HÆMOGLOBINURIA: A NEW PROBLEM ON THE INDIAN FRONTIER.

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(Continued from p. 278.)

1933.

We now come to a collection of cases from a big headquarters station, where there are well qualified specialists and an excellent laboratory at the call of the ward medical officers.

All five patients were resident in Quetta, and all developed hæmoglobinuria within a period of ten days, viz., between August 3 and 12, 1933. At this time Quetta was being visited by an epidemic of benign and malignant malaria of more than usual severity and extent.

The outbreak was isolated. No cases of this kind occurred prior to August 3, and no such cases have occurred since.

Before describing the cases in detail, it is convenient to say something now, firstly, about idiosyncrasy, individual and racial; and secondly, about batch toxicity of plasmoquine. These remarks may also be borne in mind when considering the cases (patients 1, 2, 3, 9 and 10) which occurred sporadically in stations other than Quetta.

Prior to the Quetta outbreak, it was thought that, if the 1932 hæmoglobinurias were not true cases of blackwater fever, they must have been plasmoquine idiosyncrasies.

"Does a race susceptibility exist? It has struck us as rather peculiar that the number of severe cases of toxæmia seen during our researches seems to be higher than those recorded in many instances by other workers using the same dosage. The population in our researches was an unusually healthy one, and except for occasional relapses of chronic malaria, the majority were apparently quite fit in the intervals, so the toxæmia could not be accounted for by any evident physical weakness. Our patients were all of northern European origin, as were also the severe cases of toxæmia reported by Wade (1929), Ashby (1928), and Squires (1928), and the first author notes specially that he has not observed similar symptoms among Indians receiving the same treatment. When one considers the enormous daily doses, even as high as 0·32 gramme, given by some workers to the inhabitants of southern Europe and of the tropics with few or no recorded severe ill-effects, while severe toxæmia or even death has been recorded in other places after doses as low as 0·06 gramme daily, one is tempted to think that such a racial susceptibility may exist and that possibly it may occur more commonly in persons of northern European origin than among others " [45].

The cases now under review, and our annual and special reports regard-
The treatment of malaria patients with synthetic drugs show that, in military medical practice in India, the above opinion cannot be accepted. The matter may take on a different aspect when the result of the recent reduction of Indian dosage, from 0.03 (the present British dose) to 0.015 grammes daily, manifests itself. But it will be noticed that, in the above quotation, Wade notes specially that he has not observed similar symptoms among Indians receiving the same treatment.

That is in direct conflict with our findings.

But individual idiosyncrasy is a different thing from racial idiosyncrasy; and when it is remembered that, in August, 1933, hundreds of patients, British and Indian, all over the Peninsula, were receiving plasmoquine without toxic effects, it is impossible to believe that five very susceptible persons, all of the same nationality, developed malaria in one place, Quetta, and were there poisoned within the short space of ten days. Such a combination of uncommon circumstances is incredible.

So, while the possibility of racial susceptibility and the probability of individual idiosyncrasy comparable to "quinine-intolerance" are accepted as reasonable propositions, it is safe to say that, in the Quetta series, the question of idiosyncrasy need not be considered at all.

The five Quetta cases might possibly be explained on the assumption that, as they were stricken in the same place and at the same time, they may have suffered from some antecedent disease which gave rise to disturbance of liver function, lowering of the alkali reserve, etc., and may thus have become predisposed to acute plasmoquine poisoning.

There was no evidence of any such precedent condition.

The patients came from different units, located in different parts of the cantonment. Three were Mussalmans and two were Hindus, and they belonged to different walks of life. In these important respects the absence of any common factor is striking.

As regards batch toxicity or deterioration of the drug: Although the use of plasmoquine was universal throughout India, the rest of the military population was unaffected; and in Quetta, many other patients, British and Indian, were receiving the drug. Tablets from the actual batch which may have poisoned our patients were administered to many other patients without ill-effect, not only before, but after, the outbreak. Samples of the consignment have been sent to the makers for toxicity tests. The results are not yet available. Meanwhile there is no reason to suppose that these samples will prove to be anything but innocuous in the small doses in use in military medical practice in India [45].

One other point: as soon as the third case was detected, a different bottle of plasmoquine was taken into use. This did not prevent two more cases from occurring.

Combination of plasmoquine with atebrin has already been dealt with. Combination of plasmoquine with other potentially dangerous drugs, such as the alkylamino group, need not be discussed, since—apart from
symptomatic restorative treatment—none of the Quetta or of the other cases received anything more harmful than simple alkaline mixtures [46].

