HÆMOGLOBINURIA: A NEW PROBLEM ON THE INDIAN FRONTIER.

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"... O! be some other name:
What's in a name? That which we call a rose
By any other name would smell as sweet...
"

Juliet may be forgiven that. Even a doctor, in love, may be pardoned an equally questionable pronouncement; but no doctor, in full possession of his faculties, can be allowed to use a symptomatic diagnosis or title such as "hæmoglobinuria" without protest. Explanation or excuse will be expected of him.

I plead ignorance, and the admission is a serious one, because elucidation of the conditions which give rise to the sign of hæmoglobinuria has, in this case, become a matter of some urgency and importance.

This new problem on the frontier has now reached a stage where enlightenment waits upon intelligence, and the sooner and wider such intelligence as we have at our disposal is broadcast, the quicker is the puzzle likely to be solved.

This particular form of hæmoglobinuria is connected with malaria and/or with treatment for malaria. As a preliminary, the reader is asked to be lenient when requested not to confuse hæmoglobinuria with hæmaturia. As everyone knows, hæmaturia is one of the recognized complications of malaria. It may occur in an intermittent form [1] or it may come as an acute attack [2], and it is not as uncommon as many writers lead us to suppose.

We may leave hæmaturia at that and proceed now to consider a recent and hitherto unknown phenomenon on the Indian frontier: hæmoglobinuria in some way associated with malaria and confined to Indian troops and followers. So far, we have records of ten cases, with six deaths.

Can any of these cases be labelled malarial hæmoglobinuria, i.e., blackwater fever?
Are any of them due to plasmocline toxicity?

These are the outstanding questions to which we now seek the answers. The evidence tends to show that both questions may be answered in the affirmative, but we are still in the dark regarding details of the aetiological processes involved.

Haemoglobinuria is a symptom which occurs under conditions as varied as they are numerous [3]. Fortunately, we need not here concern ourselves with most of the divers causes, and alleged causes, of haemoglobinuria. It will suffice to remember that their name is legion and to proceed at once to study the problem with one foot planted on the distinctive features and the other on the common characteristics of the cases now under review.

Geographical Distribution.

Geographical distribution is limited to the frontier, and the cases occurred by stations in the following order:—

1. Fort Sandeman, Baluchistan .. Aug. 30, 1933
2. Peshawar, N.W.F.P. .. Sept. 22, 1932
3. Kohat, N.W.F.P. .. Nov. 20, 1932
4. Quetta, N.W.F.P. .. Aug. 2, 1933
5. .. .. .. 8, 8
6. .. .. .. 8, 11
7. .. .. .. 11, 4
8. .. .. .. 11, 18
9. Wana, Waziristan, N.W.F.P. .. 4
10. Kohat, N.W.F.P. .. 18

That is, during the malaria season in 1932, three, and in 1933 (up to the month of August) seven cases of haemoglobinuria were reported from the north-west frontier of India. These cases were scattered along a line extending for 250 miles, from Fort Sandeman in the south to Peshawar in the north. Five were isolated and five—in Quetta in 1933—were grouped both as regards time and place.

As there exists the possibility of blackwater fever, this geographical distribution must at once arouse the interest, and suspicion, of the tropical epidemiologist because, up to date, no case of blackwater fever in India has been reported west of longitude 75° (Amritsar).

The nearest point to that, in our present series, is on longitude 71.5° (Kohat).

The distance from Amritsar to Kohat is nearly 250 miles.

But although the occurrence at Amritsar of blackwater fever is mentioned in Manson's "Tropical Diseases" (1929) the observation is of no general significance: the Punjab is not a recognized blackwater fever area.

"The regions in India in which haemoglobinuric fever is endemic are as follows: between the Ganges River and the Himalayas in Behar Province; between the Godavari and the Mahandi Rivers in the Madras Presidency; a region in the Punjab between Meerut and the Indus
River [4]; a region of which Nagpur is the centre; certain localities in the region of Bombay; and in Assam and upper Burmah” [5].

Byam and Archibald specify the Dooars, Assam, the Jeypore District in Madras, some parts of the Central Provinces, Bengal (Puruoia), and the Kanara District in the Bombay Presidency.

