A Study of the Clinical Features of Malaria in Rhodesia

BY

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PART II.

Haemoglobinuria, at times accompanied by renal failure due to *P. falciparum,* in African patients has been recorded in Salisbury by Dukes *et al* (1968) and Gelfand (1972). Dukes *et al* regarded this occurrence as identical with the condition known as blackwater fever, which was associated with acute attacks of *P. falciparum* malaria in Europeans, and possibly related to inadequate treatment with quinine. They consider that this syndrome now appears in Africans (rarely seen in the European) because of the reduced immunity of the now urban African whose exposure to disease is reduced. However, Gelfand in 1972, recorded cases identical to the above in African patients suffering purely from typhoid fever which raised the question of other causes — for example a G-6-P-d deficiency or a microangiopathic haemolytic anaemia.

SERUM UREA.

A serum urea determination was carried out on 217 patients with *P. falciparum.* Of these seven were below 15 mg% (3 per cent.), 128 (59 per cent.) were normal, 16 were 35 mg%. Forty-four patients had readings between 36 and 45 mg% and 38 patients (18 per cent.) were over 45 mg% but below 100 mg%, and four patients had readings between 100 and 150 mg%, five had readings between 150 and 200 mg%, one patient had a serum urea of 243 mg% and another, discussed below (Case Report 3) had one of 610 mg%.

S. UREA (217 CASES)

Cases	*Urea*
128(59%)	<15
16	35
45	36 to 45
38	45 to <100
4	100 to 150
5	150 to 200
1	243
1	610

Case Reports 4, 3 and 2 refer to patients with raised serum urea levels.

Case Report 4. One patient was found to have a raised blood urea. A 20 year old male, G.M., Hospital No. 73457, from Salisbury was admitted on 15.5.70. He complained for a week of a headache and abdominal pains. He had been to a reserve recently. He was drowsy, pyrexial, had slightly slurred speech and was suspected of having typhoid fever. His temperature was 103,6°F and the spleen was palpable.

A blood slide showed numerous ring forms of *P. falciparum*. Urobilin and urobilinogen were present in the urine but bilirubin and haemoglobin were both absent. The patient had normal levels of glucose-6-phosphate dehyrogenase, and had a normal serum haptoglobin binding capacity. His haemoglobin was 11,8 gm% and Na was 4,8 mEq/1.

Four days after admission the patient became jaundiced and his blood urea rose to 190 mg%. He was treated with chloroquin and made an uneventful recovery.

Case Report 3. A 26 year old male, L.P., Hospital No. 96996, from Salisbury was admitted on 20.3.1971, confused, with a history of vomiting and darkening of urine for three days. On examination he was found to be slightly jaundiced with a temperature of 101° F. Blood slides showed numerous ring forms of *P. falciparum*. The spleen and liver were not palpable. His haemoglobin was 8,3 gm%, platelet count 58 000, serum potassium 3,52 mEq/1, haptoglobin binding capacity was 67 per cent. (normal) and glucose-6-phosphate dehydrogenase normal. Haemoglobin and bilirubin were both present in the urine. Serum urea was 610 mg%, the Widal test was negative. The patient had been treated with chloroquin (oral) and he made a good and uneventful recovery.

Case Report 2. A 19 year old female, Hospital No. 45487 from Salisbury was admitted on 26.2.1969 and was found to have typhoid fever.

She complained of a four-day history of headache, joint pains, vomiting, diarrhoea and fever. On examination, a one finger spleen was palpable. Blood slides showed scanty ring forms of *P. falciparum*. Her haemoglobin was 12,2 gm%, reticulocytes less than 2 per cent., serum potassium of 7,3 mEq/1 and blood platelets of 115 000 per cm.

The patient was treated with chloroquine (oral) on admission. Her Widal test was positive and *S. typhi* was isolated in a blood culture. After an initial improvement she became drowsy and was discovered to be uraemic due to acute renal failure (blood urea 185 mg%). She required haemodialysis on three occasions with supplementary blood transfusion. Following this, she became febrile; this relapse was treated with ampicillin.

She then made an uneventful recovery.