**Case 4.**—A Mussalman coolie employed by the Royal Air Force.
Aged 18. Has resided continuously in Quetta for at least ten months.
July 26 to 31.—In hospital, suffering from malaria (benign tertian rings) of six days' duration.
Anemic. Spleen palpable. Fever only lasted for one day.
Treatment: Atebrin, 0.1 gramme, thrice daily, from July 26 to 30.
Total administered, 1.5 grammes.
July 31.—Discharged from hospital, excused all duties, and to attend the medical inspection room daily as an out-patient. To receive plasmoquine, 0.01 gramme in the morning and 0.02 gramme in the evening.
August 2.—Patient re-admitted to hospital, after having received 0.06 gramme plasmoquine spread evenly over two days. Plasmoquine discontinued.
Temperature 103°F. Rigor, giddiness, headache, slight cyanosis, profound anemia, abdominal pain, hiccough and—in the evening—vomiting.
Spleen palpable. Liver not enlarged.
Urine: Reaction neutral; heavy content of albumin; some red blood-cell detritus: hæmaglobin.

**August 3.**—Anuria has set in. A catheter yielded four ounces of very dark-coloured urine.
At 12.30 p.m. temperature was 99.8°F., pulse 120, and the general condition grave. Patient was semi-comatose, and the cyanotic tinge more marked.
3 p.m.: Pulse failing rapidly. Slight jaundice has appeared. The liver does not seem to be enlarged.
4.10 p.m.: Death. Post-mortem examination refused.
The laboratory reported on specimens taken on August 3 as follows:—
Blood: Red cells, 1,070,000. Anisocytosis: nucleated reds ++ + ; megaloblasts + ; polychromatophilia + + . No parasites present. White cells, 42,000. Polymorphonuclears, 72 per cent; lymphocytes, 16 per cent; large mononuclears, 6 per cent; eosinophiles, 6 per cent. Hæmoglobin could not be estimated on account of the dark grey colour of the blood.
Urine: Colour, brown-black—like stout; reaction, neutral; heavy amorphous deposit; red cell detritus ++ ; albumin +++ ; methæmoglobinuria +.

Unfortunately, at Quetta there is no spectroscope.1 Methæmoglobin could not be estimated on account of the dark grey colour of the blood.

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1 Similarly for Fort Sandeman and Wana. There are spectrosopes at Peshawar and Kohat.
globinæmia was presumed on the dark grey colour of the blood (it was
impossible to match the specimens with the standard colours of the
Tallquist hæmoglobinometer); and methæmoglobinuria on the "stout" as
opposed to the port-wine colour of the urine. But for this, we have here
a fairly complete and convincing picture, the outstanding features of
which seem to be:—

Sudden onset and dramatic swiftness of the attack.

Rapid and massive destruction of the red blood cells.

Methæmoglobinæmia, methæmoglobinuria and anuria.

An attack out of all proportion to the amount of plasmooquine given;
and a fatal issue despite the early withdrawal of the drug. Was the drug
responsible?

Case 5.—A Mussalman sepoy (a reservist up for training) of the
mechanical transport.

Aged 27. Service six years.

August 1.—Admitted to hospital with a history of rigor and fever of one
day's duration. Temperature 100° F., falling. Spleen enlarged to
3-fingers, and hard. Liver apparently normal. Blood smear contained
malignant tertian rings. Treatment: atebrin, 0·1 gramme, thrice daily.

On August 3 there was a rise of temperature, 100° to 101° F. On
August 5 there was a second rise, 99·5° to 100° F. Otherwise, the case
pursued a normal course. On the latter date the patient completed his
course of atebrin; total, 1·5 grammes, spread evenly over five days.

August 6.—Course of plasmooquine commenced, 0·01 gramme in the
evening. Progress maintained on August 7.

August 8.—Morning temperature normal. Pulse 72, and of good quality.
Is constipated and complains of abdominal pain. Rectal enema given,
with good result. On account of the pain in the abdomen it was thought
well to discontinue the plasmooquine. Total amount administered since
August 6, 0·06 gramme.

11 a.m.: Cyanosis and jaundice, both slight. No apparent change in
the liver. Patient is mentally alert, and feels comfortable.