On page 71 of Rogers’ and Megaw’s “Tropical Medicine” (1930) there is a good blackwater fever map of India. From this it will be seen that a line drawn in a north-easterly direction from Surat, on the west coast, to Dehra Dun at the foot of the hills in the north, divides the country into hæmoglobinuric and non-hæmoglobinuric areas. The portion north and west of this line is clear, and Amritsar is therefore excluded.

“In places where malarial infection is limited to a brief season in each year the disease is uncommon or unknown, even though the malaria may occur as severe epidemics. It is decidedly rare in places which are visited at intervals of several years by epidemics of malaria, even when these are very severe as in the Punjab. It is practically unknown north of 40° N or south of 20° S.”

Now the line Fort Sandeman-Peshawar lies well within these parallels of latitude, while Macedonia is actually north of 40° N. In Macedonia in the year ending October 31, 1918, there were 136 cases of blackwater fever with 36 deaths [6], and in Macedonia, malaria is just as seasonal as it is in the Punjab. The same is true of Italy, Sicily, Sardinia and Greece [5].

It is evident, then, that a northerly latitude and a seasonal prevalence of epidemic malaria do not necessarily preclude blackwater fever.

Of the exceeding rarity of the disease in the Punjab, Indian maliologists have no doubt. Sinton, in the discussion following Professor J. W. W. Stephen’s paper on the “Hæmoglobinurias,” stated: “he had no experience of blackwater fever, not having worked in such an area; for in the Punjab, in spite of the occurrence of intense autumnal malaria, largely subtertian, and of big periodical epidemics (such as that of 1908 which in three months killed 250,000 people out of a population of 20,000,000) no indigenous blackwater fever existed.” Again on October 20, 1932, at the Royal Society of Tropical Medicine and Hygiene, Sir Rickard Christophers is reported to have said that: “The Punjab is not highly endemic. We know that the spleen rate over large parts of that area is only, say, five per cent, which is not worth considering. Certainly it is not a highly endemic area. There may be hyperendemic tracts, but in such places there is not usually the susceptible population of planters and missionaries such as we find in the blackwater areas in India. In the Punjab one would not expect to find blackwater fever judging by the malaria conditions. In India, on the other hand, those areas in which blackwater fever occurs are the areas which are picked out on the map as showing high endemicity, and wherever conditions have been carefully worked out the association has held good” [7].

This statement, from so eminent an authority, is arresting, because
every military medical officer in India knows that: (a) The Indian troops are heavily infected with chronic malaria; (b) when men are apparently "cured" and proceed on leave to their homes (in most cases situated in the Punjab), they nearly always rejoin their units with fresh malarial infections; (c) the majority of these men are not natives of the "hyperendemic tracts."

We know that "the spleen index does not give so accurate an estimate of the amount of malarial infection existing at the moment as the endemic index, but, on the other hand, it gives a better idea of the degree to which malaria ordinarily prevails in the place." [8].

It is with surprise that one receives Sir Rickard Christophers' low estimate of about five per cent, especially in face of the following figures:

<table>
<thead>
<tr>
<th>The Punjab</th>
<th>Percentage of children with enlarged spleens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amritsar town</td>
<td>63.4</td>
</tr>
<tr>
<td>Amritsar villages</td>
<td>87</td>
</tr>
<tr>
<td>Palwal town</td>
<td>88</td>
</tr>
<tr>
<td>Palwal villages</td>
<td>82</td>
</tr>
<tr>
<td>Delhi</td>
<td>62 [9]</td>
</tr>
</tbody>
</table>

In the Chenab villages the percentages are given as 77, 75 and 59 for the years 1908 to 1910 [10].

The fact that these figures were obtained from areas which suffered heavily in the epidemic of 1908 does no more than mildly modify our surprise.

It will be noticed that when Sir Rickard Christophers uses the term "endemicity," he means the constant prevalence of a disease in a community. But, in the Punjab and on the frontier, although manifestations of malaria are not equal and constant throughout any one year, they are, generally speaking, fairly equal and constant over a period of years. Measured by the year, the disease is epidemic: its prevalence is periodic. Measured by years, the disease is endemic: its prevalence varies little.

These factors have been discussed in some detail, because the Punjab is the next door neighbour, and malarially speaking closely related to that section of the frontier with which we are now concerned; and although the absence of blackwater fever in the Punjab has often been commented on and stressed, in this connection the frontier seems to have been left out in the cold.

