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HAEMOLYTIC ANAEMIA WITH ACUTE RENAL DISEASE

BY

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Haemolytic anaemia is a well-recognized complication of chronic renal failure, but in patients with acute renal disease it is a much less frequent occurrence. The earliest reports were by Hensley (1952), who described 3 patients with glomerulonephritis complicated by haemolytic anaemia, and by Dacie, Mollison, Richardson, Selwyn, and Shapiro (1953), whose patient with 'atypical congenital haemolytic anaemia' was found at necropsy to have 'nephritis'. Attention was drawn to this 'Häematolytisch-urämische Syndrome' by Gasser, Gautier, Steck, Siebenmann, and Oechslin (1955), who described 5 patients. Since then a further 59 case reports have been recorded (Fison, 1956; Aherne, 1957; Allison, 1957; Robertson, 1957; Shumway and Miller, 1957; Loeb, Bartman, Dustin, and Nameche, 1959; Griffiths and Irving, 1961; Lock and Dormandy, 1961; Javett and Senior, 1962; Lamvik, 1962; Gianantonio, Vitacco, Mendilaharzu, Mendilaharzu, and Rutty, 1962). In a review of acute and chronic renal failure with overt haemolytic anaemia by Brain, Dacie, and Hourihane (1962), further cases of this syndrome were included. In these reports renal pathology has varied, and both pathogenesis and aetiology have remained obscure. We have, therefore, considered it of value to study in detail a further 9 patients who have been seen in Coventry hospitals during the past eight years.

Case Reports

Case 1. A 7-year-old boy developed coryza followed two days later by pallor, vomiting, abdominal pain, and oliguria. On admission (February 2, 1953) he was pale and slightly icteric; there was some bruising over the trunk, and hepatosplenomegaly was present. His blood pressure was 100/70 mm. Hg. He was apyrexial.

On admission the haemoglobin was 5·1 g./100 ml.; white cells, 16,000/c.mm.; platelets, 100,000/c.mm.; reticulocytes, 12% of red cells; red cell osmotic fragility, normal; anti-human globulin test, negative; blood urea, 230 mg./100 ml.; serum bilirubin, 1·3 mg./100 ml. Urine examination revealed protein 500 mg./100 ml., red cells, white cells, and numerous granular casts.

Whole blood, 540 ml., was given, the subsequent haemoglobin being 9·5 g./100 ml. Thirty-six hours after admission his temperature was 100·1° F. (37·8° C.). His haemoglobin fell to 4·7 g. A further 540 ml. of whole blood was given, following which the haemoglobin was 7·6 g. In spite of two further blood transfusions, it was not possible to maintain the haemoglobin above 8·5 g./100 ml. Eighteen days after the onset of symptoms his blood pressure rose to 160/120 mm. Hg. He developed retinal haemorrhages, persistent vomiting, and marked oliguria. He died on the 21st day of his illness.

Necropsy showed oedema and effusions into the serous cavities, left ventricular hypertrophy, and petechial haemorrhages, particularly in the cerebral hemispheres. There was iron pigment in both the liver and spleen, which were enlarged. The kidneys were also enlarged and the cut surfaces pale with numerous haemorrhagic striae in both cortex and medulla. Histological examination showed a variable degree of cellular proliferation, mainly of the endothelial cells, in all the glomerular basement membranes, and patchy periodic acid-Schiff staining fibrils which in the axial zones were sometimes nodular (Fig. 1). Occasional capillary thrombi and focal areas of necrosis were present. In some glomeruli there was proliferation of the capsular endothelium with occasional

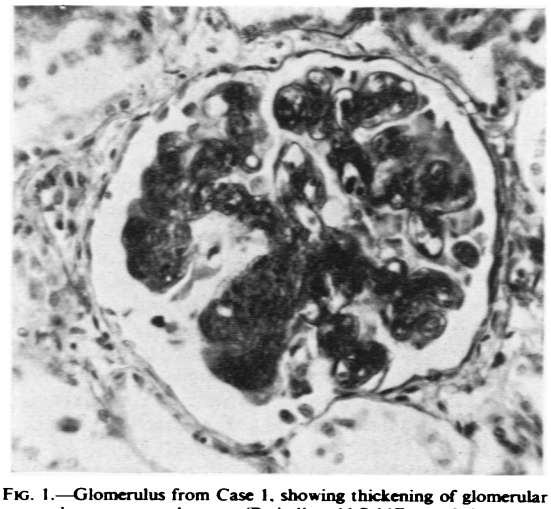

FIG. 1.—Glomerulus from Case 1, showing thickening of glomerular basement-membrane. (Periodic acid-Schiff. × 313.)

crescent formation. The proximal tubules contained protein casts. Some of the afferent arterioles showed fibrinoid necrosis. There were some interstitial haemorrhages in both cortex and medulla.

Case 2. An 8-year-old girl developed sinusitis followed 14 days later by vomiting, epistaxis, purpura and haemorrhages, slight icterus, and collapse. Her temperature on admission (March 13, 1958) was 99·8° F. (37·7° C.). There were no other abnormal physical signs. The liver and spleen were not palpable. There was no oedema, and the blood pressure was 130/85 mm. Hg.

