THE HAEMOLYTIC-URAEMIC SYNDROME

A Report of Two Cases

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IN SWITZERLAND Gasser et al. (1955) described in detail an acute fatal illness occurring in five children. Four were between 2 months and 14 months whilst the fifth was 7 years old. The four chief clinical findings were acquired haemolytic anaemia, acute renal failure, a haemorrhagic diathesis and cerebral symptoms. They considered that the accompanying thrombocytopenic purpura was similar to the thrombotic thrombocytopenic purpura of Moschcowitz (1925), Singer et al. (1947), the thrombotic microangiopathy of Symmers (1952) and the syndrome described by Evans et al. (1951) as "thrombocytopenic purpura with acquired haemolytic anaemia." At autopsy in the Swiss cases bilateral renal cortical necrosis appeared to be the cause of the renal insufficiency, and in one the basic lesion was similar to the thrombotic microangiopathy of Symmers. In three cases marked fragmentation of the erythrocytes was noticed in the blood films.

Allison (1957) described nine children who suffered from acute haemolytic anaemia associated with contraction, distortion and fragmentation of the circulating erythrocytes and stated that this picture appeared to be the result of three distinct pathological processes. In two of these there was a Heinz-body anaemia of which one type occurred only in premature infants whilst the other was due to an inborn error of erythrocyte metabolism. In the third syndrome, which was found in older children, Heinz bodies (Heinz, 1890) could not be demonstrated. Distortion of the red cells and haemolysis were associated with thrombocytopenia and proteinuria, and in some cases uraemia and haematuria. Two of Allison's cases died with multiple platelet thrombi in the kidneys and other organs, and four recovered spontaneously. He regarded the condition as a type of thrombotic thrombocytopenia, differing from the thrombotic thrombocytopenic purpura of adults in the absence of purpura, in the distortion of the circulating red cells and in the spontaneous recovery of some of the patients.

CASE REPORTS

Case I. N.E.B. was the third child born to healthy unrelated parents of local ancestry. The eldest sibling was alive and well, but the second had died in infancy from interstitial pneumonia. Following a normal birth and neonatal period the infant remained well until two days before admission, when he started to vomit and have loose motions. He was admitted to the Belfast City Hospital on the 11th March, 1964, because he had developed haematuria and jaundice.

He was a three-month old infant weighing 13 lbs. 7 ozs. The temperature was 100°F, he was slightly jaundiced, the blood pressure was 150/100 mm. Hg., but apart from this, clinical examination revealed no abnormalities. The urine was scanty and contained blood and albumin. The haemoglobin was 6.9 gm. '% and many "burr" cells and other fragmented erythrocytes were seen in the peripheral blood. (Fig. 1).

The total white cell count was 22,660 per c.mm. (Neutrophils 24%, lymphocytes 67%, monocytes 5%, meta-myelocytes 3%, myelocytes 1%, with 1 late normoblast per 100 leucocytes). Re-examination of the film in retrospect revealed very few platelets.

Fig. 1. Drawing of a peripheral blood film showing poikilocytes and several "burr" cells. (Case I).

The alkali reserve was 11 m. eq./litre, and the blood urea was 390 mg.% on the third day of illness and rose to a maximum of 500 mg.% on the fifth day. Type specific *E. coli* 026 was present in the faeces. The infant was treated with intravenous blood and the acidosis corrected with an infusion of 1/6 molar lactate. The subsequent course to complete recovery was uneventful and can be followed in the diagram. (Fig. 2).

Other investigations were carried out as follows: The direct anti-human globulin test (Coomb's) was negative. The antistreptolysin O titre was 20 units/ml. "L.E." latex and Jones Precipitation tests were negative and no "L.E. cells" were found in the peripheral blood. Total bilirubin level was 0.5 mg.% (direct 0.3). The red cell osmotic fragility at room temperature was normal, while at 37°C for 24 hours it was slightly increased. Autohaemolysis showed the increased level of 9% lysis at 48 hours. Erythrocyte glucose-6-phosphate dehydrogenase activity was normal, and no Heinz bodies were seen. Spectroscopic examination revealed no abnormal haemoglobin bands and Schumm's test (1912) for intravascular haemolysis was negative. No foetal haemoglobin was detected.