1 p.m.: Temperature 99·8° F. Pulse 110. Patient passed eight
ounces of dark, reddish-brown urine, alkaline in reaction and loaded with a
thick amorphous deposit which contained red blood cell debris. No
undamaged red cells were seen. Albumin and methæmoglobin were
present.

4 p.m.: General condition, fair. Patient again passed about eight
ounces of urine of the same characteristics as the last specimen.

Blood: Red cells, 4,930,000. No nucleated forms. White cells, 14,600.
Polymorphonuclears, 59 per cent; lymphocytes, 35 per cent; large mono-
nuclears, 5 per cent; eosinophiles, 1 per cent; hæmoglobin, about 95 per
cent, but the dirty grey colour of the blood made it difficult—indeed, almost
impossible—to match with Tallquist's hæmoglobinometer.
5 p.m.: Temperature 101.2°F. Pulse 116. Patient vomited bile-stained fluid, and passed a tarry stool which gave a positive response to a test for occult blood.

August 9.—Temperature 101°F. at 8 a.m. Patient has had a good night and feels fairly comfortable.

9 a.m.: Bile-stained fluid vomited, and tarry stool passed.

10 a.m.: Patient’s general condition is deteriorating. Anaemia, profound; cyanosis, distinct; jaundice, slight. Total amount of urine passed in twenty-four hours, 58 ounces.

Blood: No parasites present. Red cells, 1,185,000. One nucleated cell seen. Normoblasts present, of which many have two nuclei; and one with three nuclei was noted. White cells, 38,900. Polymorphonuclears, 56 per cent; lymphocytes, 35 per cent; large mononuclears, 6 per cent; eosinophiles, 3 per cent. Haemoglobin estimated at about 60 per cent, but matching was again found to be very difficult.

August 10.—Patient’s condition as recorded yesterday remained unchanged until 6 a.m. to-day, when a marked change for the worse set in. Pulse hardly perceptible, anaemia intense, cyanosis increased, jaundice moderate. Total amount of urine in twenty-four hours 48 ounces. 12.30 p.m.: Patient died.

Once more the fulminating nature of the illness is illustrated. In a matter of twenty-four hours after the onset of the acute symptoms the red blood cell count drops to 1,850,000; and in another twenty-four the patient dies, although plasmoquine was withdrawn at the earliest sign of complications.

Case 6.—A Mussalman baker, employed for the past eight years at the Government Bakery, Quetta.

Aged 38. Weight, 6 stone 4 pounds. General physique, good. No previous history of malaria elicited.

August 2.—Admitted with signs and symptoms of malaria, of twenty-four hours’ duration, and in the course of which the temperature has fallen from 101.2°F to normal. Spleen and liver seem to be normal. Blood smear contains the benign tertian rings.

Treatment: Quinine, grains 3, twice daily; and plasmoquine, 0.01 (a.m.) and 0.02 (p.m.) gramme daily.

August 3 to afternoon of August 7.—No pyrexia, or other signs or symptoms of disease.

Evening of August 7.—Temperature has risen to 101.2°F.

Morning of August 8.—Temperature 103°F. Pulse 126. Patient is slightly jaundiced and cyanosed. Spleen and liver apparently normal. No urine voided to-day. A catheter specimen, 10 ounces, is very dark coloured. A tarry stool has been passed.

Plasmoquine-quinine stopped. The patient has now had, in all, quinine 120 grains, and plasmoquine 0.18 gramme, spread evenly over six days.

The laboratory reports as follows:—
Blood: Red cells, 2,650,000. Marked anisocytosis; numerous nucleated reds and megaloblasts present. White cells, 30,600. Polymorphonuclears 72 per cent; lymphocytes 25 per cent; large monocytes 3 per cent; haemoglobin, about 85 per cent; colour of blood, a dingy grey.

Urine: Reaction, alkaline. Colour, dark reddish-brown. Heavy granular deposit of the same colour, amorphous phosphates and red blood cell debris in large masses. Methaemoglobin present.

Fæces: Occult blood test, positive.

1 p.m.: Temperature 102° F. Pulse 140. Mental condition, clear; general condition as before.

Urine: Characteristics as above, 4 ounces.

4 p.m.: Patient cyanosed and restless. Urine of the same description passed. Tarry stool passed.

August 9.—Temperature has varied between 103·2° and 101° F. Pulse 140. General condition still gives rise to anxiety. Anæmia is profound but cyanosis is less evident. Bilious vomiting is taking place. Dark coloured urine and tarry stool passed. Urine in twenty-four hours, 44 ounces.

