metastases. No comparable lesions were found in any tissue other than the tumour and its secondaries. In the larger necrotic areas there was some haemorrhage, and occasional blood vessels around the margin were filled with hyaline thrombus and their walls were necrotic. However, in the smaller lesions clumps or even single tumour cells had undergone a hyaline eosinophil necrosis without obvious change in the blood vessels.

In some of these smaller lesions and at the margins of the larger ones a series of degenerative changes were noticed. The outer zone of surviving tumour with cells arranged in solid cords surrounded an inner zone where the cells were separated, the nuclei smaller and more deeply staining, and the cytoplasm more eosinophilic. Towards the centre of the nodule the nuclei had become pyknotic and finally disappeared, leaving clumps of degenerate eosinophil cytoplasm which fused to form a central necrotic mass in which the "ghost" outline of the cells could be seen. This succession of changes suggested that cell degeneration might still have been going on at the periphery, although much more slowly than at first. It would seem that the first change had been necrosis of central tumour cells with secondary necrotic change in the stroma, where large numbers of cells had been destroyed. This stromal change is perhaps due to the release of enzymes from the damaged tumour cells. The surviving tumour is pleomorphic, with solid trabecular, small acinar, and anaplastic areas.

The lung showed bronchopneumonia and some haemorrhage into the wedge-shaped area in the right lower lobe. There were tumour emboli in the subpleural lymphatics. All secondary nodules showed central necrosis.

Discussion

There seems to be no doubt that degenerative changes in the tumour occurred shortly after bilateral adrenalectomy. Necrotic areas in rapidly growing tumours are of course commonly seen, but not as a rule involving both primary and secondary tumours simultaneously. No similar change has been seen in 29 other cases of prostatic carcinoma examined by the "big section" method using post-mortem material. Other possible causes are oestrogens, cortisone, insulin, or some other unknown agent. The first can probably be excluded because the cytotoxic changes it produces in prostatic cancer (Schenken *et al.*, 1942; Fergusson and Franks, 1953) differ from those seen in this case. There is little convincing evidence that cortisone affects the growth of human prostatic tumours (Huggins and Bergenstal, 1952), but a report on one case which showed clinical improvement after such treatment has recently appeared (Hayward, 1953).

It is also unlikely that insulin or the diabetic state could produce such massive necrotic lesions. On the whole the evidence suggested that the changes which occurred in this case were caused by the removal of both adrenals, but the possibility remains that the necrotic changes may be due to the interference with vascular supply so commonly seen in malignant tumours. The histological appearances, however, seem to show that the first degenerative changes took place in the tumour cells, and that these caused secondary changes in the stroma. If blood vessels are involved in this process an added ischaemic necrosis may occur in the area supplied by the vessel.

One further point of interest in this case is the absence of clinical evidence of regression in spite of the massive and widespread destruction of tumour cells.

Summary and Conclusions

Massive central necrosis apparently involving primary and secondary tumours simultaneously was seen in a patient dying six weeks after bilateral adrenalectomy for advanced prostatic cancer. A narrow zone of actively growing tumour cells surrounded these necrotic centres. It is highly probable (but not proved) that

these regressive changes were directly related to the removal of both adrenals. It is important that any similar material should be examined by methods which allow the extent and distribution of any degenerative changes to be appreciated.

The patient was operated on by Mr. J. D. Fergusson, and I am indebted to him and to the research department of the Institute of Urology for the clinical notes and post-mortem material: the case forms part of his series of advanced cancer cases treated by bilateral adrenalectomy, which will be described more fully later. My thanks are also due to Professor G. Hadfield for many helpful suggestions and to Dr. J. Craigie for the photographs.

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HAEMOLYTIC ANAEMIA IN TYPHOID FEVER

A REPORT OF SIX CASES, TOGETHER WITH THE EFFECT OF CHLORAMPHENICOL AND A.C.T.H.

BY

A. J. S. McFADZEAN, M.B., M.R.C.P.

Professor

AND

G. H. CHOA, M.B., M.R.C.P.

Lecturer

The Department of Medicine, University of Hong Kong

Acute haemolytic anaemia with haemoglobinuria has been reported as a rare complication of typhoid fever. Osler (1895) encountered one case in his series of 1,500. Curschmann (1898) reported two fatal cases. Musser and Kelly (1901) and Castellanos and Montero (1940) each described one case with recovery. Wright (1945) reported two fatal cases in East Africans. Batty Shaw (1951) described two cases with recovery, but one of these was subsequently thought to be a case of familial haemolytic anaemia. Gordon Smith (1951) reported one case to which chloramphenicol had been given before the onset of the haemoglobinuria.