Case II. P.S. was the fifth child of healthy unrelated parents, of local stock, whose other children were alive and well. His birth and neonatal course were normal, and he remained well until the 1st July, 1964, when his motions became loose and contained a few spots of blood. On the following day he vomited, there was blood in his urine and faeces, and he was admitted to hospital.

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On admission he was a very large fat nine months old infant weighing 28 lbs. He was pale, apathetic and listless, the blood pressure was 140/99 mm. Hg., but there were no other clinical abnormalities. The urine contained albumin and blood. On the fourth day of illness the blood urea level was 110 mg.%; it fell to 68 mg.% on the sixth day, but then gradually rose to a maximum of 142 mg.% on the ninth day.

The haemoglobin level was 5.7 gms. (38%) and the total white cell count rose to 31,000 per c.mm. The film showed an increase in granulocytes, but the striking feature was again the marked distortion and fragmentation of the erythrocytes. Late normoblasts numbered 15 per 100 leucocytes. The reticulocyte count was 22 per cent. and a thrombocytopenia was present (platelets 46,000 per c.mm.). Total bilirubin was 1.1 mg.% (direct 0.2). Red cell osmotic fragility was slightly increased, probably due to the presence of microspherocytes. Again the direct Coomb's test was negative and no Heinz bodies were seen. The alkali reserve was 16.1 m.eq./litre and he was given a transfusion of 300 ml. of whole blood, but the haemoglobin continued to fall rapidly, and three further transfusions of semi-packed cells were required. (Fig. 3).

This infant remained listless, apathetic and febrile for three weeks; the temperature then became normal, the blood urea and blood pressure fell to normal levels, the child became
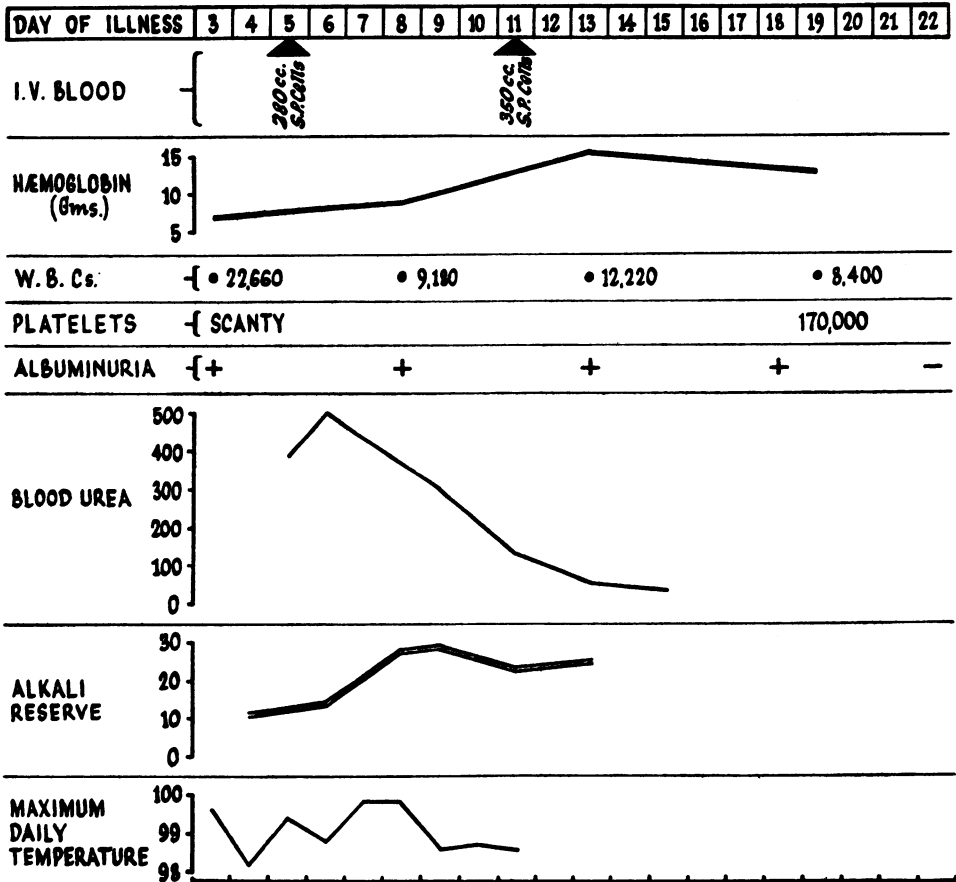