1 p.m.: General condition is improving.

Blood: Red cells, 1,325,000. Large mononuclears, 11 per cent. Haemoglobin, about 60 per cent.

From August 10 onwards, steady improvement to eventual recovery took place.

On August 20 the blood picture showed red cells, 2,225,000. Polymorphonuclears, 46 per cent; lymphocytes, 42 per cent; large mononuclears, 10 per cent; eosinophiles, 2 per cent; haemoglobin, 75 per cent.

August 26.—Convalescence definitely established.

Here, again, we have a picture just as likely to be that of blackwater fever as of plasmoquine poisoning, except for the occurrence of slight cyanosis, and what was apparently marked methaemoglobinuria. The swift and massive destruction of red blood-cells, and the comparatively high percentage of large mononuclears will have been noticed. We may agree that this patient is to be congratulated on his recovery.

The two following cases are not so alarming: Case 7.—A Hindu cook attached to the Royal Corps of Signals.

Arrived in Quetta from leave at his home, Hoshiarpur, Punjab, in January, 1933.


August 9.—Admitted with signs and symptoms of malaria, of three days' duration. Temperature 99°, 103°, 98° F. Spleen hard, and enlarged to two fingers. Blood-smear contains malignant tertian rings.

Treatment: Quinine, 20 grains, and plasmoquine, 0·03 gramme, daily.

August 10.—Temperature 97°, 101·6°, 99° F.
August 11.—Temperature normal. Patient jaundiced.
Specific treatment stopped. Total amounts given to date: quinine, 40 grains, and plasmoquine, 0·06 gramme, spread evenly over two days.
August 12.—Temperature rising. Jaundice increased. Dark coloured urine passed.
Blood: Red cells, 3,120,000. Leucocytosis. Polymorphonuclears, 72 per cent; lymphocytes, 21 per cent; monocytes, 6 per cent; eosinophiles, 1 per cent; haemoglobin, 85 per cent.
Urine: Reaction, acid. Small amount of brown amorphous deposit. Albumin and methaemoglobin present. No bile pigment detected.
Fæces: No occult blood.
August 13.—Temperature 98° to 102·4° F. Red blood-cell count, 2,160,000. Thirty-six ounces of urine passed in twenty-four hours.
August 14.—Red cell count, 2,980,000. Large mononuclears, 8 per cent; haemoglobin, 80 per cent.
August 18.—Patient is making an uninterrupted recovery.
August 25.—Convalescence established.
In this case the destruction of red blood-cells was moderately severe. Plasmoquine was stopped on August 11, and improvement set in three days later.

The next case was milder still. It is reported in order to complete the series.

Case 8.—A Hindu sepoy of a rifle regiment.
Aged 28. Service, one and a half years. Weight, 9 stone ½ pound. General physique, fair.
He was on leave at his home, Fatehgarh, Lucknow District, in September, 1932, when he had an attack of malaria. He has been stationed in Quetta since November, 1932.
August 2.—Admitted to hospital with signs and symptoms of malaria of one day’s duration. Temperature 101°, 97°, 99·4° F. Blood smear contains benign tertian schizonts.
Treatment: Atebrin, 0·1 gramme, thrice daily.
August 10.—Temperature has remained normal since August 4.
Atebrin stopped after a total administration of 2·1 grammes. Plasmoquine prescribed: 0·03 gramme daily.
August 11.—Slight jaundice has developed. Plasmoquine stopped: total taken, 0·06 gramme.
August 12.—Since August 10 patient has had an evening rise of temperature, 99° to 100° F.
Blood: Red cells, 3,080,000. Polymorphonuclears, 56 per cent; lymphocytes, 83 per cent; large mononuclears, 8 per cent; eosinophiles, 3 per cent; white cell count, 7,250; haemoglobin, 80 per cent.
Urine contains a trace of what seems to be methaemoglobin.
August 14.—Red blood-cells, 2,800,000. From this date onwards the
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patient made steady progress. Convalescence was established by August 25.