Sickling

Seventy patients were tested for sickling and three showed the sickle cell trait. These three all suffered from anaemia and jaundice and one patient was diagnosed as having cerebral malaria. All three had numerous ring forms in their peripheral blood slides. The clinical details of these three cases are given.

Case Report 10. Patient, M.M., Hospital No. 121454, a female, from Goromonzi, was referred from the maternity hospital in April (19.4.72). She had been admitted to the maternity unit in premature labour with a high fever. On admission she was comatose. Examination revealed an enlargement of the liver of two fingers. She was slightly jaundiced and her haemoglobin was 6,1 gm%. Her platelet count was 6 100. A sickle cell trait was present. Her blood urea was 174 mg%. She was diagnosed as having cerebral malaria and was treated with I.V. chloroquin and quinine. She made a full recovery.

Case Report 11. Patient, T.Z., Hospital No. 58827, a female aged 26 was admitted in March (17.3.70). She lived in Salisbury but had been to Mtoko recently. She complained of severe headache. On examination she had a three-finger enlarged spleen. She was pyrexial and showed a tinge of jaundice; her haemoglobin was 9,1 gm%. Blood slides showed numerous ring forms of *P. falciparum*. The sickle cell trait was demonstrated. She made an uneventful recovery with oral chloroquin.

Thus sickling is occasionally seen as these three cases show the person may be severely ill with the trait in his blood.

Of the 280 positive malarial cases with plasmodium parasites in their blood, only one death was recorded. The patient (M.K., Hospital No. 046259), 30 years old, was admitted from Gatooma on 9th March, 1969. On arrival, she was unconscious and had an incomplete abortion. She died 24 hours after admission. She was pyrexial, confused and comatose on admission. She was slightly jaundiced and was found to be tender over the splenic area on palpation. Her liver was three fingers enlarged. Her haemoglobin was 8,0 gm%, 100 ml, platelets 30 000,

prothrombin time 17 secs. (normal 12 secs.), blood urea 64 mg/100 ml. Her blood slide showed numerous ring forms of *P. falciparum*. Although diagnosed as having cerebral malaria, in view of her thrombocytopaenia and prolonged prothrombin time and the bleeding from her gums, we considered that she also had a coagulation disorder.

IMMUNOGLOBIN FINDINGS.

It was found that a large number of the patients tested had an increased IgM and IgG. Only seven out of 37 patients (19 per cent.) had increased IgA, 24 (25 per cent.) had increased IgM and 28 (76 per cent.) had increased IgG. (See Table VII).

Table VII.

SHOWING VALUES OF IgA, IgM, IgG.

IgA normal	(140- 420)	mg%	28
	(0- 139)	„	22
	(421- 800)	„	6
	(1200)	„	1
IgM normal	(50- 190)	mg%	33
	(0- 50)	„	3
	(191- 440)	„	23
	(950)	„	1
IgG normal	(500-1600)	mg%	29
	(0- 499)	„	0
	(1601-2500)	„	22
	(2501-5000)	„	6

Reports so far indicate that in acute malaria the IgM fraction seems raised initially and this is followed by a rise in the IgG (Beale *et al*, 1969), Beale found that many patients had a significant thrombocytopenia with raised IgM levels. In our series, we noticed that IgM levels were raised in 24 out of 49 cases tested. Of these 24 patients six had a thrombocytopenia. Of the 25 patients with normal IgM levels, nine had reduced platelet counts.

Soon after the onset of acute malaria, the IgG rises and in our series 28 showed this. In six cases the IgA also increased.

G-6-P-D *Deficiency*: Eighty-five patients were tested for G-6-P enzyme. Twenty-six were found to be deficient in it. In two patients the deficiency was marked. In 18 of them the malarial infection was moderate and eight patients had a scanty malarial infection. Of the patients showing this enzyme deficiency, six had jaundice and anaemia, and the enzyme defect may have been a factor in producing this picture. Four of the patients were confused on admission. None of them had more than a moderate infection of ring forms. Of the 59 patients who did not have the enzyme deficiency 48 had a moderate malarial infection and in 11 it was scanty.