Before 1945 the occurrence of haemolytic anaemia without haemoglobinuria was reported very infrequently. Under the guise of "acute pernicious anaemia" Mouisset, Mouriquand, and Thévenot (1906), Sicard and Gutmann (1911), Marcora (1919), and Stanzani (1924) reported, in all, five cases. There is no doubt that these were cases of severe haemolytic anaemia. According to Batty Shaw (1951), Kadrnka in 1928 described two cases of acute haemolytic anaemia complicating typhoid fever. Davidson and Fullerton (1938) reported haemolytic crises in a woman with *Salmonella dublin* infection, but she was thought to have a latent haemolytic anaemia.

Berman, Braun, and Rachmilewitz (1945) investigated 152 cases of typhoid fever and found nine cases of haemolytic anaemia of varying degrees of severity. The criteria employed were anaemia, increased reticulocyte count, retentive jaundice, and increased urobilinogen in the urine. In one case there was unequivocal evidence of haemolysis in that urobilinogen excretion in the urine and faeces was estimated quantitatively and found to be significantly raised.

One of us (A. McF.) became interested in the anaemia of typhoid during military service in the Middle East. In the course of haematological investigation of cases of typhoid fever in British and Italian soldiers it became obvious that in a small yet significant number the anaemia was haemolytic in type. Regrettably, most of the records were lost. The investigation was restarted in Hong Kong.

The purpose of this communication is to report six cases of haemolytic anaemia, one of which was associated with haemoglobinuria, occurring during the course of typhoid fever, and to report the effect of chloramphenicol and A.C.T.H. on the course of the anaemia.

Incidence.—From January, 1949, to May, 1952, 129 consecutive cases of *Salm. typhi* infection have been investigated and six cases of haemolytic anaemia encountered, an incidence of 4.6%. In the series reported by Berman *et al.* (1945) the incidence was 5.9%. No cases have occurred in a series of 47 cases of enteric fever due to *Salm. paratyphi* A, B, or C occurring in the same period.

Clinical Findings

All six patients (four male and two female) were Chinese. The age incidence ranged from 19 to 38 years: the ages of the cases are set out in Table I. There was

TABLE I.—*Relevant Clinical Findings and Bacteriological Findings in Six Cases of Haemolytic Anaemia Complicating Typhoid Fever*

Case No.	Age	Sex	Day of Disease Admitted	Toxaemia	Jaundice	Spleen	Liver	<i>S. typhi</i> Isolated		
								Sternal Marrow Culture	Blood Culture	Stool Culture
1	27	M	10	Moderate	++	7 cm.	5 cm.	+	+	+
2	32	F	14	Severe	++	6 "	4 "	+	+	+
3	19	M	11	"	+	Just palpable	4 "	+	+	+
4	28	F	12	Moderate	++	6 cm.	3 "	+	+	+
5	36	M	9	Severe	++	2 "	4 "	+	+	+
6	38	M	12	"	++	Not felt	6 "	+	+	+

neither personal nor family history of jaundice or anaemia. None had been exposed to toxic substances, nor had any taken drugs recognized as producing haemolysis. There was no history of blood loss.

All patients were admitted in the second week of the disease. With the exception of Case 6, the patient with haemoglobinuria, the history obtained was in no way different from that of uncomplicated typhoid. Again with the exception of Case 6, none of the cases were aware of being jaundiced. Case 6 had a 12-day history of increasing fever, severe frontal headache, progressive general malaise, and abdominal discomfort and distension. He was noticed to be jaundiced for 48 hours before admission. Twelve hours before admission he complained of shivering, backache, and generalized

bone-aching, and a specimen of urine passed six hours later was dark red in colour.

The salient clinical features are set out in Table I. Toxaemia was severe in four cases and moderate in two. Two cases (Nos. 1 and 3) had an unusually profuse eruption of rose spots. All six cases were mildly or moderately jaundiced on admission. The spleen was palpable in five cases, and in three of these it was larger than would be expected in cases of typhoid in the second week. The spleen was not felt in the patient with haemoglobinuria (Case 6). The liver was palpably enlarged in all cases. It was not tender.