Fig. 2. Progress chart of Case 1.

DAY OF ILLNESS | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | - - - | 27

I.V. BLOOD — 100 c.c. Whole blood | 500 c.c. S.P. cells | 400 c.c. S.P. cells | 450 c.c. S.P. cells

HÆMOGLOBIN (Gms.) 15 10 5

RETICULOCYTES % { 22 13 11 4·5 3 11

W. B. Cs. { •23,400 •31,000 •21,600 •16,100 •7,900 7,260•

PLATELETS { 46,000 80,000 78,000 192,000 410,000

ALBUMINURIA { + + + + + + + + −

BLOOD UREA 150 100 50 0

ALKALI RESERVE 25 10

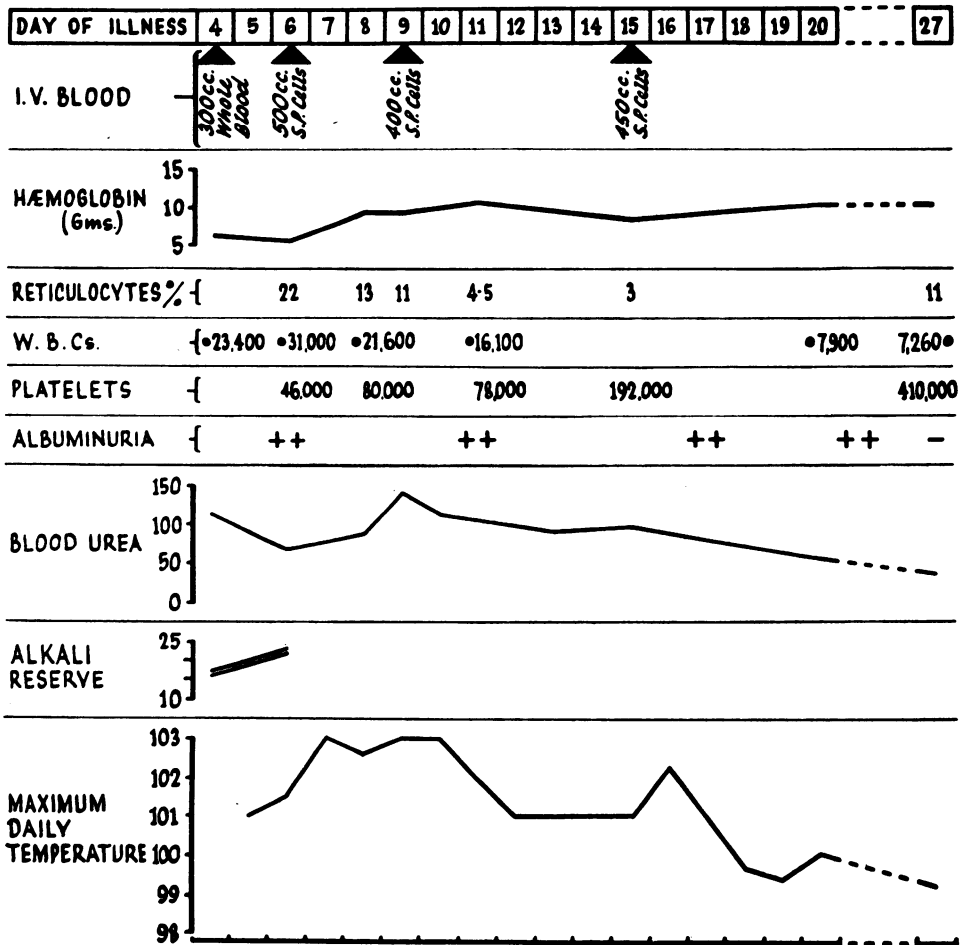MAXIMUM DAILY TEMPERATURE 103 102 101 100 99 98

Fig. 3. Progress chart of Case II.

happy and playful and regained his normal large appetite.