On admission her haemoglobin was 5·0 g./100 ml.; white cells, 12,000/c.mm.; platelets 60,000/c.mm.; reticulocytes, 20% of red cells. The red cell osmotic fragility was increased and the anti-human globulin test was negative; blood urea, 480 mg./100 ml. Urine examination revealed protein 1,500 mg./100 ml., red cells, white cells, and granular casts; haemoglobinuria was also present.

She was given 480 ml. of concentrated red cells, which raised the haemoglobin to 10·2 g. Epistaxis developed followed by haematemesis; blood pressure rose to 140/100 mm. Hg, and blood urea to 536 mg. She was given 20 mg. cortisone daily, but became oliguric, drowsy, and increasingly icteric. On the fourteenth day after admission she died.

Necropsy showed multiple petechial haemorrhages in the brain, respiratory, and gastro-intestinal tracts. There was concentric hypertrophy of the left ventricle. The liver and spleen contained iron pigment, but were of normal size. The kidneys were pale with a few haemorrhagic striae. Histological examination showed focal glomerular lesions which varied from proliferation of capillary endothelium to capillary dilatation. In these glomeruli, protein exudate was present in the capsular space, and there were occasional adhesions but no crescent formations; some showed capillary thrombi and focal areas of necrosis. Most proximal tubules were dilated and contained protein and red cell casts. Some afferent arterioles showed fibrinoid necrosis. There was a little interstitial haemorrhage into both cortex and medulla. In no other organ examined histologically were capillary thrombi found.

Case 3. A 14-week-old male infant was admitted for investigation of acute diarrhoea and vomiting with convulsions on September 6, 1959. He was pale, but there were no other abnormal physical signs.

On admission his haemoglobin was 6·2 g./100 ml.; white cells, 42,000/c.mm.; platelets, 84,000/c.mm.; reticulocytes, 6% of red cells. The red cell osmotic fragility was normal and the anti-human globulin test negative; blood urea, 42 mg./100 ml.; serum bilirubin, 1·7 mg./100 ml. Stained blood films showed red cell polychromasia and erythroblastaemia. Urine examination revealed protein 400 mg./100 ml., large numbers of red cells, white cells, and granular casts.

He was transfused with 250 ml. of concentrated red cells, but became oliguric and died on the sixth day of his illness.

Necropsy showed effusions into the serous cavities and petechial haemorrhages in the brain. There was left ventricular hypertrophy. Iron pigment was present in both liver and spleen, which were of normal size. The kidneys were enlarged, pale, and there were haemorrhagic striae in both cortex and medulla. Histological examination showed glomerular cellular proliferation, which was mainly capsular with crescent formation. In some there was capillary endothelial hypercellularity, and thrombi were also present. The tubules contained protein and red cell casts. The arterioles were normal. There was gross interstitial haemorrhage in all areas. In no other organ examined histologically were capillary thrombi found.

Case 4. An 8-month-old male infant had diarrhoea and vomiting for six days. On admission to hospital (December 2, 1959) he was pale and had hepatosplenomegaly.

On admission his haemoglobin was 5·3 g./100 ml.; white cells, 17,000/c.mm.; anti-human globulin test, negative; blood urea, 104 mg./100 ml.; methaemalbumin, absent; haemoglobin A only. Stained blood films showed red cell polychromasia, burr cells, and erythroblastaemia. Urine examination revealed protein 800 mg./100 ml., red cells, white cells, and granular casts.

He was transfused with 250 ml. of concentrated red cells, which raised his haemoglobin to 11·0 g. His clinical condition improved, and a week later his blood urea had fallen to 60 mg./100 ml., the haemoglobin being maintained at 10·5 g. After 4 weeks his urine was normal apart from a trace of albumin, but his haemoglobin did not return to a normal level for 6 months. During the convalescent period the glucose-6-phosphate dehydrogenase activity of his red cells was 140 units/100 ml.

Case 5. A 6-month-old male infant developed diarrhoea and vomiting which failed to respond to palliative therapy, and he was admitted to hospital 13 days after his illness began (September 16,1960). He was pale; the skin had a yellow hue, and hepatosplenomegaly was present. His temperature was 94·4° F. (34·6° C.).

On admission his haemoglobin was 4·0 g./100 ml.; white cells, 35,000/c.mm.; platelets, 50,000/c.mm.; reticulocytes, 11% of red cells; osmotic red cell fragility, slightly increased; anti-human globulin test, negative; blood urea, 218 mg./100 ml.; serum bilirubin, 1·2 mg./100 ml.; methaemalbumin, absent; haptoglobulin, absent; haemoglobin A only. Stained blood films showed numerous burr and triangular-shaped cells with some spherocytosis and erythroblastaemia (Fig. 2). Heinz bodies were absent. Urine examination showed protein 950 mg./100 ml., red cells, white cells, and granular casts.

He was transfused with 200 ml. of whole blood, but died 24 hours later, 14 days from the onset of his illness.