Laboratory Findings

The bacteriological findings are set out in Table I and the remaining laboratory findings in Table II. The diagnosis of typhoid fever was established by the isolation of *Salm. typhi* from both sternal marrow and blood cultures in two cases, in two cases from sternal marrow culture alone, and in one case each from blood culture and stool culture.

Cases 1 to 5 inclusive showed a marked increase in the urobilinogen excretion in the urine. This was estimated quantitatively in Cases 3, 4, and 5, and was found to be 31, 21, and 28 mg. a day respectively. In these five cases the direct van den Bergh test was negative, but the indirect van den Bergh was positive, the serum bilirubin ranging from 2.2 to 3.6 mg. per 100 ml. In Case 6 the urine contained haemoglobin and methaemoglobin and there was haemoglobinaemia.

Satisfactory collection of stools from our patients was impossible, consequently the quantitative estimation of urobilinogen in the faeces by the method described by Watson (1937a) could not be carried out. The difficulty of collecting stools from acutely ill patients was appreciated by Watson (1937b), who, to circumvent it, described an application of the qualitative test as a rough quantitative test, according to whether the intensity of the reaction is weak, moderate, or strong. These reactions are recorded as +, ++, and +++ respectively. In Cases 2, 3, 4, and 5, in which this test was carried out, the reaction was strongly positive.

The haematological findings on admission are set out in Table II. It will be seen that all cases were anaemic on admission; the red-cell counts ranged from 1.8 to 2.8 millions per c.mm. and the haemoglobin from 5.8 to 9 g. per 100 ml. The M.C.V. ranged from 100 to 120 μ^3 . The reticulocyte count was raised in all cases to between 8 and 14%. The fragility of the red cells to hypotonic saline was determined in all cases, employing in Case 6 washed red cells. The red-cell fragility range was within normal limits in Cases 1, 5, and 6, whereas it was increased in the remaining three cases. The direct Coombs test was carried out in Cases 1, 2, 3, and 4. It was strongly positive in Cases 3 and 4 and weakly positive in Cases 1 and 2.

TABLE II.—*Laboratory Findings in Six Cases of Haemolytic Anaemia Complicating Typhoid Fever*

Case No.	Urine		Faecal Urobilinogen	Serum Bilirubin (mg./100 ml.)	Total R.B.C. (mill. per c.mm.)	M.C.V. (μ^3)	Reticulocytes (%)	Osmotic Fragility Range of R.B.C.	Direct Coombs Test	Haemoglobin (g./100 ml.)	White Cell Count				Sternal Marrow	
	Urobilinogen	Haemoglobin									Total W.B.C. (per c.mm.)	Differential				
												N %	E %	L %		M %
1	++	—	Not done	3.6	2.8	111	8	Normal	+	9.0	6,100	82	2	14	2	Normoblastic erythrocytosis with hyperplasia of the erythroid series
2	++	—	+++	3.2	2.2	115	14	0.56-0.40%	+	7.0	10,200	74	—	26	—	
3	31 mg.	—	+++	2.2	2.3	102	9	0.6-0.44%	++	7.6	5,600	42	—	55	3	
4	21 "	—	+++	2.8	2.0	100	8	0.52-0.38%	++	6.9	9,000	78	—	21	1	
5	28 "	—	+++	3.4	2.1	104	10	Normal	Not done	7.1	5,200	48	—	50	2	
6	—	+++	Not done	3.6	1.8	120	8	"	" "	5.8	12,800	78	3	17	2	

The leucocyte count in Cases 2, 4, and 6 showed an increase to between 9,000 and 12,800 per c.mm. In these three cases and in Case 1 the differential count was unusual in that there was a predominance of polymorphonuclear leucocytes, which constituted from 74 to 82% of the total white cells. In Cases 1 and 6 another

unusual finding was the presence of eosinophils in the peripheral blood. Smears of sternal marrow in all cases showed normoblastic erythropoiesis with hyperplasia of the erythroid series.

Since Cases 1 and 2 occurred before the introduction of chloramphenicol and Cases 3 and 4 before A.C.T.H.

was available, the six cases may be divided into the following groups:—Group 1: Cases 1 and 2, in which the disease pursued an uninterrupted course. Group 2: Cases 3 and 4, which were treated with chloramphenicol. Group 3: Cases 5 and 6, which were treated with A.C.T.H. and chloramphenicol.

