BLACKWATER FEVER IN WEST AFRICA

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For a period of 20 months we were stationed at a general hospital in one of the West African colonies. This hospital was situated in well-drained uplands, its precincts being practically free of the anopheline mosquito, but within two miles the hills descended into large areas of swampy ground where subtertian malaria was rife. Most of the cases of malaria and all the cases of blackwater fever treated in this hospital came from these areas. During the 20-month period 2,355 cases of subtertian malaria in British and Allied personnel were admitted, the majority being from the British Army. In the same interval 7 cases of blackwater fever were admitted. There were no deaths from either disease. These cases of blackwater fever are presented because it is felt that this disease is of special importance while British and Allied troops are living and fighting in countries in which it occurs, and because it is not very rare for individuals to develop it after return to the United Kingdom from the Tropics. Such a case, rapidly fatal, was seen by one of us. An account of the clinical features and treatment of subtertian malaria in British troops in West Africa has already been given by Hughes and Bomford (1944).

Blackwater fever is a disease characterized by a sudden intravascular haemolysis, with the liberation of oxyhaemoglobin in the plasma. From this, methaemoglobin and methaemalbumin ("pseudo-methaemoglobin") are formed. Oxyhaemoglobin and methaemoglobin are excreted in the urine together with acid haematin, these blood pigments imparting the typical porter or stout colour to the urine. Methaemoglobin, with its much larger molecule, is never excreted. The two most important characteristics of the disease—namely, the haemolysis and the anuria—will be separately discussed.

Relationship to Malaria

Blackwater fever is now universally regarded as a complication of malaria, especially of the subtertian form. Stephens (1937) was able to collect only 7 cases in which it was associated with benign tertian or quartan fever. A fatal case following *P. ovale* infection is quoted by Fairley (1939). It is met with in those countries in which subtertian malaria is hyperendemic, and, as it principally affects the white races in such countries, has long been the dread of Europeans on the West African coast, being in part responsible for the unhealthy and somewhat sinister reputation enjoyed by that part of the continent. It is interesting to note that in the 20-month period only 168 African soldiers were admitted with malaria, although the total African admissions for all diseases far outnumbered the British. The West African, if he survives malaria in infancy and childhood, becomes relatively immune to it. We heard of no case of blackwater fever in a native soldier, but there were several among the Syrian settlers in the colony. It is generally stated that the seasonal incidence of blackwater fever closely follows that of subtertian malaria. This has certainly been our experience in this small series. In this colony malaria was endemic throughout the year, but it reached its peak in July and August—i.e., at the height of the rains—and five of our cases developed blackwater fever in July, August, or September.

All our cases had had previous attacks of malaria (Table I). Case VII had had only one recognized attack, but had taken no suppressive quinine, and there was reason to believe he had been very careless over antimalarial precautions in general. His malaria had been treated at another hospital with 30 gr. of quinine daily for 2 days, 0.3 g. of mepacrine daily for 5 days, and 0.03 g. of pamaquin daily for 4 days. The haemoglobinuria developed on the day after completion of the above treatment. Case III had been treated in our hospital for the sixth attack of malaria with 10 gr. of quinine and 0.3 g. of mepacrine daily for 7 days, followed by 0.03 g. of pamaquin daily for 3 days. This patient was perfectly well when dis-

charged, but he got wet through on the way back to his unit and was readmitted with blackwater fever the same evening. Three patients developed the disease during actual treatment for malaria in our hospital. In all of them the urine had been normal before the onset of the haemoglobinuria and had been kept alkaline. Thus, Case I developed it on the second day of treatment after a total of 60 gr. of quinine, Case IV also on the second day after 30 gr., and Case V on the seventh day after 150 gr. of quinine and an intramuscular injection of 0.2 g. of mepacrine hydrochloride. The latter was given as the temperature, which had almost settled, rose suddenly to 104° F., this rise probably corresponding to the onset of the haemolytic process. Haemoglobinuria followed two and a half hours after the injection. This patient was also receiving treatment for amoebic dysentery. These three cases, and also Case III, had not been thoroughly treated for previous attacks of malaria. We are of the opinion that the fact that blackwater fever may arise during what appears to be an ordinary uncomplicated attack of malaria has not been sufficiently stressed; there has been too great a tendency to regard it as developing only in subjects with malarial cachexia who have been resident in the Tropics a long time. Three of our cases had been in West Africa for less than one year. We were unable to recognize a "pre-blackwater fever" stage in any of those who developed the disease in hospital. Conversely, we saw many malarious patients in whom the cachexia and history of previous attacks led us to believe they were likely candidates for blackwater fever but who did not, in fact, develop it.