At necropsy the only macroscopic abnormality was iron pigment deposition in both the liver and spleen, which were of normal size. The kidneys were normal in size and appearance. Histological examination showed numerous hyaline capillary thrombi in many glomeruli. Others showed endothelial proliferation; while some were entirely normal. Small focal areas of the cortex showed

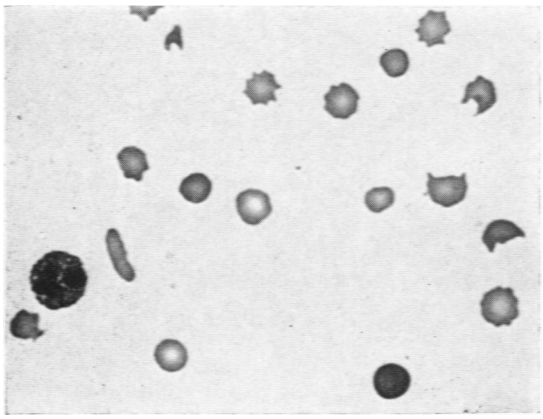

FIG. 2.—Blood film from Case 5 showing red cell fragmentation, burr cells, and spherocytosis. (Leishman. × 800.)

necrosis of glomeruli, and tubules containing protein and red cell casts. Some afferent arterioles showed fibrinoid necrosis. There was no interstitial haemorrhage. In no other organ examined histologically were capillary thrombi found.

Case 6. A 6-month-old female infant developed diarrhoea and vomiting with pyrexia up to 100° F. (37·8° C.). There was, at the time of admission to hospital (October 13, 1960), pallor of the mucous membranes with a slight yellow pigmentation of the skin, but no dehydration. While not palpable at this time, the liver and spleen became enlarged two days later.

On admission the haemoglobin was 5·7 g./100 ml.; white cells, 25,000/c.mm.; platelets, 130,000/c.mm.; reticulocytes, 8% of red cells; red cell osmotic fragility, normal; anti-human globulin test, negative; blood urea, 170 mg./100 ml.; serum bilirubin, 2·0 mg./100 ml.; methaemalbumin, absent; haptoglobin, absent; haemoglobin A only. Stained blood films showed numerous burr cells but no microspherocytes or Heinz bodies. Urine examination showed protein 600 mg./100 ml., numerous red cells, white cells, granular, hyaline, and red cell casts. Bacteriological investigation of the nose, throat, and rectal swabs proved negative, but a specimen of urine yielded haemolytic streptococci of Group G in mixed culture with *Esch. coli* and *Staph. albus*. Direct inoculation of the swabs into monkey kidney tissue cultures failed to yield a cytopathic agent after two passages. In view of the isolation of haemolytic streptococci, nose and throat swabs were later collected from the parents and brother of the patient, but no haemolytic streptococci were isolated. The serum antistreptolysin O titre was 180 units/ml. A second sample collected 14 days later was chylous, and Dr. R. M. Fry of Cambridge, who performed the estimations, considered that the titre was probably about the same as the previous one, though the end-point was difficult to determine.

Two days after admission the haemoglobin had fallen to 3·2 g., and she was given hydrocortisone, 40 mg./day, followed after one day by prednisolone 6 mg./day. Norethandrolone 4 mg./day and penicillin intramuscularly were also given. Feeds consisted of glucose-saline. Within three days there was an improvement in her clinical condition, which was followed by a rise in haemoglobin concentration to 4·8 g./100 ml. and a fall in blood urea to 42 mg. by the twelfth day of the illness. All drug therapy was then stopped, and she was allowed to go home on the 28th day, her haemoglobin having risen to 10 g. When seen a month later this was normal, and her urine contained only a trace of albumin. The glucose-6-phosphate dehydrogenase activity of the red cells at this time was 194 units/100 ml.

Case 7. (R.W.) A 5½-month-old male infant was admitted to hospital (October 25, 1960) having had diarrhoea and vomiting for seven days and pyrexia of 100·6° F. (38·1° C.). Pallor and jaundice were noticed, but no other abnormal physical signs.

On admission the haemoglobin was 3·2 g./100 ml.; white cells, 36,000/c.mm.; platelets, 80,000/c.mm.; reticulocytes, 15% of red cells; red cell osmotic fragility, slightly increased; anti-human globulin test, negative; blood urea, 160 mg./100 ml.; serum bilirubin, 2·6 mg./100 ml.; methaemalbumin, absent; haptoglobin, present; haemoglobin A only. Stained blood films showed marked red cell fragmentation with burr and triangular-shaped cells, but no microspherocytes or Heinz body formation. Urine examination revealed protein 500 mg./100 ml., red cells, white cells, and granular casts. Bacteriological examination of the throat, nose, and faeces revealed no pathogenic organisms. The serum anti-streptolysin O titre was less than 56 units/ml.

The infant was given oxytetracycline 200 mg./day, norethandrolone 4 mg./day, and prednisolone 6 mg./day, this last being reduced after 24 hours to 4 mg./day and two days later to 2 mg./day, when he was apyrexial and showed clinical improvement. The blood urea had then fallen to 80 mg. Improvement continued slowly, and the prednisolone dosage was gradually reduced. After a month, by which time the blood urea had fallen to 65 mg. and the haemoglobin had risen to 10·0 g., all drugs were stopped and he went home. When seen a month later both levels had returned to normal and there was no albumin in the urine. At this time the glucose-6-phosphate dehydrogenase activity of the red cells was 133 units/100 ml.

Case 8. A 6-week-old male infant had severe diarrhoea and vomiting for three days before admission (June 24, 1961). Apart from pallor, there were no abnormal clinical features.