Group 1

The details of the progress of Cases 1 and 2 are set out in Figs. 1 and 2, respectively.

In Case 1 the haematological findings persisted substantially unchanged until the onset of lysis on the 28th day of illness. During the course of lysis the evidence of haemolysis disappeared. There was a fall of serum bilirubin, and urobilinogen was no longer present in excess in the urine after the 34th day. The reticulocyte count declined and the red-cell count and haemoglobin rose progressively. On discharge 52 days after onset the red-cell count was 4.7 millions per c.mm., the haemoglobin 13.8 g. per 100 ml., and the reticulocytes less than 1%.

In Case 2 the severity of the anaemia increased. The red-cell count fell to 1.7 millions two days after admission, when a blood transfusion of 2 pints (1.1 litres) was given. The effect of the transfusion was transient, for after four days the red-cell count had fallen almost to the pre-transfusion level. The patient remained gravely ill for a further period of six days, when, on the 27th day of illness, resolution of the temperature by lysis began. Thereafter there was evidence of improvement. As in Case 1, the indications of haemolysis ceased during lysis. The serum bilirubin fell, and on the 39th day of illness urobilinogen was no longer detected in excess in the urine. On discharge 57 days after onset of the fever the red-cell count was 4.3 millions per c.mm., the haemoglobin 13.4 g. per 100 ml., the reticulocyte count less than 1%, and the fragility to hypotonic saline within normal limits.

In both cases the direct Coombs test, previously and repeatedly positive, became negative during the phase of resolution of the fever.

Group 2

The details of the progress of Cases 3 and 4 are set out in Figs. 3 and 4, respectively. Treatment with chloramphenicol was started in

FIG. 1.—Progress of Case 1.

FIG. 2.—Progress of Case 2.

Case 3 within 24 hours of admission and in Case 4 four days after admission. In each case a loading dose of 60 mg./kg. of body weight was given and thereafter 60 mg./kg. every 24 hours in divided doses four-hourly for 14 days.

Case 3 was apyrexial five days after starting treatment. Despite control of the infection and improvement in the patient's clinical condition there was deterioration in the blood picture. The red-cell count fell from 2.2 to 1.5 millions per c.mm. and the reticulocytes increased from 9 to 15%. Despite this increased haemolysis the serum bilirubin had fallen from 2.2 to 1.2 mg. per 100 ml. A blood transfusion of 2 pints (1.1 litres) was given on the fifth day of treatment. The effect was transient, for after four days the red-cell count had fallen to 2.0 millions per c.mm. On the 12th day of treatment, the 23rd day of illness, there was a significant drop in reticulocyte count. Thereafter the red-cell count and haemoglobin progressively rose, the reticulocyte count fell to within normal limits, and urobilinogen was no longer detected in excess in the urine on the 27th day of illness. On discharge from hospital on the 34th day the red-cell count was 4.2 millions per c.mm., the haemoglobin 12.2 g. per 100 ml., and the reticulocytes less than 1%.

Case 4 was apyrexial three days after starting treatment with chloramphenicol, but the haematological findings persisted substantially unchanged for a further period of nine days. In this period the serum bilirubin fell from 2.8 to 1.1 mg. per 100 ml. On the 28th day of illness, 12 days after starting treatment, there was a fall in the reticulocyte count. This was followed by a progressive climb in the red-cell count and haemoglobin. Urobilinogen was no longer detected in excess in the urine on the 30th day. On discharge from hospital on the 41st day of illness the red-cell count was 4.8 millions per c.mm., the haemoglobin 14 g. per 100 ml., and the reticulocytes less than 1%.

The Coombs test in each case was positive seven days after resolution of the fever, but it was negative when repeated seven days later. The red cells in both cases on

FIG. 3.—Progress of Case 3.

FIG. 4.—Progress of Case 4.

admission had shown an increased fragility to hypotonic saline. Prior to discharge the fragility was within normal limits.

Group 3

The details of the progress of Cases 5 and 6 are set out in Figs. 5 and 6, respectively.