The Indus divides the Punjab from that part of the frontier with which we are now dealing; but while this great river is a convenient, natural, and administrative boundary, its presence does not help to solve our problem because, up to a point, the country trans-Indus is much the same as the country cis-Indus. Thus, from a geographical standpoint, if haemoglobinuria is unknown in the Punjab, there is no reason why it should occur in the plains of Peshawar and Kohat.

Beyond these plains topography undergoes a marked change, and we
find that Wana and Fort Sandeman are perched on sub-montane elevations, at heights of 4,500 feet and 4,600 feet respectively, in the ranges of Waziristan and Baluchistan. Hence, while these regions do not resemble the contiguous, far-reaching plains to the east, and have no geographical or climatic affinities at all with such districts as the Dooars and Kanara, they do possess many features in common with a known blackwater fever region in the west, viz., Macedonia.

**RACE, CASTE, AGE AND OCCUPATION.**

The fact that all our patients were Indians is dead against a blackwater fever hypothesis. Europeans are more susceptible than any other race: the disease selects the immigrants rather than the indigenous inhabitants; and even if native troops and followers on the frontier be regarded as immigrants, we should still expect a heavier incidence amongst the British than amongst the Indians. Deaderick, quoting Daniels, says that although imported Indians are affected, they are only one-fourth as susceptible as Europeans [11].

Some further particulars of the patients—all men—are as follows:

<table>
<thead>
<tr>
<th>No.</th>
<th>Class</th>
<th>Age</th>
<th>Occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mussalman officer</td>
<td>45</td>
<td>Infantry</td>
</tr>
<tr>
<td>2.</td>
<td>Sikh officer</td>
<td>32</td>
<td>Medical</td>
</tr>
<tr>
<td>3.</td>
<td>Pathan N.C.O.</td>
<td>23</td>
<td>Infantry</td>
</tr>
<tr>
<td>4.</td>
<td>Baluch coolie</td>
<td>18</td>
<td>R.A.F.</td>
</tr>
<tr>
<td>5.</td>
<td>Mussalman sepoys</td>
<td>27</td>
<td>M.T.</td>
</tr>
<tr>
<td>6.</td>
<td>Baluch follower</td>
<td>38</td>
<td>Bakery</td>
</tr>
<tr>
<td>7.</td>
<td>Hindu cook</td>
<td>24</td>
<td>R.G.S.</td>
</tr>
<tr>
<td>8.</td>
<td>Hindu sepoys</td>
<td>28</td>
<td>Infantry</td>
</tr>
<tr>
<td>9.</td>
<td>Hindu follower</td>
<td>30</td>
<td>Cav. syce</td>
</tr>
<tr>
<td>10.</td>
<td>Sikh gunner</td>
<td>21</td>
<td>Artillery</td>
</tr>
</tbody>
</table>

With one exception (No. 8), all these men were natives of the Punjab or the frontier. The Hindu sepoys was a resident of Lucknow District, where blackwater fever—if it exists at all—is not common. Of the remainder, with one exception, none had lived in, or even visited, any blackwater fever area. This is not surprising, since the bulk of the personnel of the Indian Army, and the population trans-Indus, are born and remain west of the line Surat-Dehra Dun. With these classes there is very little coming and going between their native places and "down country." The exception was Case No. 1—an officer who had served in East Africa in 1915-16. He was admitted to hospital for malaria on August 24, 1932, developed haemoglobinuria on August 29 or 30, and died on the latter date. He was diagnosed "blackwater fever" by a medical officer who had had previous experience of the disease. The patient's documents contain these remarks:

"The signs were unmistakable to one who had seen cases of blackwater fever in East Africa during the War."

"Although there is now no documentary evidence in support, the late
jemadar, while ill in hospital at Fort Sandeman, told his brother (who was visiting him at the time) that his present illness was identical with the one he had in East Africa.

"Perhaps his service in East Africa had something to do with the attack of blackwater fever from which he died."

These remarks may be commented on thus:

(a) The deceased's alleged statement comes to us secondhand, through the brother.

(b) Indian troops, and their relatives, are very much alive to the advantages accruing from "attributability to service in the field."