On admission to hospital his haemoglobin was 4·4 g./100 ml.; white cells, 5,000/c.mm.; platelets, 70,000/c.mm.; reticulocytes, 9% of red cells; osmotic red cell fragility, normal; anti-human globulin test, negative; blood urea, 160 mg./100 ml.; serum bilirubin, 2·5 mg./100 ml.; methaemalbumin, present; haptoglobin, absent; haemoglobin A only. Stained blood films showed red cell fragmentation with burr cells but no microspherocytes or Heinz bodies. Urine examination revealed protein 950 mg./100 ml., large numbers of red cells, some white cells,

and many granular casts. Bacteriological examination of the throat revealed no pathogens, but the faeces contained enteropathogenic *Esch. coli* 0128.

He was given feeds of dextrose, oral neomycin, prednisolone 4 mg./day and norethandrolone 125 mg./day, followed by hydrocortisone 25 mg. and another 10 mg. six hours later. Digoxin was also given. In spite of treatment, the infant died on the sixth day of the disease.

Necropsy showed widespread haemorrhages throughout the lungs with blood-stained effusions into the pleural and pericardial sacs. The liver and spleen showed brown pigmentation due to iron deposition. The kidneys were of normal size, but after section the cut surfaces became swollen and haemorrhages into the pyramids could be seen. On histological examination most glomeruli showed marked cellular proliferation, which in some affected the capsular endothelium, giving rise to crescent formation. In some glomerular capillaries hyaline thrombi were present, occasionally associated with focal necrosis. The proximal tubules showed marked degeneration and many contained protein casts; the distal tubules contained numerous red cell casts. There were no changes in the afferent arterioles. There was marked interstitial haemorrhage, particularly into the medulla around the collecting tubules. In no other organ examined histologically were capillary thrombi seen.

Case 9. A 3-month-old male infant developed diarrhoea and vomiting with cough, nasal discharge, and pyrexia, temperature 101° F. (38·3° C.). He was admitted to hospital on the third day of his illness (December 31, 1961) when he was pale and anuric, but apart from a few râles in the chest, there were no other abnormal clinical features.

On admission his haemoglobin was 8·6 g./100 ml.; white cells, 28,000/c.mm.; platelets, 80,000/c.mm.; reticulocytes, 8% of red cells; osmotic red cell fragility, normal; anti-human globulin test, negative; blood urea, 278 mg./100 ml.; serum bilirubin, 0·3 mg./100 ml.; methaemalbumin, present; haptoglobin, absent; haemoglobin A only; glucose-6-phosphate dehydrogenase activity of the red cells, 65·5 units/100 ml. Stained blood films showed gross red cell fragmentation with burr cells, but without microspherocytosis or Heinz body formation. Bacteriological examination of the throat and faeces showed no pathogenic organisms.

The infant was treated with penicillin intramuscularly, hydrocortisone 10 mg. intramuscularly, followed by oral prednisolone 4 mg./day and norethandrolone 2 mg./day. He was given oral fluids. There was no response to treatment; the nasal discharge increased and he developed gross oedema of face. He died on the tenth day of his illness.

Necropsy showed considerable oedema of all tissues, particularly the lungs, in which pneumonic consolidation was also present. Dilatation of both cardiac ventricles was present. Both liver and spleen were soft and showed brown pigmentation due to iron deposition. The kidneys were swollen and had marked haemorrhagic striae in the cortices. Histological examination showed widespread areas of necrosis involving both glomeruli and tubules (Fig. 3). Outside these areas some glomeruli showed capillary endothelial proliferation, associated in a few with hyaline thrombi and focal necrosis; some tubules contained protein casts. The afferent arterioles were normal. There was some interstitial haemorrhage. Capillary thrombi were not found in any other organ.

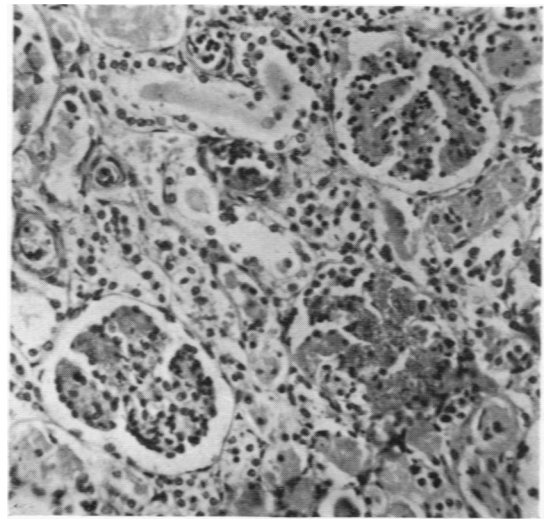

FIG. 3.—Renal cortex from Case 9 showing complete and focal necrosis of glomeruli. (H. and E. · 190.)

Discussion

Clinical Features. In this series all 9 cases were children; 7 were under 1 year old, the youngest being only 6 weeks (Table 1). Of those previously reported over 75% were infants, and of the remainder all but one adolescent of 19 years (Hensley, 1952) were children under 10 years of age. However, in their review of 25 cases of renal failure with this syndrome, Brain *et al.* (1962) reported 11 adults, but did not distinguish between those with acute and those with chronic renal disease. Of our cases 7 were boys and 2 were girls, but of the 68 cases previously recorded there was no difference in sex incidence, 34 being male and 34 being female.

