In seven patients low titre L.K.M. antibodies were found in the absence of any evidence of liver disease and in two of these their appearance was temporary. All but one of these patients suffered from collagenoses or thyroid autoimmunity. In this context it is interesting that in half of all patients having L.K.M. antibodies, irrespective of diagnosis, thyroid or gastric organ-specific antibodies also occurred. The identity of these antibodies could be shown by selective absorption of the thyroid or gastric immunofluorescent, leaving intact that due to the L.K.M. The L.K.M. antibody with its restricted organ reactivity may represent an intermediate form of auto-immunity between the strict organ specificity of the thyroiditis/gastritis/adenitis group of disorders and the complete non-organ specificity of such autoantibodies as A.M.A. and A.N.A.

Studies are in progress to attempt a separation of L.K.M.-associated active chronic hepatitis by tissue typing (Mackay and Morris, 1972) and the incidence of high titre viral antibodies, including rubella, measles, and herpes (Triger et al., 1972), from the largest group of active chronic hepatitis patients who show no autoimmunity or HBAg and from the subgroups associated with high titres of A.N.A. and S.M.A. and those showing A.M.A. in the serum.

We thank Dr. Dudley Tee of the department of experimental pathology at King's College Hospital for the immunoglobulin measurements and Dr. Richard Stern for the statistical analysis. Dr. W. D. Reed kindly made available the comparative data from a series of chronic active hepatitis cases. We also thank Mr. and Mrs. G. Swan for their skilled technical help.

ADDENDUM

Since this paper was submitted further information on the clinical significance of the L.K.M. antibody has come from Dr. J-C. Homberg, of Paris. He observed this immunofluorescence pattern independently and with other French immunopathologists collected 14 positive cases (11 F., 3 M.) over the past five years, representing about 01% of all sera tested. Ten were from patients with either active chronic hepatitis in young subjects or with unexplained cirrhosis (Homberg et al., 1974).

References

Haemolytic-Uraemic Syndrome in Typhoid Fever

N. M. BAKER, A. E. MILLS, I. RACHMAN, J. E. P. THOMAS

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Summary
Among 48 patients with a typhoid infection 6 (12.5%) developed the haemolytic-uraemic syndrome. Neither glucose-6-phosphate dehydrogenase deficiency nor therapy with chloramphenicol could be incriminated as the causal factor. Evidence presented here suggests that the mechanism is localized intravascular coagulation.

The presence of leucocytosis in typhoid fever suggests a complication and should alert one to the possibility of the haemolytic-uraemic syndrome. Furthermore, in our area typhoid should be suspected as a cause in any patient presenting with acute renal failure.

Division of Medicine, Mpilo Central Hospital, Bulawayo, Rhodesia
N. M. BAKER, M.B., M.R.C.P., Physician
A. E. MILLS, M.B., M.R.C.P., Physician
I. RACHMAN, M.B., M.R.C.P., Physician
J. E. P. THOMAS, F.R.C.P., Senior Physician

Introduction
Haemolysis and renal failure have been regarded as rare complications of typhoid fever. Retief and Hofmeyr (1965) found fewer than 40 cases of haemolytic anaemia associated with typhoid noted in the literature. Since then there have been further reports, usually of single cases. That this complication might be more common was suggested when Lwanga and Wing (1970), in a two-year retrospective study, found that of 130 patients with typhoid 7% had evidence of haemolysis, but that was in areas where glucose-6-phosphate dehydrogenase deficiency (G-6-PD) deficiency was common. Hersko and Vardy (1967) described haemolysis in five children, all with G-6-PD deficiency. Huckstep (1962) mentioned an incidence of haemolytic anaemia of 2% and of ‘‘thromboprophylaxis’’ of 1%. Gulati et al. (1968) reported two cases of nephritis among 98 patients, and Wicks et al. (1971) reported renal complications in six out of 265 patients.

Lwanga and Wing (1970) claimed the first reported case of acute oliguric renal failure after intravascular haemolysis in typhoid fever. That was in a patient with G-6-PD deficiency. Though Allen (1969) reported one case with consumption co-
agulopathy, stating that this had not been previously reported in typhoid fever, Faierman et al. (1972), who reported a case with hepatitis, nephritis, and thrombocytopenia, believed that in neither their patient nor Allen's was there sufficient evidence to support a diagnosis of consumption coagulopathy. Chloramphenicol has been incriminated as the cause of haemolysis (La Grutta et al., 1967), while McCaffrey et al. (1971) thought that chloramphenicol intensified the haemolysis seen in white G-6-PD-deficient patients with typhoid fever.

Our aim is to show that haemolysis and uraemia are more common than has been appreciated, and we discuss what we believe to be the underlying mechanism of these complications.