At subsequent follow-up examinations he has remained well with no abnormalities in his blood or in the renal tract.

VIRUS STUDIES

Fresh blood in dipotassium sequestrene from Case II, taken thirty days after the onset of illness, was injected intra-cerebrally and intra-peritoneally, into ten new-born mice. No virus was recovered, all mice developed a runting syndrome and no deaths occurred. On the fourteenth day two were sacrificed, and the ground-up suspension of one was inoculated into a further litter of seven newborn mice. One of the original litter showed no obvious lesions histologically, while the passaged suspension of the other produced no abnormality.

The blood serum from Case II was also tested against antigens for the Junin (Argentinian haemorrhagic fever), Tacaribe and lymphocytic choriomeningitis

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viruses. The complement fixation test was negative, the serum in increasing twofold dilutions, beginning at 1 in 4, failed to fix complement with any of the antigens.

Both these children lived in rural surroundings, and visits were later paid to both homes. Case II's mother had a herpes labialis infection at the time of the visit. In Case II there was fairly close contact with chickens which had stopped laying two months before the onset of his illness. These hens were subsequently seen by Veterinary Surgeons of the Veterinary Research Department of the Ministry of Agriculture, Northern Ireland, who thought it extremely unlikely that Newcastle Virus Disease was involved. However, one of us (C.C.K.) developed a conjunctivitis three days after visiting Case II's home and shortly afterwards there was an out-break of fowl pest (Newcastle Disease) in this district and other parts of Northern Ireland, something that had not occurred for 15 years. No antibodies against Newcastle Disease were detected in the sera of either the infant, the mother or C.C.K.

In both cases rats might have had access to the infants' clothing.

TREATMENT

Neither of these cases had any treatment apart from blood transfusions and correction of their acidosis. Neither had been receiving medicine at home and no raw milk had been drunk.   ·

Many forms of treatment, including splenectomy, have been tried in this con-dition, but the results generally have been disappointing. Steroids have been used by Griffiths and Irving (1961), Lock and Dormandy (1961), Javett and Senior (1962) and others, but there is no convincing evidence that they are of any value. Both Künzer and Aalam (1964), and Kibel and Barnard (1964) have suggested using heparin. On theoretical grounds this might prevent some of the thrombosis which is probably responsible for the renal cortical necrosis. However, suppression of thrombus formation may depend on the dosage of heparin, low doses having no beneficial effect (Mustard et al., 1965). Moorehead et al. (1965) employed haemo-dialysis in their treatment of four severely ill children, three of whom died. They emphasised the necessity for slow haemodialysis. Allison (1957) considered blood transfusions the only effective treatment.

COMMENT

Distorted erythrocytes have been described by Schwartz and Motto (1949), who named a peculiar poikilocyte with one or more spiny projections a "burr" cell. They observed that this occurred most frequently in uraemia, carcinoma of the stomach and bleeding peptic ulcer. Aherne (1957) investigated the clinical signifi-cance of the "burr" cell and he found it most characteristically in terminal uraemia, although it was seen occasionally in reversible anaemia. A similar cell may occur in a " treatable haemolytic anaemia of childhood," which, he noted, may be the syndrome described by Gasser et al. in 1955. Dacie (1960) distinguished three types of distorted erythrocytes which are probably distinct; "irregularly contracted erythrocytes" which are not uncommonly seen in certain types of haemolytic anaemia, the "burr" cell referred to above and the "triangular" cell (Dacie et al., 1953). The last was found in a child with atypical congenital haemolytic anaemia.