A board of medical officers investigated these Quetta cases on the spot, examined the documents and took the evidence of all medical and nursing personnel connected with the five patients. The results were nugatory. The Assistant Director of Hygiene and Pathology, Army Headquarters, then visited Quetta, and his report on the visit is attached to this communication [47]. Although the report throws no further light on the aetiology of the outbreak, it will be found of interest. It is curious that, if these cases suffered from over-doses of plasmoquine, not a scrap of evidence to that effect could be obtained; and it must be remembered that, if blackwater fever is ruled out of court, plasmoquine toxicity is the obvious—the only—resort. In other words, it is the obvious that gives birth to the suspicion; and, when there is not a particle of evidence in support, the intruguing question still remains unanswered: Can it be said that plasmoquine toxicity is the only factor in the problem? As in the case of blackwater fever—is there not a missing, a still unknown, aetiological agent concerned in this form of hæmoglobinuria?

There remains two cases to be described. Both were severe, and both ended fatally.

Case 9.—A Hindu syce attached to Frontier Force cavalry.
Aged 30. Service eight years. A small man who weighed only ninety one pounds.
July 31.—Admitted to hospital at Wana, complaining of "fever," of two days' duration. Temperature 99-2° to 103° F. Spleen enlarged two fingers. Liver apparently normal. Blood contains benign tertian rings [14].
Treatment: Quinine, grains x, and plasmoquine, 0'01 gramme, each twice daily. As the patient was a "light weight," the dose of plasmoquine was purposely kept low.
August 1 to 3.—Temperature fell during the night of July 31, and has remained normal since. Patient looks and feels well.
August 4.—This evening the temperature has risen to 100°. Pulse 102. Patient complains of abdominal pain.
Specific treatment stopped, after a total administration of quinine, grains 100, and plasmoquine, 0'09 gramme, spread evenly over a period of five days.
10 p.m.: Patient complains of severe headache.
August 5.—At 2 a.m., painful, bilious vomiting set in.
7 a.m.: Temperature 99° F. Patient's mentality is clouded. Bilious vomiting is frequent and severe. Cyanosis is distinct, and the skin, conjunctive and mucous membranes are deeply jaundiced. No urine has been passed since last night, but the bladder is not distended.
Blood: Red cells number only 562,500. White cells, 3,437. Polymorphonuclears, 64 per cent; lymphocytes, 31 per cent; mononuclears, 5 per cent. No parasites present.
10 a.m.: Patient is very drowsy. Jaundice is intense, and bilious vomiting continues to be frequent and severe. Dark coloured urine passed involuntarily.

1 p.m.: General condition grave.
Red blood-cell count is 876,500.
Eight ounces of reddish-black urine passed. Reaction, acid; albumin ++ ; large number of casts, hyaline and tubular; very few red blood-cells. Hæmoglobin present; but whether oxy- or met- was not noted.

6 p.m.; Temperature 101°F. Pulse 130. Patient unconscious. Jaundice intense. About 6 ounces of urine were passed at 5 p.m., and again at 6 p.m.

8 p.m.: General condition worse. Four ounces of dark urine passed.

August 6.—Patient died at 2.45 a.m.
A post-mortem examination did nothing to clarify the diagnosis. Nothing of significance was found in the heart or suprarenals. The spleen was enlarged, unduly hard, and contained malaria pigment. In the liver there was slight parenchymatous degeneration, and the cells contained malaria pigment. Parenchymatous degeneration was present in the kidneys: the tubules contained albuminous matter; hæmoglobin-stained casts were present, and there was a small amount of melanin pigment. In fact, the same post-mortem findings as one would expect in blackwater fever [48]. In what respects these differ from the post-mortem appearances in a human case of death from plasmoquine poisoning we cannot definitely say, because—according to the experts—patients do not die, provided the plasmoquine is cut off in time.

Nevertheless, in this instance, prompt stoppage of the small dose of plasmoquine which was being administered had no beneficial effect whatsoever.

Note the rapidity and degree of blood-destruction; the abdominal pain, intense jaundice, constant bilious vomiting and cyanosis; the decreased urinary excretion, hæmoglobinuria and stupor passing into coma.

The officer commanding the hospital in which this patient died was a skilled physician who had had experience of blackwater fever. In a detailed commentary on the case, he was inclined to make a diagnosis of plasmoquine toxicity; but it cannot be said that there is any more confidence or finality about this case than about several of the others.

Case 10.—A Sikh gunner from the Punjab. Aged 21. Service, three and a half years.

August 8.—Admitted to hospital, Kohat, complaining of "fever" of one day's duration. Temperature on August 7, 101·5°F., now normal. Patient looks ill. Spleen and liver apparently normal.
Blood smears contain malignant tertian rings.
Treatment: Quinine, grains x, twice daily.