Case 5

Treatment with chloramphenicol was started within the first 24 hours after admission in the same dosage employed in Group 2. At the same time, because of the haemolytic anaemia A.C.T.H. was given. It was administered in 5% glucose by slow intravenous drip, so adjusted that 20 mg. was given over 24 hours. Gordon, Kelsey, and Meyer (1951) have shown that A.C.T.H. by slow continuous intravenous drip induces a quantitatively greater response than does periodic administration. The response to intravenous A.C.T.H. by the method described has in our experience proved satisfactory when treatment is required only for a short period.

Clinical Response.—Improvement was noted within a few hours of starting the drip. Within 24 hours the temperature had fallen to normal and the toxæmia was so reduced that a stuporous confused patient became alert and able to carry on a normal conversation. On the third day the temperature rose to 101° F. (38.3° C.), but fell again to normal on the fourth day and remained so thereafter. On the fourth-day the dosage of A.C.T.H. was reduced to 10 mg. over 24 hours, and was discontinued on the 10th day. Chloramphenicol was continued for a further period of four days to a total of 14 days.

Haematological Response.—Two days after starting treatment the serum bilirubin had fallen from 3.4 to 1.8 mg. per 100 ml. In this period the reticulocyte count had risen by 5 to 15%, the haemoglobin by 1.2 to 8.3 g. per 100 ml., and the red-cell count by 0.5 million to a total of 2.6 millions per c.mm. From the second day of treatment there was a rapid decline in the reticulocyte count and a progressive rise in haemoglobin and in the red-cell count. Neither the reduction in dosage nor withdrawal of A.C.T.H. affected the climb. Urobilinogen was no longer detected in excess in the urine on the eighth day of treatment. Thirteen days

after starting treatment the red-cell count was 4.4 millions per c.mm., the haemoglobin 12.6 g. per 100 ml., and the reticulocytes less than 1%.

Case 6

The patient when first seen was confused and an adequate history could not be obtained. A tentative diagnosis of acute haemolytic anaemia of undetermined aetiology was made. Though the haemolysis had produced no circulatory disturbance, in view of the acute onset of the anaemia he was given a transfusion of 1 pint (570 ml.) of blood. A.C.T.H. was administered in the same dosage and by the same technique as in Case 5.

Clinical Response.—The response to treatment was as in Case 5. Improvement was noted within a matter of hours. Eighteen hours after starting treatment toxæmia was much reduced, the temperature had fallen from 104.6 to 100° F. (40.3 to 37.8° C.) and the patient was alert and able to carry on a normal conversation. His appetite returned. The temperature remained around 100° F. (37.8° C.) for a further three days, then rose to 103° F. (39.4° C.) without deterioration in the clinical condition. On the fifth day the bacteriologist reported the isolation of *Salm. typhi*, and chloramphenicol was started in the dosage as in Group 2. On the same day the dose of A.C.T.H. was reduced to 10 mg. over 24 hours. He became apyrexial on the seventh day of treatment and remained so thereafter. A.C.T.H. was withdrawn after 10 days and chloramphenicol after 14 days.

Haematological Response.—The blood transfusion raised the red-cell count from 1.8 to 2.4 millions per c.mm. A specimen of urine passed 22 hours after starting treatment

was free from haemoglobin, as was also a specimen of serum obtained at the same time. The bilirubin content of this specimen of serum was 3.6 mg. per 100 ml., and 24 hours later the serum bilirubin had fallen to 2.0 mg. per 100 ml. Three days after starting treatment the reticulocytes had fallen from 15 to 9%, and the red-cell count had risen to 2.8 millions per c.mm. Thereafter there was a rapid fall in the reticulocyte count and a progressive rise in the red-cell count and haemoglobin, which was unaffected either by reduction of the dose of A.C.T.H. or by its withdrawal. Urobilinogen was no longer present in excess in the urine six days after starting treatment. Fourteen days after starting treatment the red-cell count was 4.8 millions per c.mm., the haemoglobin 12.2 g. per 100 ml., and the reticulocytes less than 1%.

Discussion

The anaemia in all six cases can be accepted as haemolytic in origin. It was associated with an increased reticulocyte count, and sternal marrow biopsy showed a normoblastic hyperplasia. In the absence of blood loss this picture suggests haemolysis.