As a presenting feature, pallor was prominent in all cases, 6 also having an icteric tinge. Only the 2 older children (Cases 1 and 2) had haemorrhagic manifestations such as purpura, petechial haemorrhages, and epistaxis, but these were features in over one-third of the previously reported cases. Haematemesis, melaena, and haematuria have been recorded but, unlike patients with Goodpasture's syndrome, haemoptysis has not been reported as a presenting feature. The most important presenting syndrome in the infants of all series is vomiting and diarrhoea, this often leading to an initial diagnosis of

TABLE 1
CLINICAL FEATURES

Case No.	1	2	3	4	5	6	7	8	9
Sex	M	F	M	M	M	F	M	M	M
Age	7y.	8y.	3m.	8m.	6m.	6m.	5m.	1m.	3m.
Pallor	+	+	+	+	+	+	+	+	+
Jaundice	+	+	−	−	+	+	+	+	−
Diarrhoea and vomiting	+	+	+	+	+	+	+	+	+
Pyrexia	+	+	−	−	−	+	+	−	+
Respiratory infection	+	+	−	−	−	−	−	−	+
Convulsions	−	−	+	−	−	−	−	−	−
Oliguria	+	+	+	−	−	−	−	−	+
Oedema	−	−	−	−	−	−	−	−	+
Hypertension	+	+	−	−	−	−	−	−	−
Hepatomegaly	+	−	−	+	−	+	−	−	−
Splenomegaly	+	−	−	+	−	+	−	−	−
Haemorrhagic manifestations	+	+	−	−	−	−	−	−	−

infective gastro-enteritis. In no case have these symptoms been severe enough to cause dehydration, neither have they persisted longer than three to four days. About half were febrile, the temperature rarely rising above 101° F. (38·3° C.). Three cases in the series (Cases 1, 2, and 9) had respiratory infections either immediately before or during the development of the disease, this being a not infrequent occurrence in other series of cases. In a few this has progressed to bronchopneumonia (Case 9) or otitis media (Lock and Dormandy, 1961). One of our children had convulsions (Case 3), this having previously been seen in cases of Allison (1957), Loeb *et al.* (1959), Lock and Dormandy (1961), Griffiths and Irving (1961), Javett and Senior (1962), Lamvik (1962), and Gianantonio *et al.* (1962). Anuria occurred in one baby (Case 9), and oliguria was an early feature of the two older children (Cases 1 and 2) and of about half of those previously reported. It could have been unnoticed in the infants. Oedema was found in only one of our cases (Case 9), but was present in about a quarter of those previously reported, occurring particularly with bilateral cortical necrosis of the kidney (Gasser *et al.*, 1955). Hypertension developed in the two older children, the boy (Case 1) also developing retinal haemorrhages. This was a feature occasionally present in the previously reported infants and children (Dacie *et al.*, 1953; Aherne, 1957; Griffiths and Irving, 1961; Gianantonio *et al.*, 1962).

Splenomegaly and hepatomegaly are variable features in all series.

Laboratory Findings

URINE (Table 2). All cases, except the infant who was admitted with anuria, had proteinuria, the amount varying from 500 mg. to 1,500 mg./100 ml. (Case 2). Red cells in varying numbers, white cells, and granular and hyaline casts were present in each case. The older girl (Case 2) and those described by Gasser *et al.* (1955) had haemoglobinuria.

BLOOD (Table 3). The haemoglobin level, on admission, varied from 3·2 to 8·6 g., with an average

TABLE 2
URINE FINDINGS

Case No.	1	2	3	4	5	6	7	8
Protein (mg./100 ml.)	500	1.500	400	800	950	600	500	950
Red cells	+	+ +	+ + +	+ +	+ +	− +	+	+ + +
White cells	+	+	+	+	+	+	+	+
Granular casts	+ +	+ +	+	+	+	+ +	+ +	+ +
Haemoglobin	−	+	−	−	−	−	−	−

Case 9 suffered from anuria

TABLE 3
BLOOD FINDINGS

Case No.	1	2	3	4	5	6	7	8	9
Haemoglobin (g./100 ml.)	5·1	5·0	6·2	5·3	4·0	5·7	3·2	4·4	8·6
W.B.C. (thous./c.mm.)	16	12	42	17	35	25	36	5	28
Platelets (thous./c.mm.)	100	60	84	—	50	130	80	70	80
Reticulocytes (% R.B.C.)	12	20	6	—	11	8	15	9	8
Blood urea (mg./100 ml.)	230	480	42	104	218	170	160	160	278
Serum bilirubin (mg./100 ml.)	1·3	—	1·7	—	1·2	2·0	2·6	2·5	0·3
Methaemalbumin	—	—	—	Neg.	Neg.	Neg.	Neg.	Pos.	Neg.
Haptoglobin	—	—	—	—	Neg.	Neg.	Pos.	Neg.	Neg.

of 5·8 g./100 ml. Along with the fall in haemoglobin, there was a parallel drop in the packed cell volume, resulting in a normochromic anaemia. Polychromasia, sometimes with erythroblastaemia, was an almost constant feature of the stained films. The level of reticulocytosis was variable, with a range of 8 to 20% of red cells. A striking feature was the occurrence of burr and triangular-shaped red cells (Fig. 2). Similar cells were first described by Schwartz and Motto (1949) in cases of renal failure, gastric carcinoma, and bleeding peptic ulcer; and Aherne (1957) noticed that in the present syndrome they varied with the level of the blood urea. They were termed pyknocytes by Tuffy, Brown, and Zuelzer (1959), who found them in normal infants up to the age of 12 weeks. In view of their constancy in the series reported by Lock and Dormandy (1961) they gave to the condition of haemolytic anaemia with renal failure the name 'red cell fragmentation syndrome'. Microspherocytes, a striking feature in cases of acquired haemolytic anaemia, are only occasionally seen. Likewise, the red cell fragility is only rarely increased and the direct anti-human globulin test is usually negative. The latter test has, however, been reported by Brain *et al.* (1962) as weakly positive in three cases with this syndrome.