August 9.—Rigor: temperature 102·4°F. Temperature fell this evening.
August 10.—Temperature 98°8 to 99°5° F. Quinine to be continued. In addition, plasmoquine, 0·03 gramme daily, prescribed.

August 13.—Since August 10, temperature has varied between 99° and 98·2° F. This morning it rose to 102° F.

Slight icteric tinge of skin and conjunctivae is noticeable, and bilious vomiting has set in. Examination of the urine reveals nothing abnormal.

Plasmoquine discontinued, the patient having had a total of 0·10 grammes, spread evenly over three and a half days.

August 14.—Temperature has remained up in the neighbourhood of 103·5° F. Jaundice is intense, and bilious vomiting distressing.

Blood: Red cells, 2,630,000; white cells, 26,250.

Urine, port wine coloured. Reaction, slightly acid. Albumin + ; urates ++ ; bile pigment -. Hæmoglobinuria very marked.

Quinine discontinued. Total amount taken over a period of five and a half days, grains 110.

6.30 p.m.: Patient unconscious. Urine is passed involuntarily, at fairly frequent intervals, and in amounts which are estimated to be about 10 ounces. It is markedly hæmoglobinuric (port wine) in character.

8 p.m.: Gravity of the general condition remains unaltered. Dark brown stool passed.

11 p.m.: Patient died.

In this case, also, a post-mortem examination was carried out. The findings were similar to those in the preceding Case 9; but in Case 10 the pathologist stresses the following points:—

Intense icteric staining of the subcutaneous fat; high degree of anaemia and friability of the internal organs; and treble enlargement, engorgement and friability of the spleen.

The reader will be struck by the differences between these two cases (9 and 10) and those of the Quetta series. In the former we find no mention of marked cyanosis; and we read of port wine hæmoglobinuria. This colour could hardly be confused with black-brown—like stout—or dingy grey. In fact, patients 1, 2, 3, 9 and 10 bear to each other a strong family likeness. So do patients 4 to 8. But, if the two families are closely akin, it cannot be admitted that they are one and the same.

CONCLUSION.

The Indian school of thought may well exclaim: “Very good; but show us, from the area in question, a blackwater fever patient to whom—with absolute certitude—no plasmoquine has been administered.”

To that, the reply may be: “Perhaps blackwater fever is an entity. May be plasmoquine toxicity is an entity. But that is not the whole story; and the sooner plasmoquine is connected up with blackwater fever in much the same way as quinine now is, the better.”

I am indebted to Major-General Sir John Megaw, K.C.I.E., I.M.S., to
Major-General J. D. Graham, C.B., C.I.E., I.M.S., and in particular to Lieutenant-Colonel J. A. Sinton, V.C., C.B.E., I.M.S., for much valuable assistance and criticism. I would also gratefully acknowledge the help given by Major J. S. K. Boyd, R.A.M.C., and, as regards the Quetta cases, by Major D. T. M. Large, R.A.M.C.

REFERENCES.

[45] See [38], vol. xvii, pp. 805 and 806.
[47] INVESTIGATIONS REGARDING THE CASES OF ? PLASMOQUINE POISONING AT QUETTA.

This question was discussed with all the members of the Court of Enquiry, and with various others who had been interested in or concerned with the cases.

The first point to determine is the correct diagnosis of these cases.

The blood condition, as well as the other symptoms, was critically discussed with Major Large. Although he had not a spectroscope by the use of which a definite conclusion could have been reached, there is no reasonable doubt that massive methemoglobinemia was present. This contra-indicates blackwater fever (in which the condition is normally one of oxyhemoglobinemia) and in fact practically every known condition except poisoning with certain drugs. The only drug of this type which these patients received was plasmoquine, whose action in producing methemoglobinemia when given in overdoses is well known.

It appears therefore certain that these were cases of plasmoquine poisoning.

The following proposition was taken as a basis for discussion, viz.: Normal plasmoquine administered in the authorized doses to normal individuals will not give rise to toxic symptoms. Our results over two years make this statement one of fact—there is ample practical experience to substantiate it. This proposition was agreed to by everyone with whom the matter was discussed.