(c) This patient—like nearly all our Indian troops and followers—was an old malarial subject. The degree of splenic enlargement indicated that he must have suffered from repeated bouts in the past. Being an officer, it may be presumed that he "stuck it," with inadequate treatment. This type generally pays little or no attention to slight attacks of "fever." He goes to his sub-assistant-surgeon, gets a few doses of quinine, and carries on. No better preparation for blackwater fever could be imagined.

(d) Are we to believe that, when in East Africa, the patient was infected with a strain of parasite which remained alive, without giving rise to serious trouble, for a period of sixteen years; and that, at the end of that period, it suddenly flared up and killed him? If so, this series of events is not in consonance with the accepted life history of Plasmodium falciparum. It is true that this parasite may remain latent for quite a long time. "Maurel states that outbreaks of pernicious malaria may occur several years after return to France from the tropics, and without new infection" [12]; but it is too much to concede that P. falciparum will lie in the system of a soldier—exposed as he is to the climatic and physical exigencies of military service—in a condition so quiescent that, for a space of no less than sixteen years, the host has not a single admission to hospital prior to the fatal ending.

**Malarial Parasites.**

According to the case sheets, malarial parasites of the following types were identified in the blood smears: malignant tertian rings in four cases; benign tertian rings in four cases; benign tertian schizonts in one case. No parasites in one case—but this patient had a definite history of malignant malaria in 1929 and 1930, when malignant tertian parasites were found.

The apparent proportion of malignant tertian to benign tertian is therefore as 50 to 50. At this time, in all these stations, the malaria season was at its height and both forms of the disease were rife. In Quetta, the visitation was unusually severe. It is possible that some of the cases diagnosed "B.T." may, in reality, have been cases of mixed infection.

Further, it is not always easy, even for the expert, to differentiate benign tertian and malignant tertian rings with complete certitude; it may be impossible to come to a definite decision in the absence of more advanced forms of the benign tertian parasites. Hence, in the presence of rings
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only, it is often justifiable to regard the label “B.T.” with an open mind. Gordon Thompson has described, and demonstrated on slides, malignant tertian parasites showing unusually large rings. These parasites were obtained from the blood of patients in Rhodesia; but Sinton states that he has never met with such forms in India [13].

The latest work on this subject is suggestive; and I would respectfully urge those readers who are interested to study the Transactions of the Royal Society of Tropical Medicine and Hygiene, Vol. xxvi, pp. 204 to 240. Therein, Dr. George Giglioli brings forward fresh evidence in support of the theory that the causative agents of blackwater fever are special haemolytic strains of malarial parasites. The disease “is the direct result of special haemolytic strains or biological varieties of the plasmodium and more especially of P. falciparum; such strains, for the present, cannot be morphologically differentiated from the ordinary forms of malarial parasites.” Also—“The epidemiology of blackwater is governed by: (a) The geographical and local distribution and incidence of such haemolytic strains; (b) the degree of immunity of the population. Immune subjects may tolerate infection without giving clinical evidence of its nature by suffering from hæmoglobinuria.”

Whether there is anything in this haemolytic strain theory or not, modern thought is practically unanimous in favour of a direct connection between malarial infection and blackwater fever. Indeed, Megaw goes so far as to say that: “The association with malaria is so clear that the disease can rightly be called ‘malaria hæmoglobinuria’” [14]. Deaderick is equally emphatic: “Ætiologically hæmoglobinuric fever stands in the same relation to malaria as do tabes and dementia paralytica to syphilis, and may, very properly, be regarded as a ‘para-malarial’ infection” [15].

Although Giglioli lays more stress on the haemolytic character than on the type of parasite, the opinion and findings of most workers are contained in the remark of Rogers, that: “The parasite most commonly met with in blackwater fever is the malignant tertian, the other forms being rare” [16].

A table showing malarial incidence is appended [17].

DRUGS: QUININE, ATEBRIN AND PLASMOQUINE.

Let us now tackle the burning question in this series of cases—the part played by a drug, or drugs, in the production of the hæmoglobinuric state. On this point, the recognized authorities are by no means unanimous, and the subject has given rise to as much controversy as the argument as to who won the War. Megaw says: “There is a good deal of evidence that quinine and repeated infections with malaria act together in some mysterious way to make the patient susceptible”; and he adds, as a reason for withholding the drug in the active stage of the disease, that: “Quinine is one of the common exciting causes of the disease, and therefore is likely to aggravate the hæmoglobinuria” [18]. Giglioli states that: “In individuals infected with haemolytic strains (of parasites) the onset
of hæmoglobinuria may be determined . . . by quinine . . . . Quinine and malaria being everywhere intimately associated, this drug, without being specifically the cause of blackwater, acquires an altogether special importance as it tends to increase the incidence of the disease in those areas where hæmolytic strains of the malaria parasites are endemic” [19].