Clinical Features

A full account of these may be found in standard works. The most important biochemical and other details of our cases are summarized in Tables I and II.

TABLE I

Case	Age	Residence in W. Africa	Previous Attacks of Malaria	Suppressive Quinine
I	25	20 months	2	Regular
II	20	8 "	2	"
III	27	16 "	6	"
IV	31	11 "	7	"
V	23	19 "	5	Irregular
VI	36	18 "	5	Regular
VII	20	6 "	1	None

A rigor, said to be typical of the onset, occurred at the beginning of the illness in one patient only. Of the cases which developed blackwater fever during treatment for malaria, Case V, as already stated, showed a sudden rise of temperature with the onset of haemoglobinuria. In Cases II and IV the temperature also rose to 102° and 104° F. respectively. These three patients also showed a very abrupt rise in the pulse rate. Such an increase in the rate of the characteristically slow pulse of malaria is of importance, and should lead to an immediate examination of the urine for haemoglobin. Except in Case I, a rapid pulse of 100–120, of poor volume, was a constant feature in all the patients. The duration of the fever corresponded to the acuter stages of the disease, except in Cases III and IV, in which a fever of 99–99.5° F. was prolonged well into convalescence—the so-called "post-haemoglobinuric fever." Only Case I was afebrile throughout.

The jaundice, together with anaemia and cachexia, imparted a characteristic appearance which sun-tan rendered all the more striking. The general impression obtained was of great weakness; these men were disinclined to move, and a constant complaint was of feeling "very ill." In no instance was the liver palpable, although tenderness over it was elicited in three instances. In Cases II, IV, and VII the blood pressure was low during the first few days, readings of 96/40, 92/45, and 94/90 respectively being obtained. In Case VI the blood pressure, which was 108/66 on the second day of the illness, rose at the same time as the blood urea to 150/80 on the ninth day. A leucocytosis of 25,000 and 30,000 occurred on the first and fourth days respectively in Cases V and VII. Cases VI and VII developed a reticulocytosis of 5% and 9% respectively during recovery from the anaemia. Convalescence was prolonged, the average length of stay in hospital being 45 days. All patients were invalided to the United Kingdom with a recommendation that they should not again be sent to a malarious country.

The mortality varies from 25 to 50%, according to different authors. Findlay (personal communication, 1944) states that the mortality rate for the whole West African Command over a period of three years was 28.8%. We are indebted to him for permission to give this figure.

Haemolysis

In subtertian malaria a haemolytic anaemia occurs, but the reticulo-endothelial system is capable of dealing with the liberated haemoglobin, transforming it into haemosiderin and bilirubin, and only in the severer cases can free haemoglobin be demonstrated in the plasma (Stitt, 1942). In blackwater fever, however, the haemolysis occurs with such explosive

fragility of the red cells consequent upon lowering of the pH of the blood, but apparently made no actual observations in blackwater fever. They based their conclusions upon *in vitro* experiments with red cells suspended in saline buffered to different pH levels. Of more significance is the work of Maegraith, Findlay, and Martin (1943), who showed that normal human serum inhibited the haemolytic action of animal tissue upon homologous red cells. This antihemolytic effect was reduced in sera from cases of blackwater fever, especially during haemolytic crises, suggesting that the haemolysis is due to a lack of an antilytic substance rather than to the presence of a lysin. This would appear to be a promising line of investigation. Fernán-Núñez (1936) thinks blackwater fever is