It would seem that this enzyme deficiency does not protect the patient from contracting malaria. However, Maegraith (1974) claims that the carrier of the trait is protected, especially in heavy infections.

Reticulocyte Estimation: A reticulocyte count was carried out in 87 cases with malaria. In 53 per cent. the values were normal. However, in 23 cases (26 per cent.) it was slightly raised and in 21 per cent. the count was significantly elevated. One assumes that main factor causing the raised counts is haemolysis.

Reticulocyte Estimations: Nearly half the cases tested showed a reticulocytosis, mostly slight.

Table VIII.

No. of Patients Tested: 87			*Percentage*
46	normal	0,2 to 2%	53%
23		2,1 to 5%	26%
12		6 to 15%	14%
6		16 to 25%	7%

Blood Platelet Count: One hundred and fifty patients were tested and 47 per cent. of them showed thrombocytapenia, i.e., a count under 100 000/cm^3. In 34 cases (23 per cent.) it was below 50 000. (See Table IX).

Table IX.

Total No. of Patients	*No.*	*Percentage*
Up to 50 000	34	23%
5-80 000	18	12%
8-100 000	19	13%
100 000 and above	79	52%

Prothrombin Times: Forty-eight patients were tested and 2 per cent. had a normal prothrombin time. Ninety eight per cent. had prothrombin times above normal 12 seconds. (See Table X).

Table X.

Prothrombin Time	*No. of Patients*	*Percentage*
11 seconds	1	2%
12 „	0	
13 „	5	11%
14 „	15	31%
15 „	9	19%
16 „	5	10%
17 „	13	27%

Haptoglobin Binding Capacity: Fifty-seven of the 79 patients tested showed abnormal values. This is probably due to the release of excess bilirubin as a result of the haemolysis.

Jaundice: This is typically seen with lemon-tinting of the eyes but this sign is not always present. Fifteen per cent. (43) of the patients were jaundiced with some degree of icterus. (See Table XI).

Table XI.
DEGREE OF JAUNDICE.

		No. of Patients	*Percentage*
Slight		25	9
Moderate	43	15	5
Severe		3	1

Bilirubin: Of the 121 patients tested for total serum bilirubin, 47 had values 1,2 mg%. Of these 20 had a ratio between unconjugated bilirubin and conjugated bilirubin greater than one. Of the patients with a raised total serum bilirubin level (47), 18 had jaundice (See Figs. 9 and 10).

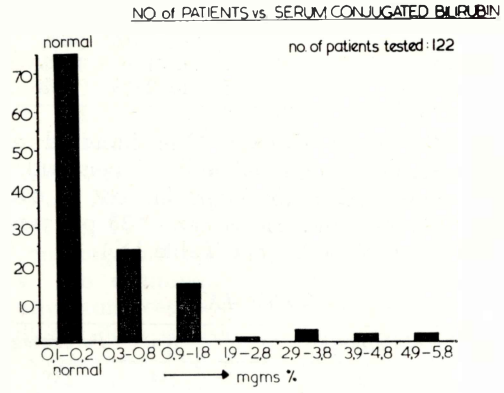

Fig. 9.

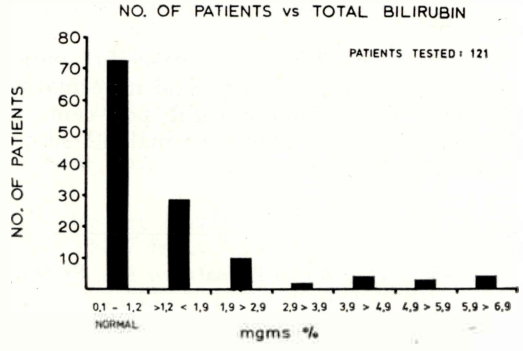

Fig. 10.

E.S.R.: One hundred and fifty-nine patients were tested. This was usually raised but not often above 100 mm/hr. Eighty-three patients (52 per cent.) had an E.S.R. below 50 mm/hr. and above 7 mm/hr. Fifty-one (32 per cent.) had above 50 mm/hr. and below 110 mm/hr. Eighteen patients had an E.S.R. above 110 mm/hr. and below 70 mm/hr. and seven patients had a normal E.S.R.