Deaderick’s conclusions are guarded. There is an excellent summary of the whole subject in pp. 160 to 173 of his book on malaria, already referred to [5]. Young [20] appears to be a left-winger: “It has even been said that quinine is the cause of blackwater fever. Veretas (Greece, 1858) originated the theory, and Tomaselli (Italy) and Koch later supported it. Much harm was done before this view was discountenanced, and it is now known that blackwater fever may develop without the previous administration of quinine. I have never seen any serious ill-effects following the use of quinine in the ordinary doses required for treatment, viz., twenty-four to thirty grains a day, and in the course of his large experience Sir Malcolm Watson has only seen one case of idiosyncrasy.”

How does the quinine hypothesis affect the series of cases now under survey?

Prior to the onset of premonitory signs and symptoms of the hæmoglobinuric state, total amounts of quinine were taken thus:

<table>
<thead>
<tr>
<th>Amounts Taken (gr.)</th>
<th>Days Spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 gr.</td>
<td>3</td>
</tr>
<tr>
<td>50 gr.</td>
<td></td>
</tr>
<tr>
<td>90 gr.</td>
<td>3</td>
</tr>
<tr>
<td>110 gr.</td>
<td>5</td>
</tr>
<tr>
<td>120 gr.</td>
<td>6</td>
</tr>
</tbody>
</table>

The three cases in which no quinine was taken belonged to the Quetta group. Two died, and one was a very mild case which recovered.

As Major Young has pointed out, blackwater may develop without the previous administration of quinine [21].

But we are not entirely concerned with blackwater fever; and the Indian malariologist will go further by asking if we are concerned with that disease at all?

What is the evidence for and against plasmoquine poisoning?

Before dealing with the question of plasmoquine toxicity, it will be convenient first to dismiss atebrin, since this drug was given to the three cases mentioned above who received no quinine; and they were the only patients to whom atebrin was administered.

Prior to the onset of signs and symptoms of the hæmoglobinuric state, total amounts of atebrin were taken thus:

<table>
<thead>
<tr>
<th>Amounts Taken (gr.)</th>
<th>Days Spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>1·5 grn.</td>
<td>5</td>
</tr>
<tr>
<td>1·8 grn.</td>
<td>6</td>
</tr>
<tr>
<td>2·1 grn.</td>
<td>7</td>
</tr>
<tr>
<td>1·2 grn.</td>
<td>8</td>
</tr>
</tbody>
</table>

1 This was followed by atebrin.
2 This was preceded by quinine.
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On this we may make three comments:—

(1) Hæmoglobinuria is not caused by an overdose of atebrin.

(2) Many cases of malaria have now been treated with this drug in military medical practice in India, and detailed records of the treatment have been kept and analysed. Certain manifestations of the drug's action are constantly noted, e.g., yellow discoloration of the skin, and persistent excretion of atebrin by the kidneys long after the administration of the drug has ceased; but it is now recognized that these are therapeutic, not toxic, effects. "The toxicity of atebrin is low" [22].

(3) Certain workers are of opinion that the action of plasmoquine is more or less intensified by the administration of atebrin. "When associated with plasmoquine its action may be compared to that of quinoplasmine; nevertheless, the addition of 0·3 of atebrin to 0·03 of plasmoquine appears to cause certain slight plasmoquine disturbances which do not occur when the same quantity of plasmoquine is administered together with 0·9 of quinine" [23].

So far as military medical practice in India is concerned, there is a mass of evidence to prove that, if atebrin and plasmoquine in association do "cause certain slight plasmoquine disturbances," these disturbances must be very slight indeed. Only one of our observers has remarked on this point. Writing on September 14, 1933, he says: "Recently I have been struck by the frequency of toxic phenomena in atebrin (plasmoquine) cases, that . . . I have suspended the treatment pending further orders." A communication was sent to this officer, and it ended thus: "What I am getting at is, of course, definite evidence of the malign evidence of atebrin. Up to date, as far as one can gather, it is a suggestion rather than a scientific observation."

