar and Claireaux (1952) in 2 infant sibs in whom various organs were infiltrated by histiocytes showing active phagocytosis of blood cells. 2 more affected infants were born subsequently to this family (Farquhar, MacGregor, and Richmond, 1958). Further reports by Nelson *et al.* (1961), McMahan, Bedizel, and Ellis (1963), Marrian and Sanerkin (1963), Varadi, Gordon, and Abbott (1964), and Goodall, Guthrie, and Buist (1965) have brought the total of published cases to 15, 4 of which had evidence of encephalitis (Nelson *et al.*, 1961; McMahan *et al.*, 1963).

The patients reported in this paper were brothers with similar clinical features including evidence of encephalitis. During the 11 years intervening between their births, 3 normal girls were born to the parents.

### Case Reports

**Case 1.** Male, birthweight 3060 g., was delivered normally at term after a normal pregnancy. Apart from two mild attacks of upper respiratory infection and an episode of gastro-enteritis, he remained well until the age of 9 months when he began to vomit and had a right-sided convulsion followed by deviation of the head toward the right, nystagmus to the right, and twitching of the right arm and leg. He had a pyrexia of 40° C. The spleen extended to just below the umbilicus and the liver to 2 cm. below the right costal margin. All other systems appeared normal.

Investigations showed: Hb 10·6 g./100 ml.; WBC 800/cu.mm. (stabs 8%, neutrophil polymorphs 12%, lymphocytes 78%, monocytes 2%); platelets 66,000/cu.mm. Bone-marrow from the sternum was normal.

CSF: 16 lymphocytes and 64 erythrocytes/cu.mm., protein 50 mg./100 ml.; sugar and chloride normal.

Blood urea 30 mg./100 ml.; serum calcium 9·5 mg./100 ml.; cholesterol 148 mg./100 ml.; serum total lipids 480 mg., fatty acid/100 ml.; bilirubin 0·5 mg./100 ml.; albumin 4·25 g./100 ml., globulin 1·47 g./100 ml.

Flocculation tests, Wassermann reaction, Price's precipitin reaction, toxoplasma tests (dye and complement fixation), Mantoux 1 : 1000 were negative.

Blood culture was sterile; no pathogens were isolated from throat, nose, rectum, or urine.

X-rays of long bones showed some banding only.

Despite treatment with antibiotics and phenobarbitone, the pyrexia and convulsions continued and within 4 days he had developed spasticity of all limbs and slight head retraction. Treatment with ACTH (ACTHAR Gel) produced no significant benefit, though the spleen became slightly smaller. His fever settled after 9 days when he developed a serosanguinous discharge from the left ear, successfully treated with erythromycin. As the neck stiffness and spasticity were increasing, a second lumbar puncture was performed. CSF contained 6 lymphocytes/cu.mm. and 85 mg. protein/100 ml. The fundi were normal. Convulsions continued for a further 9 days and he lay in a semiconscious state with head and eyes deviated to the right and the right arm and leg extended. Thereafter his condition improved slightly, and 7 weeks after the onset biopsy specimens were taken from spleen and liver at laparotomy. The spleen showed a moderate diffuse increase of reticular cells within the red pulp, but neither they nor the occasional macrophages within the sinusoids showed evidence of haemophagocytosis; the liver was histologically normal. An air encephalogram showed excess air in the subarachnoid space and slight dilatation of the lateral and third ventricles.

His condition continued to improve and the blood count returned to normal with neutrophil polymorphs reaching 2820/cu.mm. At the age of 13 months, however, he became drowsy and irritable and had a convulsion. His temperature rose to 38·9° C., and it was noted that the spleen had enlarged to just above the umbilicus. There were scattered petechiae of the eyelids and extremities, spastic weakness of the left side of the body, and his eyes failed to follow a light. Investigations at this time showed: Hb 9·6 g./100 ml., total white blood count 3800/cu.mm. (neutrophil polymorphs 46%, eosinophils 1%, lymphocytes 50%, monocytes 3%); platelets 174,000/cu.mm. CSF contained 106 lymphocytes/cu.mm. and 100 mg. protein/100 ml., while sugar and chlorides were normal.  $\beta$ -haemolytic streptococci and pneumococci were isolated from the throat, and the urine contained a trace of protein. An air ventriculogram showed no obvious abnormality.