A polymorphonuclear leucocytosis was present in all but one of our patients, and thrombocytopenia of some degree was present in all those where a platelet count had been performed. This was also the finding in the previously reported cases, the average platelet level being around 80,000/c.mm. Particularly low numbers were reported in cases of Allison (1957) and Javett and Senior (1962).

The level of bilirubin tended to vary inversely with the level of haemoglobin: the highest figure recorded was 2·6 mg./100 ml. When raised, it was always in the unconjugated form. Methaemalbumin was found in the serum in only one out of six cases, but haptoglobin was absent in four out of the five sera tested. The blood cells of Case 9 were examined during the acute phase for activity of the enzyme glucose 6-phosphate dehydrogenase, a level of 65·5 units/100 ml. being recorded (lower limit of normal, 120 units). The three cases who recovered had normal levels of activity during their convalescent period.

All but one patient had some degree of azotaemia, the levels ranging from 160 to 378 mg./100 ml. The infant whose level was reported as 42 mg./100 ml. died a few days later and the kidneys showed extensive glomerulonephritis, so this single reading must be regarded with suspicion. Of the previously reported cases, higher levels tended to occur in the older children and adults, though one infant (Case 2, Lock and Dormandy, 1961) had a blood urea of 630 mg./100 ml.

Renal Pathology. The most striking lesions seen in the kidneys of the six cases who died affected the glomeruli. In 3 (Cases 2, 4, and 9) not all of the glomeruli were abnormal, and in some the lesions were confined to an area within a single capillary tuft. All, however, showed some degree of endothelial proliferation, this being particularly marked in the capsular endothelium of Case 3. The capillary basement membrane showed marked thickening in Case 1 (Fig. 1). Exudate into the capsular space with adhesions was seen in one (Case 2), and crescent formation was present in two (Cases 1 and 3). Intracapillary thrombi were a constant feature, being the most prominent in Case 5. They were sometimes associated with necrosis, either affecting whole areas of cortex, single glomeruli (Cases 5 and 9—Fig. 3), or part of a glomerulus (Case 8). Some degree of tubular necrosis was present in each case, but as all specimens were obtained at necropsy after autolysis had taken place, its importance is difficult to ascertain. Protein and red cell casts were a common feature. In both of the older children (Cases 1 and 2) who developed clinical evidence of hypertension, the afferent arterioles showed fibrinoid necrosis, this also being seen in one baby (Case 4). Interstitial haemorrhage was present in those who had thrombocytopenia.

The development of crescent formation and arteriolar necrosis in cases of acute renal disease was described by Ellis (1942) under the heading, 'Rapidly progressive type of glomerulonephritis'. Capillary thrombi in the glomerular tufts have been described in cases of acute proliferative glomerulonephritis by Bell (1946) but as a special feature of a particular group of cases. The frequency of their association with haemolytic anaemia seems to be more than coincidence. Of the 30 previously reported cases where histological examination of the kidneys was made, 14 were regarded as having changes of glomerulonephritis. In only 2 of these were the presence of capillary thrombi specifically mentioned (Fison, 1956). One case of Hensley and 3 of Gianantonio *et al.* (1962) had an acute necrotizing inflammatory process. A case of Lamvik (1962) showed hyaline necrosis of capillaries which contained amorphous material. These lesions have similarity to some of the present series and also to polyarteritis nodosa (Davson, Ball, and Platt, 1948). The occurrence of cortical necrosis of the kidneys in cases with this syndrome was found by Gasser *et al.* (1955), Lock and Dormandy (1961), and Gianantonio *et al.* (1962). In 4 cases reported by Allison (1957)

and in 1 each by Gasser *et al.* (1955), Shumway and Miller (1957), and Loeb *et al.* (1959) there were 'platelet thrombi' similar in appearance to the hyaline capillary thrombi seen in Case 5. Such lesions are similar to the thrombotic occlusions of arterioles and capillaries in cases of thrombotic thrombocytopenic purpura (Gore, 1950). In this disorder, however, acidophilic material is also seen beneath the endothelium and may replace the media and adventitia of the vessels. These changes may be present without local thrombosis. No lesions of this nature were seen in any of the kidneys studied in the present series.