On October 30, 1933, a telegram was received from the same officer. It read: "Recent experience with atebrin satisfactory, but supply exhausted. Please arrange supply four bottles 300 tablets each urgently . . ."

There is no doubt that a fillip was given to the atebrin-plasmoquine toxicity view by certain occurrences on a tea garden in Assam: but these have been satisfactorily explained away [24] and now merely serve as a medical lesson with a moral.

Let us now consider the case of plasmoquine.

Prior to the onset of the premonitory signs and symptoms of the hæmoglobinuric state, total amounts of plasmoquine were taken thus:—

By 4 patients, 0·06 grm., spread evenly over 2 days

<table>
<thead>
<tr>
<th>Patient</th>
<th>0·06</th>
<th>0·03</th>
<th>0·09</th>
<th>0·10</th>
<th>0·13</th>
<th>0·18</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td></td>
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<tr>
<td>3</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
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</tbody>
</table>

So, before the attack of hæmoglobinuria set in, six patients were on quinine, three on atebrin, one on quinine followed by atebrin, and all of them received plasmoquine.
The comparatively small dosages (daily, and total) of each of these drugs will be noted.

It is reasonably certain that some of the patients—and particularly those comprising the Quetta group—may have suffered from plasmoquine toxicity; and this form of poisoning has received a good deal of attention in recent tropical medical literature [26]. We may open the discussion with two quotations:

"Quinine cannot be safely administered to such cases of blackwater fever because of the danger of producing further hæmolysis. On the other hand, plasmoquine can be safely used at any stage of the disease and apparently possesses sufficient action to control the infection until such time as quinine can be given. This drug should be equally useful in treating malaria attacks in individuals who suffer from hæmoglobinuria as a result of quinine intolerance" [27].

"Hæmolytic rabbit serum injected into dogs with a properly balanced dose of antilysin is harmless; quinine will upset this balance and precipitate hæmoglobinaemia and hæmoglobinuria. Cinconine, plasmoquine, antipyrin and phenacetin have no such action." The authors (Nocht and Kikuth) suggest that quinine plays a similar rôle in the presence of the hæmolytic substance which is responsible for malarial hæmoglobinuria [19].

Were it certain that all our cases were due to plasmoquine poisoning or idiosyncrasy alone, the optimism pervading these remarks as regards the use of the drug in blackwater fever might be received with satisfaction; but whatever the part played by plasmoquine in our series may have been, it is far from certain, yet, that accident or intolerance can account for the whole story. Hence, at present it behoves us to accept such statements with reserve, unless we belong to the not insignificant band of die-hards who deny the dangers of quinine therapy in hæmoglobinuria [28].

It is unsafe—indeed, it is impossible—to dogmatize, for the intimate pathological anatomy of, and processes concerned in, blackwater fever and other forms of hæmoglobinuria are largely matters of conjecture, and literature on the subject still pours out in an unending stream. For instance, one might take it as settled that hæmoglobinaemia is a certain forerunner of hæmoglobinuria; and that the greater the degree of hæmo­globinaemia, the greater the hæmoglobinuria. However, these are by no means accepted facts. Professor Warrington Yorke points out that: "Some deny the existence of hæmoglobinaemia in this disease (blackwater fever) and argue therefrom that the hæmoglobinuria results from a primary hæmorrhage into the kidneys. . . . What is certain is that the degree of hæmoglobinaemia is remarkably small" [29]. "In severe cases of the disease there was never any doubt about the presence of hæmoglobinaemia, but in the less severe cases it was, in many instances, difficult to satisfy oneself that hæmoglobinaemia much in excess of normal was present. Moreover, the phenomenon was usually of short duration in uncomplicated cases" [30]. "In paroxysmal hæmoglobinuria the serum is generally
stated to be of a red colour. In blackwater fever there is some doubt as to whether this is necessarily the case; and one of us with Dr. Stephens has recorded cases where haemoglobinemia was not evident. . . . We have only once seen haemoglobin so great in amount as to give a rosy colour to the serum, and its presence is generally only indicated by an orange tint” [31].