The pyrexia subsided after 5 days of penicillin

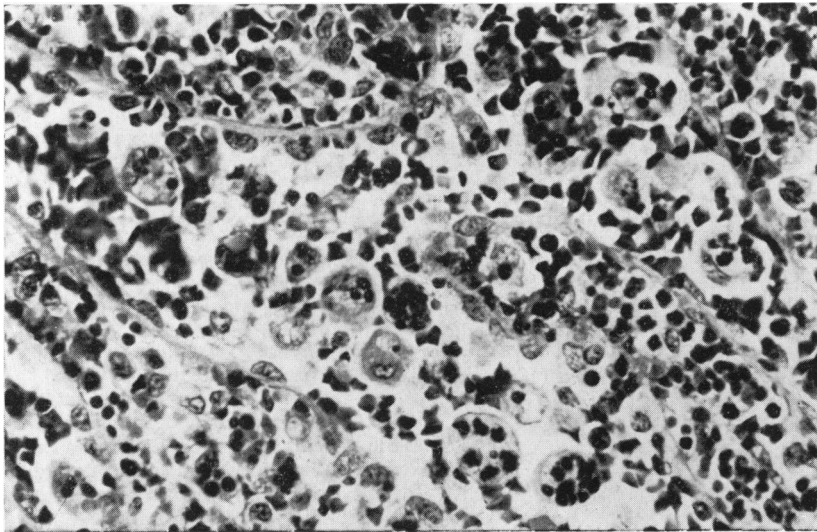


FIG. 1.—Case 1. Photomicrograph of spleen showing sinusoid containing phagocytes engulfing blood cells. (H. and E.  $\times 490$ .)

therapy, but during the next 4 weeks severe convergent strabismus appeared. 4 weeks before death he developed a high fever which failed to respond to antibiotics and continued thereafter. The peripheral blood showed pancytopenia with Hb 7.4 g./100 ml., WBC 600/cu.mm. (metamyelocytes 1%, stab cells 11%, neutrophil polymorphs 33%, lymphocytes 46%, monocytes 9%); platelets 15,000/cu.mm.; there were 2 normoblasts/100 WBC. He finally developed bronchopneumonia with jaundice and gross aminoaciduria and died at the age of 15 months.

**Necropsy findings.** An obese male measuring 73 cm. in length; circumference of head 43 cm.; moderately jaundiced.

The *spleen* (237 g., normal 27 g.) extended for 6 cm. below the left costal margin and showed no Malpighian bodies to the naked eye. Microscopically there was moderate proliferation of large reticular cells with vesicular nuclei and pale cytoplasm replacing the Malpighian bodies, and lying between the sinusoids of the red pulp. Most sinusoids and some cords contained large, round macrophages whose cytoplasm was filled with erythrocytes sometimes accompanied by degenerate neutrophil polymorphs and lymphocytes (Fig. 1).

The *liver* (550 g., normal 320 g.) showed fatty change at the periphery of the lobules. Some Kupffer cells were enlarged and showed haemophagocytosis.

*Lymph nodes* from various parts of the body and *bone-marrow* contained scattered phagocytes ingesting erythrocytes but were otherwise normal.

Both *kidneys* showed small subcapsular scars suggestive of previous pyelonephritis.

*Brain* (575 g., normal 975 g.); the cerebral hemispheres were symmetrical and covered by slightly thickened leptomeninges. The gyral pattern was normal though

the gyri of the posterior parietal, occipital, and temporal lobes were atrophic and separated by wide sulci. On section there was moderate dilatation of both lateral ventricles which had a smooth lining. The white matter was of about normal thickness but showed some small, darker patches of firmer consistency. The cortex of the frontal lobes appeared normal, but posteriorly it was considerably reduced in thickness, and over much of the occipital lobes and the inferior surfaces of the temporal lobes it could barely be differentiated from the underlying white matter. The brain-stem, cerebellum, and spinal cord showed no gross changes.

Microscopically, granulomatous foci consisting of mononuclear cells with vesicular nuclei, lymphocytes, and a few proliferated neuroglia were found throughout the central nervous system (Fig. 2). In the occipital and temporal lobes the deeper strata of the cortex were destroyed and partially replaced by this tissue, but elsewhere the cerebral cortex was retained, though many small, round granulomata were scattered throughout the white matter. Most vessels were surrounded by small numbers of lymphocytes and mononuclears. Many similar lesions were present in the midbrain, pons, and cerebellum, but they were scanty in the medulla and spinal cord where the inflammatory reaction was reduced to lymphocytic infiltration around some vessels. The leptomeninges over the cerebrum were infiltrated by moderate numbers of mononuclears with some lymphocytes.