Pathogenesis and Aetiology. The mechanism of acute haemolysis in these patients remains open to conjecture. It is not due to any of the more common causes such as hereditary spherocytosis, haemoglobinopathy, chemical poisons, burns, or septicaemia. The not infrequent incidence of a respiratory tract infection before its development and the frequency of gastro-intestinal disturbances suggest that an infective organism may have given rise to a hypersensitivity state. The failure to demonstrate coating of the red cells by globulin in the majority of cases makes this hypothesis doubtful as a cause of haemolytic anaemia. The possibility that the haemolytic anaemia is secondary to the renal disease is more likely. Diminution of red cell life span, with consequent anaemia, has been shown to occur in cases with chronic renal failure (Chaplin and Mollison, 1953). The presence of burr cells has always been associated with azotaemia, though it can occur in other disorders, and Tuffy *et al.* (1959) found them physiologically in infants up to the age of 12 weeks. These authors also described 11 infants with a severe haemolytic anaemia in which 50% of the red cells were fragmented. None of these infants showed any evidence of renal failure; neither were any of the known causes of increased haemolysis detected. These findings correlate with the known susceptibility of some infant erythrocytes to damage by a variety of agents, of which the water soluble analogues of vitamin K are an example. This has been shown to be due to deficiency of a red cell enzyme, glucose-6-phosphate dehydrogenase. An excess of this enzyme was found by McMichael (1961) in the affected kidney of renal ischaemia, with a corresponding deficiency in other body tissues. It is, therefore, tempting to postulate in Case 9, where a sub-normal level of this enzyme was found, a disturbance of red cell enzyme function as the cause of the haemolytic anaemia. Furthermore, in this infant the degree of anaemia was the least severe, so that in those not tested even lower levels might have been obtained. The presence of normal levels in the four survivors excludes the possibility of an hereditary deficiency of this enzyme. Further investigation of this and other red cell enzymes might prove of value in the elucidation of this type of haemolytic anaemia.

After considering the possibility of a red cell enzyme disturbance in this condition, Brain *et al.* (1962) discounted the hypothesis because the severity of the anaemia has little or no correlation with the degree of azotaemia, a fact borne out by the biochemical findings in our cases (Table 2). These authors also found absence of correlation between the number of burr cells in the peripheral blood, the blood urea level, and the degree of anaemia. They suggested that the haemolytic anaemia was related to the vascular abnormalities and that possibly the red cells were destroyed by their contact with the diseased capillary walls. While such a mechanism remains obscure, the high incidence of vascular lesions in the kidneys of the six cases histologically examined in this series strongly supports the thesis of direct relation between these lesions and the haemolytic anaemia and thrombocytopenia.

Renal lesions associated with acute haemolysis, such as are seen following incompatible blood transfusions, affect mainly the tubules rather than the glomeruli. This also applies where a haemolytic anaemia with renal damage has occurred as a direct toxic effect of heavy metals or of such drugs as phenacetin or sulphonamides. It seems unlikely, where the renal damage is mainly glomerular, that these changes are secondary to the haemolytic anaemia. The histological appearances are, however, varied and do not conform with any single pathological type of renal disorder, but their closest resemblance is to the lesions seen in cases of acute glomerulonephritis. Cortical necrosis is not usually associated with this disorder and where present is probably a result of arteriolar thrombosis. The association of capillary lesions with haemolytic anaemia and thrombocytopenia suggests a relation with thrombotic thrombocytopenic purpura, but here the vascular lesions are widespread and they differ histologically from those in the present disorder. Apart from the incidence of haemorrhage in patients with nephritis there is little similarity with Goodpasture's syndrome, where bleeding occurs exclusively into the lungs without evidence of thrombocytopenia or haemolytic anaemia (Rusby and Wilson, 1960). It does seem likely, however, that the lesions in all these disorders are reactions to circulating antigen-antibody complexes, and in this way they may be related to those seen in systemic lupus erythematosus and polyarteritis nodosa.

The aetiology of the disease remains obscure. No

familial or predisposing features are evident. While a prodromal respiratory tract infection is frequent, no bacterial or viral agent likely to cause the disease has been identified in this or any other series. The occurrence of 9 cases of a comparatively rare disease in one district, 3 of whom lived in the same town and were admitted to hospital within a period of two months, suggests an epidemiological relation. This could not be established. If the renal changes are due to a circulating antigen-antibody complex, consideration must be given to possible sensitizing antigens. In the cases examined there was no rise in the anti-streptolysin O titre, as is found in some cases of glomerulonephritis, but further investigation for this and for an immune response to viral agents should be considered in future cases. Hypersensitivity to drugs is a further possibility. This has been established as a cause of proliferative glomerulonephritis; and drug hypersensitivity has been known to exist in cases of polyarteritis nodosa and of thrombotic thrombocytopenic purpura (Wile and Sturgeon, 1956). In all of these conditions sulphonamides have been most frequently implicated, but cases of penicillin hypersensitivity have been described (Gendel, Young, and Kraus, 1952; Rich, 1958). None of the patients in the present series had received sulphonamides or penicillin before admission to hospital, but in at least 4 cases some other form of antibiotic had been administered. While there remains no supporting evidence for this hypothesis, investigation for the presence of drug antibodies in the sera of future cases might be of value. As the condition is mainly a disease of infancy, the possibility of food allergy might also be considered. It is unlikely, however, that a single aetiological agent is responsible for all cases, and more likely that the syndrome is a response to a variety of sensitizing antigens in a constitutionally predisposed individual.

Prognosis and Treatment (Table 4). In the 6 cases that ended fatally, renal failure was the immediate cause of death. Analysis of the previously reported cases and those presented here shows that the degree of azotaemia is of the greatest prognostic importance. All the patients with an initial blood urea level of over 260 mg./100 ml. died; whereas the majority of the survivors had initial levels below 200 mg. The haemoglobin concentration, on the other hand, had little prognostic importance. One baby (Case 8) died within four days of onset without the haemoglobin falling below 8·6 g./100 ml., while two babies who survived (Cases 6 and 7) had haemoglobin levels as low as 3·2 g. at some stage of their illness. Haemorrhage due to thrombocytopenia is rarely a cause of death, and platelet counts as low as 25,000/c.mm. have occurred in cases that have survived (Javett and Senior, 1962). Neither the age of the patient nor the development of hypertension has any importance with regard to prognosis.