TABLE II.—Details of Cases

Case	Parasites in Blood	Red Cell Count and Hb %	Urine			Blood Urea Mg. per 100 c.cm.	Blood Transfusions	Intravenous Fluids	Remarks
			Hb Pig.	Alb.	Casts				
I	Scanty (1)	4,140,000 Hb 82 (4) 5,060,000 Hb 100 (8)	+ (1-2)	+ (1-2)	+ (1)	95 (4) 70 (7) 27 (13)	None	None	Mild case. No jaundice or vomiting
II	Absent	3,670,000 Hb 72 (2) 3,080,000 Hb 56 (4) 3,720,000 Hb 55 (6)	+ (1-2)	+ (1)	None	25 (3) 20 (4)	None	Sod. bic. soln. 30 oz.; N. saline 20 oz.	Moderately severe case. Slight jaundice; no vomiting
III	Absent	4,750,000 Hb 90 (2) 3,150,000 Hb 53 (4) 1,320,000 Hb 30 (9) 2,200,000 Hb 36 (11) 4,540,000 Hb 72 (29)	+ (1-5)	+ (1-8)	+ (4-11)	25 (2) 30 (5)	1 pint* (4) 12 oz.* (5) 15 c.cm.* (9) 1 pint (10)	Plasma 14 oz.; sod. bic. soln. 5 pints; glucose-sal. 6 pints	Severe case. Jaundice; vomiting; spleen palpable; loin pains
IV	Absent	4,210,000 Hb 80 (1) 3,280,000 Hb 60 (3) 3,900,000 Hb 60 (6)	+ (1-3)	+ (1-3)	+ (1-2)	45 (2) 30 (5)	None	Sod. bic. soln. 60 oz.; glucose-saline 20 oz.	Moderately severe case. Slight jaundice; vomiting; loin pains
V	Absent	3,200,000 Hb 63 (1) 3,140,000 Hb 62 (3)	+ (1-3)	+ (1-3)	None	37 (2) 30 (6)	None	Sod. bic. soln. 40 oz.; plasma 20 oz.	Moderately severe case. Slight jaundice; vomiting; spleen palpable
VI	Scanty (2) (3)	3,820,000 Hb 80 (1) 930,000 Hb 18 (5) 800,000 Hb 20 (7) 1,600,000 Hb 43 (10) 2,500,000 Hb 56 (35)	+ (1-3)	+ (1-15)	+ (1-13)	45 (3) 135 (6) 185 (11) 30 (35)	20 oz.* (5) 20 oz.* (7) 40 oz.* (8) 12 oz.* (11)	Sod. bic. soln. 67 oz.; glucose-sal. 40 oz.; sod. lact. soln. 40 c.cm.	Very severe case. Marked jaundice; severe vomiting; persistent hiccup; anuria 6th-7th day lasting 22 hours
VII	Absent	1,050,000 Hb 28 (2) 2,100,000 Hb 50 (4) 2,900,000 Hb 50 (7) 4,000,000 Hb 77 (15)	+ (1-4)	+ (1-7)	+ (4-5)	40 (3) 26 (5)	20 oz. (2) 20 oz. (3)	Sod. bic. soln. 60 oz.; glucose-saline 8 oz.	Severe case. Jaundice; vomiting; loin pains

Figures in brackets = days of disease. * Transfusion reaction.

suddenness that the renal threshold for haemoglobin is exceeded and this pigment appears in the urine. The cause of this sudden haemolysis is still unknown. The mystery is further increased when it is considered that severe cases of subtertian malaria, in which there is a profound anaemia and in which a large percentage of the circulating red cells may be parasitized, are quite common; and yet this is not the type of case which develops blackwater fever. Preceding and during the disease parasites are scanty in the peripheral circulation, often entirely disappearing early in the illness.

For nearly a hundred years quinine has been considered a precipitating factor, and recently Cust (1943), Frewen (1943), and others have reported cases arising during quinine therapy, while Foy and Kondi (1938) state that the relation of the last dose of quinine to the onset of blackwater fever is so significant as to be more than casual. Fairley and Murgatroyd (1940) describe a patient with blackwater fever in whom four recurrent attacks of haemoglobinuria occurred, each precipitated by quinine. The relationship of the haemoglobinuria to the taking of quinine has already been mentioned in our cases. Yet the disease has occurred during treatment with mepacrine or pamaquin and in patients who have never received any quinine at all. In Case I haemoglobinuria returned after mepacrine treatment had inadvertently been started on the second day of the illness and disappeared as soon as the drug was discontinued. The part played by quinine in the aetiology is, of course, obscured by the fact that most patients with malaria are treated with this drug. In this connexion the statement by Findlay (personal communication, 1944), that the incidence of blackwater fever in the West African Command has considerably diminished since the substitution of mepacrine for quinine as a suppressive and as the therapeutic drug for uncomplicated malaria, is of great significance.