Arising from this the following points are to be discussed in relation to these cases:

1. Was the plasmoquine unduly toxic?

In discussion with Lieutenant-Colonel Sinton in Kasauli on September 10, 1933, it was pointed out that, in the early days of the experiments at the Malaria Treatment Centre, on one occasion there was a sample of plasmoquine which was definitely more toxic than normal. This belonged to a newly-received consignment and was spotted more or less at once, as the toxic symptoms occurred as soon as the new sample was taken into use. The history of the present sample is as follows:

10,000 tablets each of 0.02 gramme and 0.01 gramme of plasmoquine were received on one indent on January 17, 1933. The consignment was in five bottles of 2,000 tablets of each size.

Two bottles were used without any untoward effect. The first of the cases in the above series was treated from the last two tablets of the third pair of bottles. The remaining four were from the fourth bottles, which were then withdrawn. The fifth bottles were taken into use and have since been finished. The fourth bottles are now again in use without any untoward effects.

There is now only about one-fourth of a bottle left. Total used to date of this consignment is 9,500 tablets. At 21 tablets per case this equals 452 cases. Actually many more than these have been treated, as large numbers of cases have been treated with atebrin and plasmoquine, where only 5 tablets of each are used.

Taking into consideration the fact that many patients were treated with this batch before any toxic cases occurred, and again that many have been treated subsequent to the occurrence of the cases, and as all five cases occurred within nine days, it can safely be said that the balance of evidence is strongly against the suggestion that this is a toxic batch of plasmoquine. Further evidence of its toxicity would definitely have cropped up in other cases. Under the circumstances the occurrence of a batch of five cases in nine days caused by toxicity of the sample is outside the bounds of reasonable possibility.
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A further suggestion has been made that these bottles of tablets may have been made up from different "brows," and that certain tablets may have had toxic properties while the majority had not. This is of course possible, but in the ordinary course of events unlikely. Unless there were present a very few highly toxic tablets, it is difficult to understand why only five men out of the many who were under treatment should have been affected in this way. Also similar cases would have occurred in other parts of the country where the remainder of the toxic brew was used.

(2) Were the patients unduly susceptible?

(a) Idiosyncrasy is of course a possibility, but this can be excluded for the same reason as is given above. A group of 5 cases all with an idiosyncrasy is not likely—in fact highly improbable.

(b) Were the men of unduly poor physique? Inquiries elicit that the first case—Cooly Habib—was definitely a weakly, small man. The others were average.

There is therefore nothing to suggest that the occurrence can be explained by the physical condition of the patient.

(3) Is there any possibility of any other drug having enhanced the toxicity of plasmoquine?

No other drugs except quinine or atebrin were given to these cases. Quinine is supposed to reduce the toxic action of plasmoquine. According to some the use of atebrin may enhance the toxicity. Taking these five cases plus the one case from Kohat, both these contentions seem to be disproved.

Three had atebrin. Two died and one was a mild case. Three had quinine. One died, one was a severe and almost fatal case, and one was moderately mild.

Honours are therefore easy. The evidence in these cases that atebrin was responsible for the mischief because of its conjoint action with plasmoquine is nil.

(4) Was an overdose of plasmoquine given?

According to the evidence brought forward in the Court of Enquiry, no overdose was given.

The inquiry therefore reaches a blank wall. As far as possible everything has been investigated and no answer to the conundrum has been found.

It remains to reconsider the above points and determine if in any of them the evidence is weak.

Of the four points only one rests on verbal evidence only. This is number (4)—the question of overdose.

This was discussed in every detail with the President and members of the Court of Enquiry. There was no evidence whatsoever to suggest that an overdose had been given. The personnel looking after these cases had all been doing this same work for some time previously. Those responsible for issuing treatment were quite familiar with the different appearance of tablets of atebrin and plasmoquine.

In spite of this evidence, the impression remained in the minds of those who inquired into the cases at the time of their occurrence that in some unexplained way an overdose, or a series of small overdoses, may conceivably have been taken by the patients.

To summarise, there is no evidence from which a definite conclusion can be reached regarding these cases. There is a vague possibility that an overdose may have been given despite evidence to the contrary. The overdose at the worst cannot have been a massive one.

It seems possible that the margin of safety for Indian troops is less than it should be, and, in consequence, the policy of lowering the dose by 50 per cent for Indian troops seems wise, especially in view of recent work which suggests that smaller doses are equally satisfactory.

There is no tangible evidence to incriminate atebrin as a contributory factor.

Of the British troops treated, no cases have shown any toxic symptoms whatever, either from quinine plus plasmoquine or atebrin plus plasmoquine.

[48] See [5], pp. 180 to 183, and [33], pp. 90 to 92.