The Haemolytic-Uraemic Syndrome of Infancy and Childhood

A REPORT OF ELEVEN CASES

BY

P. J. BARNARD, M.D., M.R.C.P. (Edin.)

AND

M. KIBEL, M.B., B.CH. (Rand.), M.R.C.P. (Edin.), D.C.H.

The Medical Research Centre, Bulawayo, Rhodesia.

PART II

A list of references is given at end of Part II.

We now examine here some mechanisms capable of explaining the haemolytic-uraemic syndrome.

Thrombotic thrombocytopaenic purpura (TTP, also known as micro-angiopathic haemolytic anaemia, with or without the prefix "thrombotic" (Symmers; 1952; Brain *et al.*, 1962).

A close parallel may be drawn between this condition and the haemolytic-uraemic syndrome of infancy and childhood, but there are important points of difference. Diarrhoea is far from being common in TTP, as it is in the haemolytic-uraemic syndrome. Uraemia is a dominant feature of this syndrome; it is found at the start of the illness and is a grave clinical problem up to recovery or death. In TTP, by contrast, though renal involvement is almost invariable, uraemia is not a consistent element in the disease. Renal cortical necrosis is common in the haemolytic-uraemic syndrome, but rare in TTP among adults. Cases of the syndrome recover in substantial numbers; TTP is almost invariably fatal. Neurologic disturbance is an early and persistent element of TTP, but in our cases this was a terminal event. In Rhodesia and South Africa the syndrome has occurred in clusters of cases. This would be strange behaviour for TTP, a condition regarded by most as a "collagen" disease. During a period of some seven years in this city the authors know of only one probable case of TTP in an adult. MacWhinney *et al.* (1962) have reviewed reports of TTP in childhood and described two cases of their own. These cases did not resemble ours. Cases 4 and 5 of Allison (1957), aged two and six months respectively, had diarrhoea and the blood alterations which TTP may have in common with the haemolytic-uraemic syndrome. They lived only a few days, and at necropsy the diagnosis of TTP was made. In our view, however, these cases could just as well now be ascribed to the haemolytic-uraemic syndrome from comments already made here, and some others to follow (McKay and Wahle, 1954).

The microscopic form of polyarteritis nodosa is another condition in which haemolytic anaemia, thrombocytopaenia, nephropathy and abnormally shaped erythrocytes may be found in association. It does not occur in "runs." Further characteristics are acute necrotising arteritis with inflammatory reaction affecting mainly renal arteries of interlobular size or larger; necrosis of glomeruli and peri-glomerulitis are accompanying features (Brain *et al.*, 1962; Davson *et al.*, 1948). Changes like these seem to be exceptional in the haemolytic-uraemic syndrome of young subjects.

The generalised Saranelli-Shwartzman phenomenon. There is an experimental model for cases of the haemolytic-uraemic syndrome in which the renal lesion is cortical necrosis. Such necrosis is characteristic of the Saranelli-Shwartzman phenomenon in rabbits and is associated with intraglomerular deposition of material staining as fibrin or fibrinoid (Thomas and Good, 1952; Good and Thomas, 1953; Thomas *et al.*, 1953). Disseminated intravascular thrombosis contributes to the phenomenon (McKay and Shapiro, 1958). Cases of the generalised phe-

nomenon with renal cortical necrosis have been recognised in human adults (McKay *et al.*, 1959; Graber *et al.*, 1960; Matthes, 1962), and Shumway (1962-63) has pointed out the resemblance between the haemolytic-uraemic syndrome with renal necrosis and this phenomenon.

In cases of the haemolytic-uraemic syndrome in young subjects in whom renal necrosis was absent, there is, however, no matching model. Rabbits either die with renal necrosis or they recover, and no renal lesions except intravascular thrombi in some instances are discovered. Also, the incessant haemolysis and thrombopaenia, and the distorted erythrocytes so typical of the human syndrome, are missing in the rabbit.

In a condition as puzzling as the haemolytic-uraemic syndrome of young subjects, hypothesis is permissible. Restricting ourselves to cases as seen in Rhodesia and South Africa, a plausible hypothesis would need to account for the following central features: relationship of the illness to diarrhoea, the intestinal lesions, the renal lesions, damage to vascular endothelium elsewhere (as in brain and heart), continuous haemolysis with bizarre erythrocytes and thrombocytopaenia.