Death was due to pneumococcal bronchopneumonia.

**Case 2.** Male, birthweight 3795 g., brother of Case 1, was delivered normally at 39 weeks' gestation after a pregnancy complicated by pre-eclamptic toxæmia. Progress was satisfactory until the age of 10 weeks

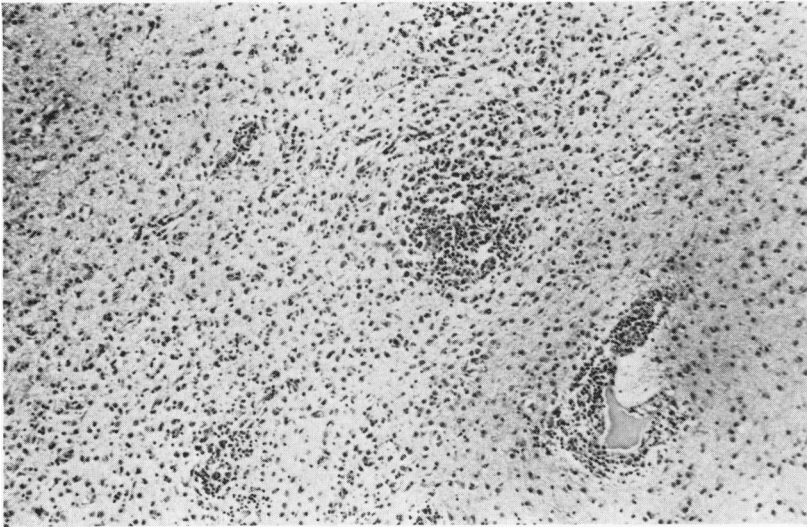


FIG. 2.—Case 1. Photomicrograph of right temporal lobe of brain showing inflammatory focus in softened tissue and perivascular infiltration in relatively normal brain tissue. (H. and E.  $\times 106$ .)

when he developed a fever with drowsiness and irritability, which failed to respond to treatment with tetracycline. Three days after the onset his rectal temperature was  $38.8^{\circ}\text{C}$ ., he was pale and irritable, the liver and spleen were enlarged, and there were a few petechiae on the abdomen.

Investigations showed: Hb  $8.1\text{ g./100 ml.}$ ; film, some hypochromia with anisocytosis and polychromasia. WBC  $5000/\text{cu.mm.}$  (neutrophil polymorphs 32%, lymphocytes 64%, monocytes 4%); platelets  $84,000/\text{cu.mm.}$  ESR 18 mm. in one hour.

Bone-marrow biopsy of tibia showed a cellular marrow, with very active normoblastic erythropoiesis and normal leucopoiesis. Megakaryocytes were present but platelets were scanty. A striking feature was the presence of erythrophagocytic histiocytes, large cells with deeply basophilic cytoplasm, and a large nucleus with open chromatin network; within vacuoles of the cytoplasm there were normoblasts of all degrees of maturity. Single histiocytes showed up to 10 engulfed normoblasts, but in no instance were phagocytosed leucocytes, platelets, or mature red cells seen (Fig. 3).

CSF, throat swab, blood culture, urine, and chest x-ray showed no abnormality.

Though pyrexia of up to  $39.4^{\circ}\text{C}$ . continued and the liver and spleen progressively enlarged, he continued to gain weight. At the age of 15 weeks he weighed  $6.6\text{ kg.}$  and was alert and responsive. There were no skin lesions or significantly enlarged lymph nodes. The liver was smooth and firm with its lower border  $4\text{ cm.}$  below the right costal margin. The spleen was firm and extended  $7.5\text{ cm.}$  below the left costal margin. The head circumference was  $41\text{ cm.}$  and the anterior fontanelle  $3.5 \times 3.5\text{ cm.}$ , with normal tension. The fundi were normal and there was no neck stiffness.