Patients and Methods
The 48 cases of proved typhoid fever in Africans admitted to Mpilo Hospital during the two-year period 1 January 1971 to 31 December 1972 were reviewed. Haemoglobin estimations and full blood counts were made with a Coulter model S electronic cell counter. Blood urea was estimated by a standard diacetylmonoxyne method with an Autoanalyzer, serum bilirubin by the Malloy-Evelyn method as described by Wootton (1964), and plasma fibrinogen by a modified Ellis-Stransky method (Burmester et al., 1970). Serum fibrin and fibrinogen degradation products were assessed later in the study by a commercial latex method (Thrombo-Wellcotest), and in the earlier months by a modified Fi test (Hyland Laboratories Ltd.) as described by Merskey et al. (1966).

Other haematological investigations included platelet count by the Brecher-Cronkite method with phase microscopy, reticulocyte counting, Schum's test, and estimation of red cell G-6-PD activity (Morulsky method), prothrombin index by Quick's method (calibrated with Manchester thromboplastin and reported as British corrected ratio. Kaolin activated partial thromboplastin time, whole blood coagulation time (Lee and White's method), and direct Coombs tests were performed by standard techniques as described by Dacie and Lewis (1968). The presence of fragmented red cells was confirmed by one of us (A.E.M.) using multiple fresh blood films. Bacteriological isolation and identification was performed by standard techniques (Kauffman, 1965). Blood urea rose to very high levels at a level of 410 mg/100 ml and haemoglobin 41 g/100 ml, with evidence of haemolysis. He was treated with peritoneal dialysis, blood transfusion, chloramphenicol, and heparin 1,000 U four-hourly. One month after admission he was discharged fully recovered.

Case 4.—A 20-year-old man had a two-week history of headache, abdominal pain, constipation, and epistaxis. He was confused, emaciated, dehydrated, jaundiced, and anaemic. Two days later he was found to be very ill, with anaemia, acidotic breathing, and uraemic froth. Temperature was normal. Blood urea was 840 mg/100 ml and haemoglobin 41 g/100 ml, with evidence of haemolysis. He was treated with peritoneal dialysis, blood transfusion, chloramphenicol, and heparin 1,000 U four-hourly. One month after admission he was discharged fully recovered.

Case 5.—A 36-year-old woman had been unwell and febrile for one week and had abdominal pain and diarrhoea for one day. She was pyrexial, ill, and anaemic. The progression of the anaemia, uraemia, and thrombocytopenia and response to peritoneal dialysis, heparin, and chloramphenicol are shown in fig. 1. She was discharged fully recovered six weeks after admission.

Results

Evidence of Typhoid Fever.—S. typhi was cultured from each of the 48 patients; 42 had positive blood cultures with or without positive stool or urine cultures or both, 4 had positive stool cultures, and 2 had positive urine cultures.

Evidence of Haemolytic-Uraemic Syndrome.—In six patients there was evidence of the haemolytic-uraemic syndrome (table I). The clinical course of these patients is summarized below.

Case 1.—A 45-year-old man had been ill for three weeks with headache and abdominal pains, and for two weeks he had had loose stools and occasional vomiting. On examination he appeared ill, dehydrated, and slightly jaundiced but was apyrexic (indeed, there was no significant fever at any stage). The spleen was slightly enlarged. Blood urea was 543 mg/100 ml and haemoglobin 65 5/100 ml. There was evidence of intravascular haemolysis. He was treated with intravenous heparin 2,000 U four-hourly for 10 days, blood transfusions, and correction of the fluid and electrolyte balance. Chloramphenicol was begun on the third day and given for 21 days. After an initial deterioration and a haematemesis on the tenth day he slowly improved. He was discharged well two months after admission. Two years later the haemoglobin, blood urea, and urine were normal.

Case 2.—A 26-year-old man had been ill for eight days with headache, abdominal pain, fever, and, later, vomiting and dark urine. He was ill and febrile and had abdominal tenderness. Typhoid was diagnosed, and chloramphenicol and chloroquine were begun immediately. Two days later he had deteriorated. His haemoglobin had fallen from 12.6 to 7.9 g/100 ml, with evidence of haemolysis, and his blood urea was 320 mg/100 ml. Heparin was not given. He died on the third day. At necropsy typhoid enteritis was confirmed.

Case 3.—An 18-year-old man had been ill with headaches and abdominal pain for two weeks and diarrhoea for two days. On admission he was found to be very ill, with anaemia, acidotic breathing, and uraemic froth. Temperature was normal. Blood urea was 840 mg/100 ml and haemoglobin 41 g/100 ml, with evidence of haemolysis. He was treated with peritoneal dialysis, blood transfusion, chloramphenicol, and heparin 1,000 U four-hourly. One month after admission he was discharged fully recovered.