It seems that malaria does not cause greatly increased E.S.R. levels as is found in rheumatic fever and tuberculosis. See Fig. 11.

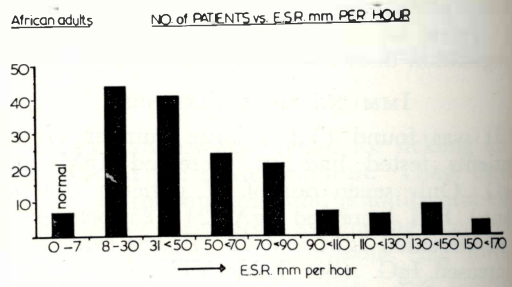

Fig. 11.

Alkaline Phosphates: As shown by Fig. 12. 92 out of the 122 (75 per cent.) patients tested had normal alkaline phosphatase levels.

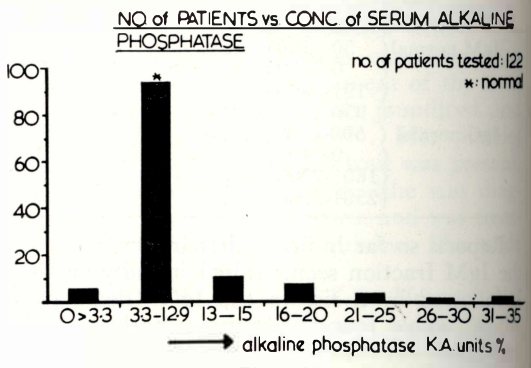

Fig. 12.

Serum Glutamic-pyruvic Transaminase: SGPT, as seen by Fig. 13 was mostly normal and in only a few areas an elevation was noticed.

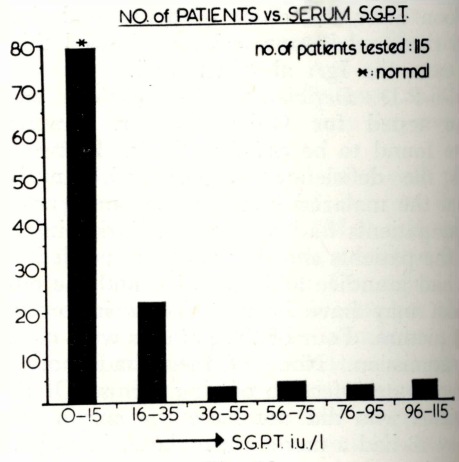

Fig. 13.

Serum Glutamic-oxoloacetic transaminase: Of the 109 patients tested only 47 (43 per cent.) had normal SGOT levels. This perhaps suggests some degree of liver damage in acute malaria. (See Fig. 14).

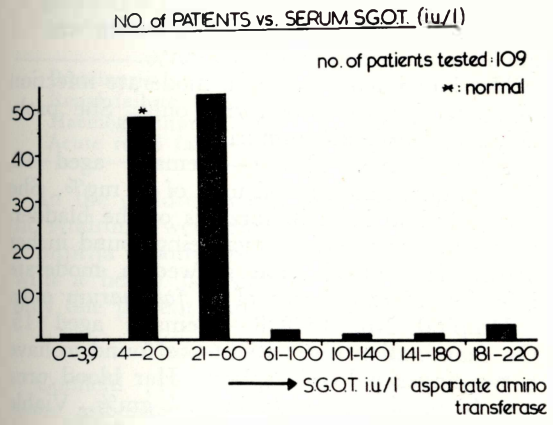

Fig. 14.

Serum Sodium: Of the 222 patients tested only 21 (9 per cent.) had a normal level of serum sodium while two patients had a raised serum sodium level. The remaining patients (199) had hyponatraemia. (See Fig. 15).