Investigations showed: Hb  $9.6\text{ g./100 ml.}$ ; PCV 31%, MCHC 31%; film anisocytosis and poikilocytosis, with some hypochromia and polychromasia; reticulocytes 3.2%; WBC  $5400/\text{cu.mm.}$  (neutrophil polymorphs 9%, lymphocytes 87%, monocytes 4%); platelets  $10,000/\text{cu.mm.}$ , direct Coombs test negative; bilirubin less than  $0.5\text{ mg./100 ml.}$  ESR 10 mm. in one hour. SGOT 248 and SGPT  $274\text{ }\mu\text{M}$  pyruvate/100 ml. serum per hour; alkaline phosphatase  $1.4\text{ KA units/100 ml.}$ ; calcium  $9.8\text{ mg./100 ml.}$ ; inorganic phosphate  $4.8\text{ mg./100 ml.}$ ; urea  $52\text{ mg./100 ml.}$ ; electrolytes normal; serum total protein  $5.4\text{ g./100 ml.}$ , electrophoretic strip, slightly raised  $\alpha_1$ - and  $\gamma$ -globulin and decreased albumin; immunoglobulins, IgG  $520\text{ mg./100 ml.}$ , IgA 19% and IgM 132% of reference 'normal' sera. Urine: no protein, white cells, or excess of sugars, amino acids, or mucopolysaccharides. CSF: 5 lymphocytes/cu.mm., protein  $200\text{ mg./100 ml.}$ , sugar  $44\text{ mg./100 ml.}$ ; cultures of blood, CSF, urine, throat swab, and stool produced no pathogens, and no virus was isolated. The toxoplasma dye test and Wassermann reaction were negative in both the patient and his mother. A glucagon test showed a slightly delayed but otherwise normal hyperglycaemic response. A leucocyte function test showed that the patient's leucocytes were able to phagocytose *Staphylococcus aureus in vitro*, and to destroy intracellular bacteria in a normal manner. X-ray of the chest and skull were normal, but the long bones showed dense metaphyses, with some cupping and fraying of their ends (Fig. 4). A chromosome preparation of peripheral blood cells showed a normal male karyotype. Bone-marrow biopsy from the iliac crest confirmed the above findings and again showed the presence of erythrophagocytic histiocytes. Liver biopsy showed non-specific changes only; there was some focal infiltration

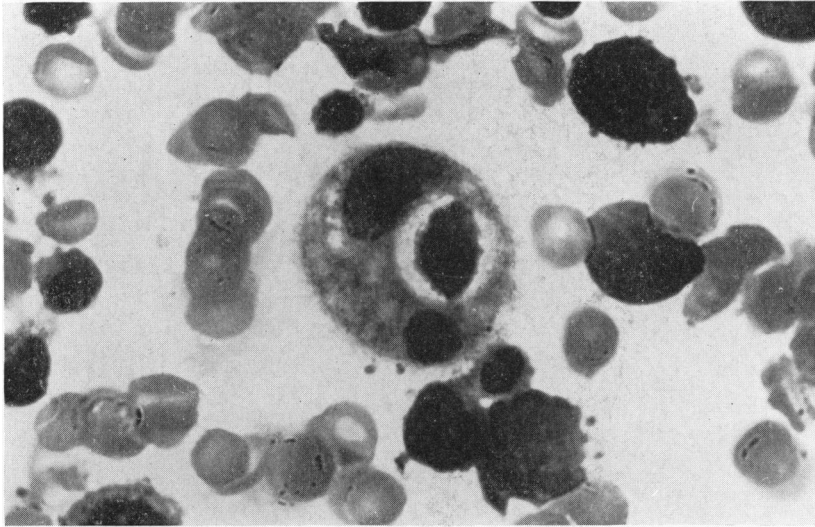


FIG. 3.—Case 2. *Histiocyte phagocytosing two normoblasts in bone-marrow.* (Leishman.  $\times 1320$ .)

with small mononuclear cells throughout the biopsy specimen, not related to any necrosis, and no erythrophagocytosis was seen. Post-mortem splenic aspiration showed pronounced erythrophagocytosis.