Gasser et. al. (1955) were of the opinion that the haemolytic-uraemic syndrome arose in most cases in association with a mild or severe infection. Shumway and

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Miller (1957) described a case of the haemolytic-uraemic syndrome in a child, 6 years 9 months of age, who had had several recurrences of haemolytic anaemia, thrombocytopenia and renal disease over the previous five years. They considered that the sydrome represented a form of "hypersensitivity" and might be related to thrombotic thrombocytopenic purpura. Lock and Dormandy (1961) named the condition "red cell fragmentation syndrome" in their description of five cases in infants; and they suggested that it is better regarded as an occasional manifestation of primary renal failure (from whatever cause) in young children than as a disease entity. In South Africa Javett and Senior (1962) reported five cases of the haemolytic-uraemic syndrome in infancy, where circumstances pointed strongly to infection, but bacterial cultures of stools, blood and urine were negative, and all attempts to recover a virus proved abortive. They suggested that the disease mechanism might be an allergic response to a viral infection. Moolten et al. (1953) wrote of three cases in which acute haemolytic anaemia and certain autohaemagglutinative phenomena were associated with a Newcastle Disease viraemia. In two of these there was contact with fowl. In man, however, Newcastle Virus Disease usually manifests itself as an acute transient conjunctivitis, with or without malaise, preauricular adenitis, fever and chills (Hanson and Brandly, 1958). Betke et al. (1953) reported acute acquired haemolytic anaemia in a 3 year old child who ten days earlier had had a Coxsackie A virus infection. Todd and O'Donohoe (1958) recorded the case of a child with acute acquired haemolytic anaemia associated with herpes simplex infection. More recently Mettler et al. (1963) reported from Argentina virus studies on fifteen infants and young children (aged 4 to 30 months) in their series of 58 children with the haemolytic-uraemic syndrome. A complement fixation system was obtained with one of the isolated strains and a significant titre of antibodies was demonstrated. The virus is antigenically related by complement fixation test to the Junin virus and Tacaribe group. Later, Gianantonio et al. (1964) reported on the same fifty-eight cases, where a virus was isolated from the blood of 5 patients and significant viral antibody titres were demonstrated in 15 others during convalescence. The overall mortality was 29%.

Attention has been drawn to the "patchy" incidence of the haemolytic uraemic syndrome by Kibel and Barnard (1964). They point out that it is common in Johannesburg, but is seldom seen in Durban or Cape Town; and while eleven cases have been recognised in Bulawayo, Southern Rhodesia, no case has been seen in the larger city of Salisbury. At a recent paediatric conference McLean (1964) reported on ten cases in a single district in North Wales, where the condition reached near-epidemic proportions in a few weeks. In England Miller et al. (1964) recognised three cases of the disorder in infants in a period of three months. Shinton et al. (1964), in Warwickshire, reviewed in retrospect 9 cases of haemolytic anaemia in children with acute renal disease in the period 1953 to 1961, and 6 may well have had the haemolytic-uraemic syndrome.

This disorder was unknown in the British Isles until 1957 when Allison reported six cases. Recently cases have occurred in Liverpool, Derby, Coventry, Ipswich, Greenwich and Newcastle (Miller, 1964), so it would seem important that all cases of this disorder be investigated as fully as possible, as a common finding might provide a clue to the aetiology. While a virus aetiology is likely the pattern of the

disease suggests that this is not the full explanation. The recent recognition of this syndrome as a separate entity may mean either a true increase of the incidence or increased awareness and better diagnostic facilities.

SUMMARY

Two cases of the haemolytic-uraemic syndrome in infants have been described. Both presented with bloody diarrhoea, vomiting and listlessness, and the characteristic morphological changes in the red cells were associated with proteinuria, hypertension and uraemia.

Both patients were treated with blood transfusions and correction of acidosis, and both made a full recovery.

The literature of the condition has been reviewed.

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