In Case 6 there was unequivocal evidence of haemolysis. In the remaining cases there was a retentive jaundice. Urobilinogen, measured by the intensity of the qualitative reaction, was present in excess in the urine, and in the three cases in which it was quantitatively estimated the excretion in 24 hours was greatly increased. Faecal urobilinogen, estimated by the intensity of the qualitative reaction as described by Watson (1937b), was increased in the four cases in which it was done. This test has been performed on a series of 20 uncomplicated cases of typhoid, and a strongly positive reaction has never been encountered.

The evidence supports a diagnosis of acquired haemolytic anaemia. There was an absence of family history of

FIG. 5.—Progress of Case 5.

FIG. 6.—Progress of Case 6.

anaemia or jaundice. The Coombs test was positive in the four cases in which it was done, and in Cases 2 and 3 blood transfusion had only a transient effect. Furthermore, the haematological response to A.C.T.H. would appear to confirm this diagnosis. Dameshek (1950), Gardner (1950), Dameshek, Rosenthal, and Schwartz (1951), Davidson, Duthie, Girdwood, and Sinclair (1951), and Clearkin (1952) have reported the satisfactory response of symptomatic or "idiopathic" acquired haemolytic anaemia to A.C.T.H. The haematological response of Cases 5 and 6 to A.C.T.H. was satisfactory. The manifestations of haemolysis ceased, and within 48 hours there was evidence of increase in the red-cell counts and haemoglobin levels, an increase which was progressive. The response of Case 5, to which chloramphenicol was coincidentally administered, can be attributed only to the A.C.T.H., since no response to chloramphenicol alone was encountered in Cases 3 and 4 and since A.C.T.H. alone in Case 6 produced a similar response.

The haemolysis would seem to be intimately associated with the typhoid infection. There was no evidence of exposure to toxic substances or of the taking of drugs recognized as producing haemolysis. There was no previous personal history of jaundice or of anaemia. Although there is no direct evidence of the precise time of onset of the anaemia, in view of the absence of previous history and the cessation of the haemolytic process with resolution of the disease it would seem reasonable to assume that the haemolysis began during the course of the disease. With this assumption, in the present series the onset of haemolysis was in the first two weeks of the disease. Although haemoglobinuria occurred in Case 6 on the 11th day, because of the appearance of jaundice 48 hours before it would seem that haemolysis had already occurred and the haemoglobinuria was due to an exacerbation of the haemolytic process. The time of onset—that is, in the first two weeks—is in agreement with that reported by Berman *et al.* (1945). They record the day of disease in which five of their nine cases were admitted. All five showed evidence of haemolysis on admission; four were admitted towards the end of the second week and one at the end of the first week. Of the 10 cases of haemoglobinuria complicating typhoid fever found in the literature the haemoglobinuria occurred in the first week in five, in the second week in three, and in the third week in two. As in Case 6, the onset of haemoglobinuria does not necessarily indicate the time of onset of haemolysis; for example, the case reported by Gordon Smith (1951) was jaundiced for three days before the onset of haemoglobinuria.

The pathogenesis of the haemolysis is obscure. Members of the *Salmonella* group are normally anhaemolytic, but, as originally shown by Friedberger and Vallen (1923), the addition of bacteriophage to a freshly inoculated sheep-blood-agar plate may turn an anhaemolytic culture of *Salm. typhi* into a haemolytic one. Schiff and Bornstein (1940) confirmed these findings, and concluded that haemolysis occurs if a potentially haemolytic culture is combined with a specific phage of adequate strength. With a surplus of phage no haemolysis occurs, because the phenomenon is bound to the presence of live bacteria. On the other hand, no haemolysis is obtained with too small amounts of phage. It is most unlikely that this mechanism plays a part *in vivo*, for the following reasons. The bacillus/phage haemolysis has been found for sheep's red cells but not for human red cells. As the process requires a nice adjustment of phage and organism it cannot explain the persistence of haemolysis despite control of the infection by chloramphenicol in Cases 3 and 4. Finally, Clearkin (1952) has shown that in guinea-pigs A.C.T.H. does not prevent the action of haemolytic sera *in vivo*; consequently it is unlikely that the effects of a bacillus/phage haemolytic agent would be inhibited.

In Cases 1 and 2, in which the disease pursued an uninterrupted course, the haemolytic process ceased during lysis. This also was the finding of Berman *et al.* (1945). Coincidental with the cessation of haemolysis the direct

Coombs test became negative in both cases. Spontaneous resolution consequently results in the removal of the agent responsible for the haemolysis.