When it comes to a question of blackwater fever versus plasmoquine poisoning, oxyhaemoglobinæmia with oxyhaemoglobinuria is indicative of the former; methæmoglobinæmia with methæmoglobinuria points to the latter. But differentiation is not just as simple as this bald statement might lead one to suppose, because, although oxyhaemoglobinæmia is not a result of plasmoquine toxicity, methæmoglobinæmia is frequently found in blackwater fever [32]. It would seem that, in plasmoquine toxicity, the conversion of haemoglobin into methæmoglobin is an intra-corpuscular reaction, and that only subsequently is the methæmoglobin liberated into the plasma; but, when methæmoglobinæmia occurs in blackwater fever, its formation is not intra-corpuscular; the change to methæmoglobin occurs at some stage subsequent to the liberation of the haemoglobin into the plasma. “In no case to my knowledge is methæmoglobin alone present” [33].

From what has now been said it will be plain that: (a) When haemoglobinæmia is slight, very transient or even absent; and (b) methæmoglobinæmia and methæmoglobinuria are present, differential diagnosis is beset with pitfalls.

Sinton and other writers have presented us with a clear picture of what is known as plasmoquine poisoning. There is an excellent summary of this condition, and of the literature thereon, in pp. 195-196 of the Tropical Diseases Bulletin, April, 1933, Vol. XXX. “Severe toxic symptoms sometimes arise with startling suddenness, but more often the onset is less abrupt; cyanosis of the lips or griping pains are warning signs, and if the plasmoquine is stopped at once the symptoms pass off. If, on the contrary, it be continued, the cyanosis spreads to the palate, gums and finger-nails, the temperature rises and an attack resembling blackwater fever develops, accompanied by destruction of red cells, haemolytic jaundice and black urine containing methæmoglobin . . . certain individuals are peculiarly sensitive to the drug . . . . Severe cases of poisoning are less common now that smaller doses are given.”

Already the reader will have been struck by the close resemblance, especially on the clinical side, between blackwater fever and plasmoquine poisoning. Presently, we believe, he will notice that several of the cases in the series now under review more closely resemble blackwater fever than they do plasmoquine poisoning.

As regards plasmoquine dosage Sinton states that doses as high as 0·20 and 0·32 grammes daily have been given [34]. Dr. W. Fletcher quotes 0·18 grammes as not infrequent and 0·1 grammes per day as common. It will be remembered that, in the present series, the greatest amount taken was 0·18 grammme and that that amount was spread evenly over six days.
In discussing the dose of 0.03 gramme per day, Fletcher remarks that even this small amount has been known to produce hæmoglobinuria. But, on the whole, it appears that this dose is reasonably safe, provided that it is given for a period of not longer than six or seven days without a break. Macphail treated several thousands of people in Guatemala with a daily dose of 0.03 plasmoquine combined with 20 grains of quinine over a period of six days, and toxic symptoms were observed in only one case. A daily dose of 0.02 gramme of plasmoquine, together with 24 grains of quinine, is the standard treatment on the United Fruit Company's plantations.

One of our patients took 0.04 gramme per day for two days, another had 0.02 gramme per day four and a half days, and the remainder were on 0.03 gramme per day, the average for these eight patients working out at a little over three days each.

Up to August, 1933, the standard dose throughout the Army in India was 0.03 gramme daily. This dose was based on results obtained from Army practice from the introduction of the drug in 1929 up to the end of 1932. These results indicated that this dose was safe, and that a dose of 0.02 gramme gave indifferent therapeutic action. In the case of the British troops mild toxicity is occasionally noticed; severe poisoning has never been reported. But it is well known that the safety margin is small. "With the 0.04 gramme dose of plasmoquine daily there was definitely a slight cyanotic or greyish tinge noticed and one could always pick out the men in the ward who were on plasmoquine; it was especially noticeable in men who were attending hospital. The patients themselves did not notice it nor did they complain in any way. Men who were constipated appeared more prone to this cyanotic tinge. In the few cases in which cyanosis was marked, discontinuance of the drug for a few days with a brisk purge rendered the patients able to continue their course almost at once. It would appear that plasmoquine is cumulative. The reduction of the dose to 0.03 gramme daily prevented any cyanosis whatever" [34].

In the case of the Indian troops and as a direct result of the Quetta outbreak, the standard dosage was reduced fifty per cent as from August, 1933. Since that date no fresh cases of hæmoglobinuria have been reported, i.e., up to mid-December, 1933.