He was treated with iron and vitamin supplements only, but his condition soon began to deteriorate. He became increasingly pale, less alert, and less eager to feed. The liver and spleen enlarged progressively. Hb fell to 7.0 g./100 ml., WBC 2400/cu.mm., and platelets to 3000/cu.mm. No cause for his fever could be found. Empirical treatment with ampicillin and prednisone was started, and there was an apparent brief response when his fever subsided for 48 hours, and Hb level, white blood cell count, and platelets increased. However, he then developed signs of meningeal irritation, an intermittent convergent squint, and had several *grand mal* fits. CSF showed 14 lymphocytes/cu.mm., protein 300 mg./100 ml., and sugar 48 mg./100 ml. Film, culture, and viral studies showed no abnormality. Serial EEGs showed a gross generalized abnormality more obvious over the temporal and posterior temporal regions than elsewhere, with occasional multifocal discharges maximal about the left temporal region. The features were compatible with a diffuse cerebral lesion. The fits responded to phenobarbitone and phenytoin. He developed a generalized macular erythematous rash which cleared when ampicillin was stopped. A trial of cyclophosphamide was initiated but it caused severe neutropenia and was discontinued. The liver and spleen enlarged to 9 cm. and 14.5 cm., respectively, below the costal margin and he developed a severe pancytopenia, Hb 5.7 g./100 ml., WBC 1600/cu.mm. (neutrophil polymorphs 23%, lymphocytes 74%, monocytes 3%), normoblasts 2/100 WBC, and platelets 5000/cu.mm. He developed an ear infection and bleeding from the nose and mouth, his condition rapidly



FIG. 4.—Case 2. *Radiograph of forearm showing dense metaphyses with cupping and fraying of distal end of ulna.*

deteriorated, and he died at the age of 7 months. Permission for necropsy was refused.

**Discussion**

The disease as outlined by Farquhar and Claireaux (1952) is characterized by hepatosplenomegaly associated with pancytopenia and atypical cells in the peripheral blood, and the post-mortem demonstration of phagocytosis of erythrocytes and leucocytes by histiocytes infiltrating the bone-marrow, spleen, liver, and lymph nodes. One of two further affected babies in their original sibship was the only patient reported to have survived (Farquhar *et al.*, 1958); she showed atypical large lymphocytes in the peripheral blood, but neither pancytopenia nor enlargement of liver and spleen were present and haemophagocytosis was not demonstrated. The remaining 12 infants and 4 older children recorded in the literature died after illnesses lasting up to 7 months (Table).

The first patient to be diagnosed in life without a previous family history was described by Varadi *et al.* in 1964. Diagnosis was made by the demonstration of haemophagocytosis in a bone-marrow preparation and was confirmed at necropsy. In 1965, Goodall *et al.* described 3 infants in a sibship of 10. In their third case, biopsies of liver and lymph node showed no specific changes, there were focal aggregations of histiocytes but no haemophagocytosis in the marrow, while a few histiocytes ingesting blood cells were found in the spleen. These findings compare with those in Case 1 where biopsies of liver, spleen, and bone-

marrow failed to reveal any evidence of haemophagocytosis though it was widespread at necropsy. They illustrate the difficulties of diagnosis during life and suggest that remissions occur during the course of the disease or that, in some cases, haemophagocytosis may only become extensive shortly before death.

In 1961, Nelson *et al.* described a sibship of 3 children all dying with haemophagocytic reticulosis in whom there was clinical evidence of meningo-encephalitis. Necropsy showed infiltration of the meninges by histiocytes and lymphocytes and there was perivascular infiltration by these cells in the white matter. One of two sibs recorded by McMahon *et al.* (1963) had convulsions, neck stiffness, and generalized spasticity, and died 7 months after the onset; necropsy showed extensive meningo-encephalitis, with nerve cell degeneration and necrosis. Both the present cases showed clinical features of meningo-encephalitis and this was confirmed at necropsy in Case 1. It is interesting to note that meningo-encephalitis occurred in 3 of the 7 families recorded, and that in 2 of these families it probably complicated the disease in all affected children.

In their search for an aetiological factor, Nelson *et al.* (1961) carried out extensive tests for viruses, bacteria, protozoa, and fungi, all with negative results. Though 2 of his patients became ill during the same year, the third affected child had died 8 years previously; this compares with the interval of 11 years between our 2 cases, and suggests that an infective element is unlikely. By radioactive