Cases 3 and 4 responded satisfactorily to chloramphenicol and were afebrile in five and three days respectively. There was, however, no immediate change in the intensity of the haemolytic process; indeed, in Case 3 it was intensified. In this case blood transfusion had a transient effect even though administered while the patient was afebrile. There was no indication of improvement in the blood picture for seven and nine days respectively following resolution of the fever. The reduction of serum bilirubin which occurred in this period must be attributed to improvement of liver function consequent upon the control of the infection. Furthermore, the direct Coombs test was positive in both cases seven days after the fever had resolved. It was negative when repeated on the 14th day after resolution of the fever. I am aware of only one case of typhoid fever complicated by haemolysis treated with chloramphenicol, and that is the case reported by Gordon Smith (1951). Although haematological details are lacking in his report, it would appear that for 11 days after the patient became afebrile no improvement in the haematological findings occurred. The significant time lag following control of the infection before cessation of haemolysis and disappearance of the auto-antibody suggests that the typhoid bacilli are not directly responsible for the haemolytic process.

Dameshek and Rosenthal (1951) analysed 36 cases of acquired haemolytic anaemia and found 8 to be idiopathic and 28 symptomatic. Of these 28, 8 were due to chronic lymphatic leukaemia, 4 to Hodgkin's disease, 2 to reticulum-cell sarcoma, 2 to lymphosarcoma, and 1 to infectious mononucleosis. It seems reasonable to suggest that, if these pathological conditions of lymphoid and reticulo-endothelial tissue can result in the appearance of auto-antibody and the occurrence of acquired haemolytic anaemia, the haemolytic process occurring in *Salm. typhi* infection may result from the hyperplasia of lymphoid and reticulo-endothelial tissue which occurs as an essential part of the pathology of the disease. The response of Cases 3 and 4 supports this conception, for resolution of the pathological changes produced by the infection is delayed for a significant period of time following control of the infection by chloramphenicol.

Berman *et al.* (1945) considered that in their series dietary deficiency may have played a part in the production of the haemolysis. In our series the nutrition of all six patients was satisfactory and there was no evidence of any deficiency state.

The effect of A.C.T.H. upon the typhoid state was impressive. The reduction in toxæmia was rapid, improvement being obvious within a few hours. Within 24 hours a stuporous patient in low muttering delirium became alert and rational. This reaction to A.C.T.H. has been reported by Roche (1951). Further experience in the treatment of the severe typhoid state with a combination of A.C.T.H. and chloramphenicol has shown that the response is not invariably so dramatic as in the two cases reported here, but A.C.T.H. is a useful adjunct in the management of typhoid with severe toxæmia in the first few days of chloramphenicol treatment.

Summary

Six cases of haemolytic anaemia, one of which had haemoglobinuria, were encountered in an investigation of 129 cases of *Salm. typhi* infection.

The relevant clinical and laboratory findings are described and discussed.

Evidence is presented that the anaemia is a symptomatic acquired haemolytic anaemia intimately related to the typhoid infection.

The response to chloramphenicol of two patients indicates that the salmonellae are not directly responsible

for the haemolysis. It is suggested that the haemolysis may be related to the reticulo-endothelial hyperplasia which occurs in typhoid.

The administration of A.C.T.H. in two cases controlled the haemolytic phenomena and produced prompt improvement in the typhoid state.

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MYXOEDEMA COMA

BY

V. K. SUMMERS, M.D., M.R.C.P.

Consultant Physician, Walton Hospital, Liverpool

In the report of a committee of the Clinical Society of London (1888) on myxoedema it was stated that "intense anaemia, and a variety of nervous symptoms, such as maniacal excitement, coma, etc., precede the fatal event." Scant reference to coma as a terminal event in the natural history of myxoedema is made in modern textbooks or in recent accounts of the disease. The modern tendency is to look upon myxoedema as a readily curable disease and, indeed, hardly to consider it as a cause of death. Le Marquand *et al.* (1953) call attention to the scarcity of recent references to myxoedema as a cause of death and report two fatal cases. The purpose of this paper is to call attention to a terminal coma which is often the manner of death in myxoedema.