REFERENCES AND NOTES.

[3] The literature on the subject is voluminous, e.g., see DEADERICK'S "Practical Study of Malaria," 1911. STEPHENS, in the Transactions of the Royal Society of Tropical Medicine and Hygiene, 1927, vol. xx, pp. 401-411; and numerous other authorities.
[4] Here there seems to be an error in geographical definition or nomenclature.
Hæmoglobinuria: A New Problem on the Indian Frontier


[14] Rogers and Megaw. Ibid., p. 73.
[17] "Malaria, Indian Troops, 1932-33,"

<table>
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<th>Year</th>
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<td>Sept.</td>
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[18] Rogers and Megaw. Ibid., pp. 73 and 77.
[21] See also The Indian Medical Gazette, March, 1933, vol. lxviii, p. 149. In this communication N. G. Banerjee and P. Brahmacari describe a case of blackwater fever in which: (1) No hemoglobinuria developed when the patient was under treatment with quinine; (2) an attack of hemoglobinuria occurred when the patient was being treated with atebrin and plasmoquine; (3) the administration of the above drugs failed to avert an attack of hemoglobinuria.

[24] "The Non-Toxicity of Plasmoquine and Atebrin" (MoQueen) ; and "The Synthetic Anti-Malaria Compounds" (the Editor). The Indian Medical Gazette, June, 1933, vol. lxviii, pp. 323 and 339.
[25] It is uncertain whether, in this case, plasmoquine was given at all, and exhaustive inquiries have failed to clear up the point. Although the case is now reported and commented on as if the drug was, in fact, administered, the writer has not taken this course without misgiving. The following are the ascertainable facts:

(a) The case sheet contains these entries, made by the medical officer in charge of the patient—

- "16 Nov., '32. Treatment: give atebrin, A.2. course, as follows: '01 (sic: obviously stands for '10) grm. at 08.00 hrs., 12.00 hrs., and 17.00 hrs. daily. Discontinue Mist. Quinine."
- "17 Nov. Continue A.2. course, i.e., atebrin, t.d.s., for 7 (seven) days."

The above course of treatment was stopped on November 20, the patient was given quinine, 10 gr. t.i.d., on November 21, and again from November 24. He died on November 26.
The ward treatment book is kept up by, and is in charge of, the senior nursing sister of the ward. This book has been examined, and its entries are in agreement with the medical officer's case sheet. Neither in the book nor in the sheet is there any mention of plasmoquine.

In the hospital in question (Kohat) "A.2." stands for "Atebrin-Plasmoquine Course of Treatment," which consists of atebrin 0.3 grm., t.d.s., for seven days, followed by plasmoquine 0.02 grm., daily, for five days. Hence, if the patient's illness had pursued a normal course, plasmoquine would have been administered as from November 23.

So certain was the medical officer that plasmoquine was out of the question, that he took special pains in investigating and writing up the case under the diagnosis of "Atebrin Poisoning." This diagnosis is, of course, erroneous; but blackwater fever is possible and, since the fatal termination of the case, the medical officer has twice re-affirmed his conviction that no plasmoquine was given.

Justifiable criticism has been aroused by certain entries on the patient's temperature chart. These entries have never been satisfactorily explained away. They are:

- **November 16**  A.1.
- **17**  A.2.  P.1.
- **18**  A.3.  P.2.
- **19**  A.4.  P.3.

The critics say that, in view of the patient's signs and symptoms, and of inability on the part of those responsible adequately to explain the above cryptic "P" entries, it is highly probable that 0.02 grm. plasmoquine was administered, daily, on November 17, 18 and 19.

It seems to us to be scientifically safer and sounder to give the critics the benefit of the doubt.

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[26] For instance, see "[25]," p. 360: a letter signed by Captain G. S. Chawla, I.M.S.
[31] "Blackwater Fever," CHRISTOPHERS and BENTLEY, Scientific Memoir (Medical), Government of India, No. 35, 1908.
[33] Ross. Ibid., p. 110.
[34] "A Report on Six Hundred Cases of Malaria Treated with Plasmoquine and Quinine," H. B. P. DIXON, Journal of the Royal Army Medical Corps, June, 1933, p. 106.

(To be continued.)