TABLE  
Familial Haemophagocytic Reticulosis, 17 Cases

| Author                        | Sex | Age of Onset | Duration of Illness | Encephalitis | Necropsy | Haemophagocytosis |             |
|-------------------------------|-----|--------------|---------------------|--------------|----------|-------------------|-------------|
|                               |     |              |                     |              |          | During Life       | Post Mortem |
| Farquhar and Claireaux (1952) | M   | 8 wk.        | 3 wk.               | —            | +        | —                 | +           |
| Farquhar and Claireaux (1952) | F   | 8 wk.        | 3 mth.              | —            | +        | —                 | +           |
| Farquhar <i>et al.</i> (1958) | F   | 6 wk.        | Surviving           | —            | —        | —                 | —           |
| Farquhar <i>et al.</i> (1958) | M   | 14 wk.       | 9 wk.               | —            | +        | —                 | +           |
| Nelson <i>et al.</i> (1961)   | M   | 11 wk.       | 4 dy.               | +            | +        | —                 | +           |
| Nelson <i>et al.</i> (1961)   | F   | 7 yr.        | 2 mth.              | +            | +        | —                 | +           |
| Nelson <i>et al.</i> (1961)   | M   | 36 mth.      | 5 mth.              | +            | +        | —                 | +           |
| McMahon <i>et al.</i> (1963)  | F   | 8 wk.        | 1 mth.              | 0            | +        | —                 | +           |
| McMahon <i>et al.</i> (1963)  | M   | 9 wk.        | 7 mth.              | +            | +        | —                 | +           |
| Marrian and Sanerkin (1963)   | M   | 8 wk.        | 3 wk.               | —            | +        | —                 | +           |
| Marrian and Sanerkin (1963)   | F   | 4 mth.       | 4 wk.               | —            | +        | —                 | +           |
| Varadi <i>et al.</i> (1964)   | M   | 3 yr.        | 6 wk.               | —            | +        | +                 | +           |
| Goodall <i>et al.</i> (1965)  | F   | 9 wk.        | 5 dy.               | —            | +        | —                 | +           |
| Goodall <i>et al.</i> (1965)  | M   | 7 wk.        | 3 wk.               | —            | —        | —                 | 0           |
| Goodall <i>et al.</i> (1965)  | M   | 16 mth.      | 4 mth.              | —            | —        | —                 | +           |
| Case 1                        | M   | 9 mth.       | 6 mth.              | +            | +        | —                 | +           |
| Case 2                        | M   | 10 wk.       | 20 wk.              | +            | —        | +                 | +           |

0 = Not examined.

chromium studies Farquhar *et al.* (1958) were able to demonstrate rapid removal of red cells from the circulation and postulated that the anaemia was due to haemophagocytosis.

The diffuse infiltrative character of the reticulosis serves to distinguish it from the granulomatous lesions of Letterer-Siwe disease, but differentiation from histiocytic medullary reticulosis (Scott and Robb-Smith, 1939) may be less convincing. Farquhar and Claireaux (1952) considered the condition to be a variant of histiocytic medullary reticulosis and, in view of the relatively late age of onset at 3 years, Varadi *et al.* (1964) thought their case formed a link between the two conditions. Most examples of histiocytic medullary reticulosis occur in adults, though Fowler (1960) records it in a 4½-year-old child. Marshall (1956) states that the proliferation of histiocytes in histiocytic medullary reticulosis is mainly in lymph nodes and liver, destroying their normal architecture and frequently associated with necrosis, haemorrhage, and exudation of fibrin, features lacking in familial haemophagocytic reticulosis. Fatal granulomatosis of childhood (Holmes *et al.*, 1966) is a sex-linked condition, characterized clinically by chronic progressive suppurative lesions unresponsive to antibiotics, in which histiocytes ingest blood cells and organisms but are unable to destroy them. *In vitro* tests in Case 2 showed normal phagocytic behaviour. Though our cases occurred in male sibs while 3 sisters escaped, the over-all sex-ratio is 11 M : 6 F.

### Summary

Two brothers born at an interval of 11 years developed haemophagocytic reticulosis with men-

ingo-encephalitis during infancy; their 3 sisters were unaffected. Though the condition of the first affected sib was not recognized until after death, the second child was diagnosed during life by demonstrating haemophagocytosis in the bone-marrow.

The literature is reviewed and the disease is differentiated from Letterer-Siwe disease, histiocytic medullary reticulosis, and fatal granulomatosis of childhood.

We are indebted to Dr. Ursula Shelley for permission to publish the clinical details of Case 1 and to Dr. D. G. Cottom and Dr. E. Hinden for Case 2. We wish to thank Dr. L. Crome for examining sections of the brain of Case 1, Dr. A. E. Claireaux for histological reports of Case 2, Dr. C. L. Berry for chromosomal studies, Dr. G. Pampiglione for EEG reports, Dr. G. W. Manley for assessing mucopolysaccharide excretion, and Dr. R. D. S. Barnes for performing the leucocyte function test.

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