Other theories may be briefly discussed. Smith and Evans (1943) attempted to prove that the haemolysis is due to increased

an allergic reaction to the malaria parasite protein, and claims that persons liable to the disease show a positive reaction to the intradermal injection of non-infective suspensions of *P. falciparum*.

Cold seems to be a precipitating cause (Case III). There is here an analogy with paroxysmal haemoglobinuria, but in blackwater fever the Donath-Landsteiner reaction is negative.

The Anuria

Amongst other lesions the kidneys show blood-pigment casts in the tubules that are generally thought to be composed of acid haematin. Yorke and Nauss (1911) were able to produce renal obstruction by injection of haemoglobin into animals provided they were kept on a dry diet. They considered the obstruction was due to precipitation of acid haematin in the tubules from a concentrated urine. Baker and Dodds (1925), from similar experiments, considered that whether obstruction developed or not depended on the reaction of the urine. Obstruction occurred if this was acid but not if alkaline. Treatment of blackwater fever with alkalis, in an attempt to prevent anuria, became almost universal as a result of these experiments. Foy *et al.* (1943), in a review of the problem, point out that anuria in blackwater fever may develop in patients who have had a small haemolysis and who pass alkaline urine and, conversely, may not occur after a large haemolysis when the urine is acid. They also state that anuria is no less common since the introduction of alkali treatment. Maegraith and Havard (1944) share this view and emphasize the dangers of indiscriminate alkali therapy. Bywaters and Dible (1942, 1943), however, state that the renal lesions in cases of mismatched blood transfusion, crush syndrome, paralytic myohaemoglobinuria, and blackwater fever are very similar. In all these conditions pigment casts occur in the tubules, and although these observers do not consider they are the chief cause of the anuria, their cases of crush syndrome apparently

benefited by alkali therapy. In addition to the pigment casts there is a catarrh of the whole nephron, falling with especial severity on the ascending loop of Henle and the second convoluted tubule. They point out that it is in these portions of the tubules that acidification of the urine probably occurs, and that the selective damage to these structures which can be produced by the injection of uric acid and acid sodium phosphate into animals has been attributed to this. They consider that the anuria in the above conditions is chiefly due to reabsorption of glomerular filtrate into the blood stream through damaged tubules. Maegraith and Havard (1944) state that the greatest damage in blackwater fever is in the distal convoluted tubule. As in blackwater fever an acidosis is usually present, the urine is highly acid, and the alkali reserve is lowered, there would appear to be a good argument in favour of alkali treatment. Those who state that it is of little value do not indicate whether this is still true if it is used early in the disease. We consider it should be used as early as possible—in fact, the urine of all our cases of malaria was kept alkaline as a routine. Thus Cases II, IV, and V had alkaline urine before the onset of the haemoglobinuria. In only Case VI did anuria develop, and then for a relatively short period. With care there is little danger of alkalosis, but alkalis should be stopped or be used sparingly if anuria or oliguria occurs, for there is then a danger of alkalosis even if the urine is still acid.

It should be emphasized that dehydration from excessive vomiting and sweating is probably an important factor in the production of anuria and oliguria in many cases. In Case VI, for instance, vomiting was unusually prolonged and severe. Loss of chloride in vomitus and sweat will, moreover, augment the danger of alkalosis from indiscriminate alkali therapy and will also increase the tendency to nitrogen retention. We thus consider that an ample fluid intake by oral and intravenous routes is just as important as alkali therapy, and, in addition to alkaline solutions, we used glucose-saline or normal saline to replace chloride loss (Table II). In all our patients save Case VI urinary excretion was kept abundant throughout the course of the illness by these means.