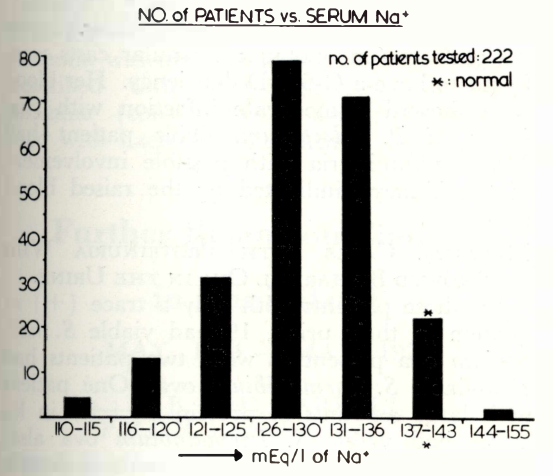

Fig. 15.

Dunn (1969) suggests that the hyponatraemia and hypokalemia may occur because of the parasitic involvement of the red blood corpuscle. He suggests that malaria alters erythrocytic sodium transport and thus interferes with the NaK pump. A second graph shows that only 81 of the 207 patients tested for serum potassium levels had normal readings.

Serum Proteins: These results were difficult to interpret because the serum protein levels are so often abnormal in the African population (Carr and Gelfand, 1960). Also the abnormal reading may not be attributed to malaria. It is difficult to rule out involvement of the liver. In these patients, however, marked changes were seen in the total serum protein levels. They were usually raised globulin levels and decreased albumin levels. (Maegraith 1974). (See Table 12 and Fig. 16).

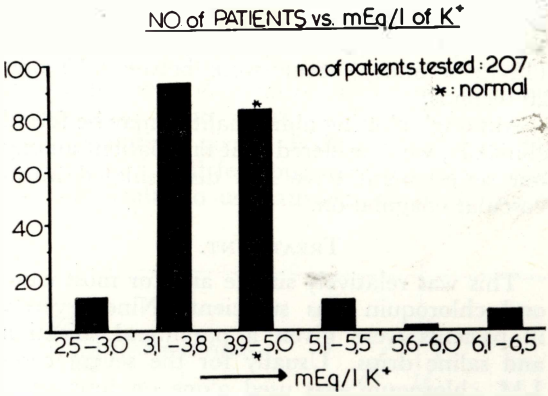

Fig. 16.

Table XII.
SHOWING RESULTS.

Globulin Fraction 29 Cases were elevated above normal.	*No. of Patients*
2,1 to 3,7 mg% (normal)	96
3,8 to 4,5 „	0
4,6 to 5,0 „	22
5,1 to 5,5 „	6
5,6 to 6,0 „	1
Albumin Fraction 86 Patients had a lowered albumin fraction.	*No. of Patients*
1,0 to 1,5 gm%	2
1,6 to 2,0 „	8
2,1 to 2,5 „	29
2,6 to 3,0 „	47
3,1 to 4,5 „	37
A/G Ratio.	*No. of Patients*
0,3 to 0,5 gm%	14
0,6 to 0,7 „	31
0,8 to 0,9 „	41
1,0 to 1,1 „	31
1,2 to 1,8 „	11
Total Serum Proteins If one takes 6,2 mg% as normal there were 58 cases who had serum proteins.	*No. of Patients*
4,0 to 4,5 gm%	2
4,6 to 5,0 „	2
5,1 to 5,5 „	11
5,6 to 6,1 „	43
6,2 and above (normal)	69

Possible D.I.C. Disease.

In our series, platelet counts were carried out in 25 cases and considering a count of less than 100 000 as reduced, there were 16 cases with a thrombocytopaenia count. Nine of these had a count below 50 000. F.D.P. tests were carried out in 27 cases and were found to be positive in 19 of these. Fibrinogen levels were tested in five cases and found to be reduced in two of these.

The prothrombin time was mostly normal (12-15 seconds), seven were between 15 and 20 seconds.

Although clotting abnormalities may be found clinically, we considered that one patient among our series might have had disseminated intravascular coagulation.

Treatment.

This was relatively simple and for most cases oral chloroquin was sufficient. Nine severely ill patients were given a parenteral injection and saline drips. Usually for the severe cases I.M. chloroquin was used alone on four occasions combined with I.V. quinine or three and I.V. quinine alone in four cases with one I.M. quinine alone. Oral chloroquin alone (600 mg% immediately followed by 300 mg daily for two days) was used for 261 cases. Six were given oral quinine alone and one case had oral chloroquin and primaquin.