In fatal cases death usually occurs within three weeks of the onset of illness, the average duration of the disease being only six days. An illness of two years with death from renal failure occurred in the case reported by Dacie *et al.* (1953). Those that survive usually improve rapidly, the average time from onset to clinical recovery being six weeks, but

TABLE 4
TREATMENT AND SUBSEQUENT COURSE

Case No.	Treatment	Outcome
1	Blood transfusion 3rd, 5th, 14th, and 20th days	Died 21st day
2	Blood transfusion 3rd day; cortisone 10th day onwards	Died 14th day
3	Blood transfusion 4th day	Died 6th day
4	Blood transfusion 3rd day	Recovered rapidly; 10th day, blood urea: 60 mg. 100 ml., Hb: 10·5 g./100 ml. 4 weeks, blood urea: 45 mg./100 ml., Hb: 12·8 g./100 ml. urine: albumin trace
5	Blood transfusion 13th day	Died 14th day
6	Hydrocortisone 4th day; prednisolone 5–12th day; penicillin G 5–12th day; norethandrolone 5–12th day	Recovered rapidly; 12th day, blood urea: 42 mg./100 ml. Hb: 4·8 g./100 ml. 4 weeks, Hb: 10 g./100 ml.; urine: albumin trace
7	Prednisolone 2–36th day; terramycin 2–36th day; norethandrolone 5–18th day	Recovered gradually 4 weeks, blood urea: 65 mg. 100 ml.; Hb: 10 g./100 ml. urine: no albumin
8	Prednisolone 2nd day onwards; neomycin 2nd day onwards; norethandrolone 2nd day onwards	Died 6th day
9	Hydrocortisone 2nd day; prednisolone 3rd day onwards; penicillin G 2nd day onwards; norethandrolone 3rd day onwards	Died 10th day

proteinuria may persist in some for six months. One case of Shumway and Miller (1957) had recurrences over a period of nine months before gradually making a complete recovery.

It follows that treatment must be primarily aimed at mitigating the effects of renal failure. In all our cases control of fluid and electrolyte balance was attempted with attention also to the maintenance of an adequate caloric intake. An anabolic agent, norethandrolone, was given to four of the infants (Cases 6, 7, 8, and 9), two of whom died. McCracken and Parsons (1958) have suggested that these agents have benefit only in cases where acute renal failure occurs as a complication of pregnancy, probably as a result of their progestational activity.

The place of blood transfusion is difficult to determine. In the present series only 1 patient who was given blood recovered, whereas 2 out of 4 not transfused did recover. Other authors have had more success with this form of treatment, Allison (1957) advocating its use when the number of burr cells seen in the stained blood film showed any increase. Of the 6 cases he treated in this way, 4 survived, the highest level of blood urea being 125 mg./100 ml. Analysis of all the previous case reports shows that following blood transfusion half survived. While death has supervened in the remainder, there is no evidence to suggest that this was related to the transfusion, and the consistent absence of blood group antibodies in this disease removes this factor as a possible objection to transfusions of concentrated cells given slowly, which may be a valuable supportive measure.

Steroids were given to 4 cases in our series, 2 of whom survived. While they have been used in previously reported cases (Hensley, 1952; Gasser *et al.*, 1955; Griffiths and Irving, 1961; Javett and Senior, 1962), blood transfusion has also been administered at the same time so that a separate assessment of their effects is difficult. If the disease is accepted as a hypersensitivity state, then steroids should be beneficial.

Splenectomy has been performed in three cases (Dacie *et al.*, 1953; Allison, 1957; Shumway and Miller, 1957). Though the case reported by the latter authors survived, there is no indication that this was a direct outcome of the operation which does not appear to have any place in the treatment of this type of haemolytic anaemia.

Exchange transfusion and peritoneal dialysis have been recommended by Gianantonio *et al.* (1962), but while they report good clinical responses, the survival rates of their cases were no better than in other series. In one severely uraemic child, however, extracorporeal dialysis resulted in subsequent recovery. It therefore seems rational to use blood transfusion as a supportive measure and haemodialysis if renal failure persists.

Summary

Nine patients with the syndrome acute haemolytic anaemia with fragmentation of red cells, thrombocytopenia, and acute renal disease are described, and the relevant previous case reports reviewed.

The syndrome is almost completely confined to childhood and is more frequent in infancy. Both sexes are equally susceptible.

Pallor, with gastro-intestinal disturbance, is the most common presenting feature. The possibility of renal failure must be considered in infants and children who develop these symptoms.

The onset is fulminating, death occurring within a few days in about half the cases diagnosed.

The renal lesions are variable, but vascular abnormalities, particularly thrombi in the glomerular tufts and areas of cortical necrosis, are frequent.

The aetiology and pathogenesis remain obscure, but the renal lesions are probably the result of an antigen-antibody reaction. The haemolytic anaemia and thrombocytopenia are more likely to be the result of the vascular lesions in some unexplained manner.

In the more severely affected treatment of the renal failure by dialysis is recommended; in the less severely affected small transfusions of concentrated red blood cells are advised. Steroid therapy may have a place in treatment.

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