Case 6.—A 15-year-old girl complained of headache, vomiting, and diarrhoea for two days. She was ill, febrile, dehydrated, and drowsy. Haemoglobin was 11.6 g/100 ml and blood urea 91 mg/100 ml. She was treated with chloroquine and, as typhoid was suspected, chloramphenicol. Despite an apparently adequate urine output the blood urea rose to 260 mg/100 ml over the next four days. Haemoglobin fell to 8 g/100 ml and fibrin degradation products and fragmented erythrocytes were found in the blood. Intravenous heparin 1,000 U four-hourly was added to her treatment and two weeks later she had recovered.
### Table I—Clinical and Laboratory Data in 6 Cases of Typhoid in which Haemolytic-Uraemic Syndrome developed. Only the most Abnormal Values are shown

<table>
<thead>
<tr>
<th>Duration of illness at time of admission</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocytes/mm³</td>
<td>41,300</td>
<td>9,600</td>
<td>13,100</td>
<td>33,700</td>
<td>10,400</td>
<td>7,800</td>
</tr>
<tr>
<td>Evidence of typhoid:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>Blood</td>
<td>Pos. x 1</td>
<td>Pos. x 1</td>
<td>Pos. x 2</td>
<td>Pos. x 1</td>
<td>Pos. x 4</td>
</tr>
<tr>
<td></td>
<td>Stool</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Widal test</td>
<td>Screen</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Titre</td>
<td>O1/16;H1/320</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Evidence of haemolysis:**

- Haemoglobin (g/100 ml)
- Reticulocytes (%)
- Schumm's test
- Serum bilirubin (mg/100 ml)
- Coombs test
- G-6-PD
- Fragmented R.B.C.s

**Evidence of consumption coagulopathy:**

- Platelets/mm³
- Plasma fibrinogen (mg/100 ml)
- P.T.T.K. (sec)
- Prothrombin index
- Fibrin degradation products
- Evidence of renal failure:
  - Blood urea (mg/100 ml)
  - Urine output (ml/24 hr)

*British corrected ratio.
†Modified Fi test (see text).

### Table II—Outcome of Treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Chloramphenicol</th>
<th>Heparin</th>
<th>Other</th>
<th>Chloroquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>500 mg x 4 daily</td>
<td>2,000 U 4-hourly</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>500 mg x 4 daily</td>
<td>1,000 U 4-hourly</td>
<td>—</td>
<td>Chloroquine course</td>
</tr>
<tr>
<td>3</td>
<td>500 mg x 4 daily</td>
<td>4,000 U 6-hourly Transfusion, frusemide</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>500 mg x 4 daily</td>
<td>4,000 U 6-hourly Transfusion, peritoneal dialysis</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>500 mg x 4 daily</td>
<td>1,000 U 4-hourly</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>500 mg x 4 daily</td>
<td>4-hourly</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died on 5th day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Commentary

Except for case 1 no evidence of significant gastrointestinal or other haemorrhage was found in these cases. Cases 1 and 3 were virtually apyrexic throughout the illness. In no patient was the blood pressure notably raised at any stage, though this has been reported to accompany the haemolytic-uraemic syndrome in children.

**White Blood Count.**—We feel that the leucocyte count is of special interest. Instead of the usual leucopenia found in typhoid fever the lowest count was 7,800/mm³ and the highest was 41,300/mm³ (table I).

**Treatment.**—When the diagnosis of haemolytic-uraemic syndrome was made heparin was given (table II). Low dosages have been advocated (Bernstock and Hirson, 1960), and these were used in cases 1, 3, and 6. The initial dose was roughly assessed by dividing the platelet count by 50 (Hardisty and Ingram, 1965). After obtaining a whole blood clotting time 1,000 or 2,000 U of heparin was given as an intravenous bolus at four-hourly intervals. Heparin was administered in a higher dose in cases 4 and 5, and in the only fatal case (case 2) it was not used at all.

### Discussion

Altogether six of our 48 patients showed evidence of both haemolysis and renal failure. Further cases might possibly have been found had the less seriously ill patients, with features such as moderate anemia, been as fully investigated as those described.