Treatment

The general treatment consists largely in skilled nursing, which in no other disease is of greater importance. The patient is often in a condition resembling shock, and death from circulatory failure is therefore a danger. Complete rest on a low pillow is necessary and the patient is forbidden to sit up or feed himself. In West Africa, cases diagnosed in units, unless close to the hospital, were not moved, but were treated in their own lines by a mobile medical team based on the hospital. A full description has been given of these teams by Findlay (1943). Large quantities of water and fruit juice with glucose should be given, and all other food except small amounts of milk or junket withheld until acute symptoms have subsided. The daily fluid intake by the mouth should be at least 8 pints. Proteins should be restricted until well into convalescence. Fluid intake and output charts should be kept. Individual symptoms such as vomiting, hiccup, and hyperpyrexia must be treated as they arise. In Case VI all attempts to arrest the distressing hiccup, including cocaine by the mouth, failed. For severe loin pains, atropine 1/200 gr. was of value in Case VII. Oxygen, nikethamide (coramine), adrenaline, and bed blocks must be available for circulatory failure. It is useful to keep successive samples of urine in test-tubes so that the reaction and the degree of pigmentation can be easily observed, while a red cell count and a haemoglobin estimation should be undertaken daily.

Blood Transfusion

This is necessary if a dangerous degree of anaemia develops after massive haemolysis, but considerable judgment must be exercised in individual cases in deciding when to transfuse. Blood should never be given if oliguria is present. It is stated that in blackwater fever the donor's cells are liable to haemolysis as well as those of the recipient. Consequently, cross-grouping is always necessary. In spite of this precaution two of our cases had severe reactions (Table II). In Case III attempts at transfusion were persisted in; the fourth, which was uneventful, undoubtedly saved the patient's life. This transfusion was given very slowly, a pint being administered in 4½ hours. In

Case VI the first transfusion was continued in spite of a rigor, as the patient was moribund. The anuria which followed this was possibly precipitated by it. The absence of reactions and the non-appearance of haemoglobinuria during subsequent transfusions in this patient suggest that the failure of these to raise the red cell count was at least as much due to the normal haemolytic process of the disease as to haemolysis induced by the transfused blood. In Case VII we transfused early on the second day of the disease while haemoglobinuria was still present. One pint was given at the rate of 8 drops to the minute, being preceded and followed by one pint of 2% sodium bicarbonate solution. A similar procedure was carried out the next day, 10 oz. of blood being followed by one pint of sodium bicarbonate solution and then by a further 10 oz. of blood. In this patient, a rise of one million red cells per c.mm. was obtained in 48 hours in spite of continued haemolysis, and no reactions were observed. This method would appear worthy of further trial.

Prevention of Anuria

On diagnosis an intravenous drip of 2% sodium bicarbonate was set up immediately, 1 to 2 pints being administered fairly slowly—i.e., 1 drop every 2 seconds. A rate of three pints in 24 hours was never exceeded, but recourse was had to intravenous saline, saline-glucose, or plasma to keep the excretion of urine abundant and to replace chloride loss. At the same time, sodium bicarbonate 1 dr. four-hourly was given by mouth and as much bland fluid as the patient could be made to take. In the Tropics a urinary output of from one-half to two-thirds of the intake appears to be satisfactory in blackwater fever. In Case VI the injection of 20 c.cm. of a mixture of equal parts of saturated sodium bicarbonate and 3-mol. sodium lactate was tried, as recommended by Findlay (1942), because difficulty was experienced in maintaining alkalinity of the urine. This was without effect, probably because the kidneys were failing. The first specimens of urine passed after 22 hours' anuria were still acid. Possibly alkalis were pushed too hard in this case, but they nevertheless seemed to do no harm. This patient was, in any event, desperately ill. The treatment of established anuria consists in the application of heat to the loins, and dry cupping may be tried. In Case VI this was apparently successful. As already stated, alkalis should be discontinued.

In order to treat the accompanying malaria, a course of mepacrine, starting in small doses—e.g., 0.1 g. daily, gradually increasing to 0.3 g. daily—should be given during convalescence. It is probably best to give mepacrine even if no parasites are present in blood films—which is usually the case—as otherwise a malarial relapse may occur. Anaemia should be treated by good food and large doses of iron.

Summary

Seven cases of blackwater fever in British Service personnel in the West African Command are described.

The relationship of the disease to subtertian malaria and the mechanism of the haemolysis and the anuria are discussed. Special reference is made to treatment with blood transfusion, alkalis, and a large fluid intake. Evidence is produced to show that alkalis are probably of value in preventing anuria.

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