Saranelli, whose experiments antedated those of Shwartzman, gave rabbits an intravenous injection of live cholera vibrios and 24 hours later an intravenous injection of sterile filtrate from *E. coli* or *proteus* organisms. Most of the animals died with haemorrhagic intestinal lesions and renal cortical necrosis (Thomas and Good, 1952). We postulate that some cause of diarrhoea in infants and young children, as, for instance, some strain of pathogenic *E. coli*, acts as a general preparatory factor for a reaction akin to that of Saranelli. It is well known that some strains of the same organism have little or no potency as preparatory factors. The Saranelli-Shwartzman phenomenon has been responsible for death in infantile diarrhoea due to *E. coli*, type O-111 (McKay and Wahle, 1954). At necropsy there was intestinal inflammation with oedema, ulceration and haemorrhage and fibrin deposition in capillaries and arterioles of many organs, particularly the kidneys. These cases (McKay and Wahle, 1954) and Cases 4 and 5 of Allison (1957) could have been of this type and suggest connecting links with ours. The failure to isolate pathogenic organisms from all but one of our cases might derive from the fact that the patients had been ill for at least a week before we saw them and all had received sulphonamides or antibiotics for the diarrhoea. Subsequent absorption from damaged gut of some antigen, not necessarily from a pathogenic organism, then challenges the vasculature at large. The case reported by Graber *et al.* (1960), in which the Saranelli-Shwartzman phenomenon followed septic burns, is relevant to our atypical case, there having been no initial diarrhoea, but infected burns of the hands instead. The kidneys, because of their concentrating function, are especially at risk. Depending upon intensity of action, kidneys will either undergo cortical necrosis or survive to develop lesions other than necrosis. Too little is known of Saranelli-Shwartzman responses in man to conclude that renal lesions necessarily follow the "all-or-none" pattern observed in rabbits. In view of the characteristic pattern of onset followed by cases of the haemolytic-uraemic syndrome in Rhodesia and South Africa, it is reasonable to think that one is dealing, at least in this particular group of cases, with the same disorder, whether or not the renal lesion is cortical necrosis. We have recently seen slides from a case diagnosed in South Africa in which incomplete bilateral renal cortical necrosis was present. Surviving renal tissue showed proliferative glomerular and vascular changes similar to those found in our cases, thus providing a link between the cases with complete cortical necrosis and cases without cortical necrosis, but with proliferative glomerulonephritis. Utian (1963) has reported two similar cases, there being incomplete cortical necrosis and adhesions between glomeruli and Bowman's capsules. Shumway (1962-63) mentions intestinal lesions in three cases. This was also found in three of ours, all of whom had diarrhoea, but was not found in our fifth fatal case or in the fourth, which had no diarrhoea but a history of upper respiratory infection and septic burns to the hands. We believe that inflammation of the bowel in the cases here reported played an early and probably causative part, and consider it most unlikely that diarrhoea was entirely a result of the arterial lesions. These lesions could have resulted from the same process that caused arterial lesions in the kidneys, or they could have arisen from the action of local factors. We surmise that on challenge, renal arterioles contract and they, as also glomerular capillaries, undergo ischemic and perhaps toxic damage as well. This leads to local clotting with deposition of fibrin, but in conformity with animal experiments, fibrin embolism is also probable. Damaged but viable endothelium and epithelium react by proliferation, the intensity of which varies from case to case. Subsequently the products of cellular proliferation and degeneration may be-

come superadded to confuse interpretation by means of stains. Of special interest in some cases is glomerular capillary blockage by distorted erythrocytes with subsequent "sludging" of these cells.

It is reasonable to expect a variable renal picture, depending upon features such as intensity of inflammatory response, its duration and whether recurrent, amount of fibrin deposition and extent of red cell sludging. So far we have not invoked the aid of immune responses. Vassalli *et al.* (1963) have studied the nephropathy due to intravascular coagulation in rabbits, brought about by a number of different clotting agents. The lesions found covered the gamut of changes in the cases here reported. Of special interest was their observation that deposition of fibrin led to progressive glomerular obliteration, when massive or repeated deposits were produced. They also described transitional forms between fibrin and fibrinoid in the glomeruli. There is also evidence that thromboplastin and thrombin are able to elicit glomerular changes resembling those of toxaemia of pregnancy (Hopper *et al.*, 1961).

The early age at which the haemolytic-uraemic syndrome has arisen in many subjects militates against a mechanism like that accepted for classical glomerulonephritis, which condition is exceptional in the very young. Nevertheless it cannot be excluded that such reactions played a part in patients surviving some weeks. Immune complexes also produce considerable deposition of fibrin in experimental animals (McCluskey and Vassalli, 1963; Lee, 1963).

Little is presently known concerning the cause of the haemolytic anaemia and the bizarre erythrocytes, which have been described as contracted, distorted, fragmented or as schistocytes, triangular, helmet and burr cells. These abnormalities are not necessarily ascribable to uraemia, though presence of diseased kidneys is common. They have been observed also in carcinomatosis, malignant hypertension and, in a case where a jet of blood impinged upon a "Teflon" graft, used to repair an interatrial septal defect (Sayed *et al.*, 1961). Both the haemolytic anaemia and the distorted erythrocytes disappeared following further surgical repair. Three children have since been described who had severe haemolytic anaemia with fragmented red cells, following surgical correction of atrioventricular canal defects (Sigler *et al.*, 1963). It was concluded that these cases represented prototypes of mechanical haemolysis hitherto studied only *in vitro*. We think that some such mechanism operated in our cases, its basis being vascular damage in the kidneys and elsewhere. Antiglobulin tests on the erythrocytes of our cases were negative, as in the vast majority of reported cases. Gasser *et al.* (1955) reported a positive Coombs test in one of their cases. Haemolysis was apparently not influenced by corticosteroids in the four cases of ours in which this treatment was tried.

The low platelet count of the haemolytic-uraemic syndrome may be due to excessive consumption of platelets from adhesion to damaged endothelium and perhaps also to intravascular coagulation. There is no evidence that platelet production is diminished, for marrow megakaryocytes are normal in appearance and increased in numbers, nor is there any laboratory support for a lytic mechanism (Brain *et al.*, 1962).

SUMMARY

Eleven cases of the haemolytic-uraemic syndrome in patients aged five to 36 months, including one in an African, have been reported here. Ten of these followed a similar pattern characterised by diarrhoea, acute renal failure, haemolytic anaemia with distorted erythrocytes and thrombocytopaenia. One case was atypical because there was an antecedent history of upper respiratory infection and recent septic burns to the hands.

The racial and geographic distribution of the syndrome in Southern Africa has been described and reasons given for our opinion that it constitutes a definite disease of common pathogenesis. The usefulness of peritoneal dialysis in the management of this condition is stressed.

The pathologic changes in the five cases who died have been given and proposals concerning pathogenesis critically discussed. An hypothesis, that the haemolytic-uraemic syndrome of young subjects with and without renal necrosis is basically a reaction akin to the generalised Sarinelli-Shwartzman phenomenon, has also been outlined.

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