The haemolytic-uraemic syndrome constitutes a condition in which acute renal failure is associated with microangiopathic haemolytic anaemia and in which, therefore, the presence of red cell fragmentation is essential for establishing the diagnosis. Red cell fragmentation was present in five cases and not recorded in the sixth. Microangiopathic haemolytic anaemia was originally described by Brain et al. (1962). Since then it has been shown that red cell fragmentation results from mechanical damage to the erythrocytes as they pass through fibrin strands deposited in damaged small blood vessels (Bull et al., 1968). It is now generally recognized that the deposition of fibrin results from intravascular coagulation (Brain, 1969). What is pertinent to this series, however, is the growing awareness that intravascular coagulation need not always be of the widely disseminated type or so-called disseminated intravascular coagulation but may be of a localized type; and recent work suggests that the primary lesion of the haemolytic-uraemic syndrome is intravascular coagulation localized in the renal microvasculature (GIChris et al., 1969; Gervais et al., 1971). A proposed scheme for the pathogenesis of the haemolytic-uraemic syndrome in typhoid fever, adapted from Brain (1968), is shown in fig. 2.
for diagnosis differ from those of disseminated intravascular coagulation in that it is unnecessary to obtain evidence of massive consumption coagulopathy in the form of hypofibrinogenaemia, but sensitive procedures to detect activation of the coagulation mechanism, such as tests for increased fibrin degradation products, are usually positive. In four out of five cases in which the level of fibrin degradation products was recorded it was, in fact, increased. The platelet count is often subnormal, as in cases 1, 4, 5, and 6 (table 1), and fragmented red cells are invariably present, accompanied by a variable degree of haemolytic anaemia and renal failure. (Though platelet count and red cell fragmentation were not documented in case 2 the patient had been included because he had anaemia with a positive Schumm's test, a high blood urea, and a poor urinary output.) Fibrinogen levels may actually be raised in the haemolytic-uraemic syndrome (Gilchrist et al., 1969), as was found in case 1. Increased plasma fibrinogen levels in cases of typhoid fever were recorded by Ogston et al. (1964).

Apart from diagnostic considerations the concept of localized intravascular coagulation may also have therapeutic implications. If the role of heparin is accepted it appears rational to infer that localized intravascular coagulation could be controlled by lower doses of heparin than are required for disseminated intravascular coagulation. The outcome was certainly satisfactory in the three cases in our series in which this low dosage scheme was used.

We have been unable to account for the high incidence of the haemolytic-uraemic syndrome in our cases of typhoid as compared with the published experience of others. G-6-PD deficiency was not detected in the four patients in whom it was sought. Except for case 2 the haemolysis and renal failure occurred before treatment with chloramphenicol was started, and this drug can therefore be excluded as the causal agent in these five cases. We found no positive evidence to implicate the traditional herbal remedies as a precipitating factor.

Attention has been drawn to the absence of leucopenia in our cases. A neutrophil leucocytosis in typhoid suggests a complication and could well be another pointer to the development of the haemolytic-uraemic syndrome in this infection. Furthermore, typhoid must be suspected in any case of acute renal failure seen in this region, even if the patient is apyrexial, as were two of ours.

We should like to thank the Secretary for Health, Rhodesia, for permission to submit this paper.

References


Renal Tubular Obstruction by Mucoproteins from Adenocarcinoma of Pancreas

J. R. Hobbs, D. J. Evans, O. M. Wrong

British Medical Journal, 1974, 2, 87-89

Summary

We report a case in which mucoproteins from an adenocarcinoma of the pancreas, released into the ascitic fluid and serum, were filtered through the renal glomeruli to form very viscous casts which obstructed the renal collecting tubules and caused the patient's death from oliguria.

Tumour Biology Group, Westminster Hospital Medical School, London S.W.1
J. R. Hobbs, M.D., F.R.C.P., Professor of Chemical Pathology
Royal Postgraduate Medical School, London W12 OHS
D. J. Evans, M.B., B.CH., Senior Lecturer in Pathology
University College Hospital, London WC1E 6AU
O. M. Wrong, M.D., F.R.C.P., Professor of Medicine

Introduction

Obstruction of the renal collecting tubules with protein casts occurs in up to 30% of patients with myelomatosis (Heptinstall, 1966). It is most often associated with Bence-Jones proteinuria, but occasionally with other proteinuria—for example, IgA (Hobbs, 1966). Oliguric renal failure sometimes occurs with prominent tubular casts in nephrotic patients with heavy albuminuria (Chamberlain et al., 1966). We report a patient who died because his renal tubules were obstructed by the mucoproteins from an adenocarcinoma of the pancreas.

Case Report

The patient was a civil servant aged 43 years. In mid-April 1967 he developed nausea, vomiting, and abdominal pain. On 27 April he was admitted to a local hospital as an emergency. No abnormalities were found on physical or barium meal examination, the blood urea was 32 mg/100 ml, and his uric acid 6 mg/100 ml. His urine contained protein. The symptoms subsided on a milk diet and be