The following account is based on five examples of coma seen in four cases of myxoedema during the past few years; in all the cases the diagnosis was subsequently confirmed at necropsy. In one case two episodes of coma occurred.

Case 1

A man aged 59 was admitted to hospital in January, 1950, with a history of watery eyes for 10 weeks and of puffiness of the face for three weeks. There was little of significance in his past history, and apart from malaria during the 1914-18 war he had enjoyed good health. For many years he had complained of "rheumatism" in his right knee. A few days before admission he burned his right leg whilst sitting close to the fire. His face was puffy, especially round the eyes, the lips were thick, and the skin was pale. Axillary hair was absent and the pubic hair scanty. Cerebration was slow, but it was possible to obtain a reasonable history from him. His condition on admission did not give rise to any anxiety, and a series of investigations were planned to assess his endocrine state.

Within 72 hours of admission his condition greatly deteriorated; he became very confused mentally and had delusions of a persecutory nature. Next day he became very drowsy and it was extremely difficult to rouse him; 12 hours later he was stuporous and the plantar responses became extensor. His rectal temperature was 83° F. (28.3° C.). Thyroid extract, 1 gr. (65 mg.) thrice daily, was given as soon as the change in his state was observed, and when he became too drowsy to take oral therapy thyroxine sodium, 1 mg., was given subcutaneously every six hours. This treatment had no effect whatsoever and he died about 96 hours after the first change in his condition was noticed.

Post-mortem examination confirmed the clinical diagnosis of myxoedema. Sections from both lobes of the thyroid showed marked fibrosis. The adrenal glands were of normal size and showed no histological change. The pituitary was normal.

Case 2

A woman aged 65 was admitted to hospital in March, 1951; she had been in hospital on four occasions, and in 1946 a diagnosis of myxoedema was considered. At the time of her admission in 1951 she presented a typical myxoedematous appearance, with a puffy sallow face, sparse head hair, and thin eyebrows. Her voice was croaking. The mental state was one of stupor which gradually, within 48 hours, progressed into deep coma. The vaginal temperature on admission was 75° F. (23.9° C.) and the systolic blood pressure was 70 mm. Hg. The pulse was thin and the rate 60 a minute. The skin was pale and cold; the limbs were flaccid; the deep reflexes could not be elicited, and the plantar responses were extensor.

Thyroxine sodium, 2 mg., was given subcutaneously every six hours from the time of admission. In view of the pronounced hypothermia, and of previous successful experience in hypopituitary coma of raising the temperature by means of immersion in a hot bath, it was decided to attempt this method of treatment. The temperature was raised from 75 to 98.6° F. (23.9 to 37° C.) by immersion in a bath of water, the temperature of which was gradually raised (to avoid burning) to 98.6° F. (37° C.). This procedure had no effect on the coma, and, although the vaginal temperature remained at 98.6° F. (37° C.), the patient died on the following day.

Post-mortem examination showed an extremely small thyroid; in the right lobe was a nodule the size of a cherry stone and in the left a nodule the size of a small bean. Histologically the gland tissue was completely replaced by fibrous tissue in which there were a few groups of shrunken acini. The pituitary and adrenal glands were normal.

Case 3

A man aged 63 was admitted to hospital in February, 1952. Myxoedema had begun about four years previously, and he had taken thyroid intermittently until about a year before his final admission. Clinically he presented gross myxoedematous features, with a flabby yellow face, oedematous infra-orbital tissues, dry swollen hands, thin eyebrows, and sparse head hair. Axillary hair was completely absent and the pubic hair scanty. The voice was croaking and deafness was severe. The blood pressure was 155/100 and the pulse 66. He was mentally clear but sluggish. The rectal temperature was 91.4° F. (33° C.). An electrocardiogram showed slow voltage complexes with flat T waves in all leads. The haemoglobin was 11 g. per 100 ml. and the red-cell count 3,700,000 per c.mm.

Within 48 hours of admission the patient became drowsy, and, with the experience of the previous two cases as a guide, treatment was begun immediately. Thyroid siccum, 1 gr. (65 mg.) thrice daily, was given by mouth, and cortisone, 100 mg., and deoxycortone acetate, 10 mg., were given via an intravenous saline drip. There was no change in his condition during the next 24 hours, but on the following day he was stuporous. The rectal temperature was now only 87.5° F. (30.8° C.), and it was decided to substitute thyroxine