Renal Involvement.

Protein in Urine:

Table XIII.
Showing Protein in Urine.

	No. of Patients
Negative	30
+	145
++	18
+++	6

Individual Reports of those Patients Found to Have a Large Excess (+++) of Protein in Their Urine.

Hospital No. 102834 — Female, aged 18. On examination, this patient was found to have puffy eyes and to be oedematous. She also had a two-finger palpable spleen. Her serum albumin was 1,6 gm% and serum globulin was 5,1 gm%. A 24-hour urinary sample contained 2,26 gm of albumin. Her blood urea was 17 mg%, blood cholesterol 93 mg%, haemoglobin 7,2 gm%.

Her blood slide showed a moderate infection of *P. falciparum* and *P. malariae*.

She was treated with chloroquin and made an uneventful recovery, and diagnosed as not having a nephrotic syndrome.

Hospital No. 45466 — Female, aged 6. On examination, this patient was found to have no splenomegaly. Her blood urea was 24 mg%, haemoglobin 6,5 gm%, serum albumin was 2,7 gm%, serum globulin was 3,3 gm%.

Her blood slide showed a moderate infection of *P. falciparum* ring forms only. She probably had febrile albuminuria.

Hospital No. 105569 — Female, aged 18. This patient had a blood urea of 29 mg%. She was found to have bilharziasis of the bladder, viable *S. haemotobium* ova being found in her urine. Her blood slide showed a moderate infection of ring forms of *P. falciparum* only.

Hospital No. 137888 — Female, aged 15. On examination, the patient was found to have a two-finger palpable spleen. Her blood urea was 46 mg%, haemoglobin 11,1 gm%. Viable *S. mansoni* ova were found in her stool.

A blood slide showed numerous ring forms of *P. falciparum*.

She probably had febrile albuminuria.

Hospital No. 117396 — Female, aged 35. Her blood urea was 52 mg%, haemoglobin 12,2 gm%, haptoglobins 58 mg% (normal), reticulocytes 12 per cent. serum albumin was 2,5 gm%, serum globulin Granular casts were found to have a G-6-P-D deficiency. Her blood slide showed a moderate infection with ring forms of *P. falciparum*. This patient had febrile albuminuria with possible involvement of the kidneys, indicated by the raised blood urea.

Malarial Cases with Proteinuria Who Showed Bilharzial Ova in the Urine.

Of those patients with only a trace (+) of protein in their urine, 19 had viable *S. haetobium* ova present as well; two patients had non-viable *S. haematobium* ova. One patient with large amounts of protein (+++) in his urine had viable *S. haematobium* ova also; two patients with moderate amounts of protein (++) in their urine also had viable *S. haematobium* ova.

Raised blood urea: This has been previously discussed.

Haemoglobinuria: This has also been previously discussed. Also refer to Case Reports 8 and 9.

Nephrotic Syndrome: This was seen in the children's cases. Also refer to Case Report 13.

Glomerulo-nephritis: This was also only seen in the children's cases. Refer to Case Report 14.

Renal Involvement.

Sitprija (1970) in Thailand, found renal involvement in 67 per cent. of his patients. Table 14 shows a comparison with our results.

Table XIV.

	Thailand	*Rhodesia*
Proteinuria	28,6%	60,4%
Renal failure (azotaemia)	14,3%	33,0%
Haemoglobinuria	2,4%	0,7%
Acute renal failure	21,0%	0,7%

In the children series, two cases of nephrotic syndrome were encountered.

Sitprija usually associated acute renal failure with a heavy parasittaemia but in our cases only one patient had a heavy infection.

Major Complications.

Confield (1969) lists the major complications associated with malaria in patients in Vietnam as acute renal insufficiency 0,6 per cent. cerebral malaria, 0,5 per cent. and pulmonary oedema in 0,1 per cent and haemotologic complications (figure not given). The major complications of the disease found amongst our patients were mainly cerebral malaria 3,2 per cent. and renal involvement, 34,4 per cent. Our results show that severe anaemia was uncommon except as in the form described with microangiopathic haemolytic anaemia (consumptive coagulopathy) associated with haemoglobinuria and oliguria.