REPORT ON A TRIAL OF PLASMOQUINE AND QUININE IN THE TREATMENT OF BENIGN TERTIAN MALARIA.

By Major J. A. Manifold, D.S.O., Royal Army Medical Corps.

(Continued from p. 338.)

Effects of the Treatment on Splenic Enlargement.

Brosius (1926), Baermann and Smits (1927), and Manson Bahr (1927) (a), have recorded their opinion that plasmoquine rapidly reduces the size of the spleen. Green (1929) found that in both subtertian and quartan cases of malaria enlarged spleens were reduced in size more rapidly in his plasmoquine plus quinine-treated series than in his quinine-treated controls.

Sinton, Smith and Pottinger (1930) state that the spleen rate in their series of cases was 25 per cent before the commencement of treatment, and in no case was splenic enlargement detected after completion of treatment. They did not find, however, that the rate of decrease was more rapid amongst their plasmoquine series than among the controls.

A few details have been given by some hospitals on this point.

Hospital 1 states: Of the 121 cases treated, 62 had spleens enlarged up to plus 2 on admission. In all these cases the splenic enlargement had disappeared on completion of treatment. Thirteen cases with splenic enlargement varying from plus 3 to plus 5 showed very little reduction in the size of the spleen on completion of treatment.

Hospital 2 (91 cases treated). Treatment was highly successful not only in the prevention of relapses, but in diminishing enlarged spleens. Thus, of 31 cases of enlarged spleen before treatment, only 4 remained palpable on completion of treatment.

Hospital 3 (20 cases treated). The spleen in some of the cases diminished in size remarkably quickly, but in others the drug appeared to have had no effect on the spleen (details not given).

Hospital 4 (253 cases treated). In cases of benign tertian, fresh infection with palpable spleen, the effect of the combined plasmoquine and quinine treatment is practically the same as that of the ordinary quinine treatment, the spleen being reduced to normal size within seven to ten days after the temperature has come down to normal.

With regard to chronic cases with enlarged spleen (plus 2 or more), no marked effect was noticed with either treatment, 46 cases being kept under observation for one month without marked improvement, but, on being put on spleen mixture, in 22 cases the spleen was completely reduced to normal size, while 24 showed marked improvement. Quinine sulph. gr. v, ferri
sulph. gr. iii, mag. sulph. ʒi, acid sulph. dil. ںx, aq. ad ʒi, was the spleen mixture used.

Hospital 15 (306 cases treated). In so-called cases of malarial cachexia with greatly enlarged spleens, the spleens were reduced from umbilical level to one finger after seven days plasmoquine and quinine treatment (details not given).

Opinions therefore remain very divided as to the effect of the treatment in the reduction of chronic enlargement of the spleen. It appears to be accepted, however, that in acute enlargement the treatment is effective in reducing the spleen to normal size, at least in the usual time, if not actually quicker than the normal quinine treatment.

Suitability of the treatment for the control of pyrexia.

As very few comments have been made by any hospital on this point it may be accepted that, as a rule, the control of pyrexia was at least as efficacious as with the usual quinine treatment.

In the Southern Command "it was found on the whole that patients responded more rapidly to treatment with plasmoquine and quinine than quinine alone. In no case was it necessary to give intravenous or intra-muscular quinine" (note of medical specialist Southern Command).

One hospital in the Northern Command also noted that the combination of the two drugs reduced the temperatures quicker than quinine alone.

It was found necessary, however, in a few cases with heavy infections to increase the quinine to thirty grains per day until the malarial paroxysms were checked, when the quinine was reduced to the usual twenty grains. This point is brought to notice by two hospitals and by the medical specialist in the Lahore District, but is not mentioned by other hospitals.

Relapses.

As stated earlier in the report, it was considered impossible to exclude fresh infections from relapses in many stations. Therefore the relapse rate among the cases treated in certain hospitals must be considerably greater than the true relapse rate. On the other hand it is possible that a few cases which did relapse after a change of station were not reported as such in spite of the instructions that all such relapses were to be notified to the officer keeping the records of the cases. Such cases would help to counter-balance the number of fresh infections, but from a study of the hospital registers it appears that they cannot have been very many.

The period of observation of the cases discussed in this report varied from three to six months with an average of four and a half to five months. Any cases treated after December 31, 1929, are not included. The percentage of relapses among the cases treated in various military hospitals is given in Table IX. The comparatively high percentage in highly malarious stations, compared with other less malarious stations, should be noted.
The relapses appear, therefore, to have been surprisingly few, the average for all classes and all stations being 5·2 per cent. If cases relapsing after what may be roughly called the end of the malarial season in the various stations only were accepted as relapses, the relapse-rate would be as low as 2·4 per cent.

**TABLE IX.**

<table>
<thead>
<tr>
<th>British Military Hospital</th>
<th>Admission ratio per 1,000 Sept., 1930</th>
<th>Cases</th>
<th>Relapse percentage after treatment</th>
<th>Indian Military Hospital</th>
<th>Admission ratio per 1,000 Sept., 1930</th>
<th>Cases</th>
<th>Relapse percentage after treatment</th>
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<tbody>
<tr>
<td>Poona</td>
<td>4:3</td>
<td>97</td>
<td>1:06</td>
<td>Nasirabad</td>
<td>85:2</td>
<td>170</td>
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<tr>
<td>Mhow</td>
<td>28:4</td>
<td>110</td>
<td>3:2</td>
<td>Jubbulpore</td>
<td>14:1</td>
<td>125</td>
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<tr>
<td>Nasirabad</td>
<td>96:0</td>
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<td>Nowshera</td>
<td>19:7</td>
<td>106</td>
<td>0:0</td>
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<tr>
<td>Jubbulpore</td>
<td>14:2</td>
<td>5:0</td>
<td>9:0</td>
<td>Rawalpindi</td>
<td>39:2</td>
<td>248</td>
<td>5:6</td>
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<tr>
<td>Nowshera</td>
<td>7:4</td>
<td>27</td>
<td>5:0</td>
<td>Lahore</td>
<td>31:8</td>
<td>801</td>
<td>10:6</td>
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<tr>
<td>Rawalpindi</td>
<td>1:9</td>
<td>(6 cases)</td>
<td></td>
<td>Peshawar</td>
<td>31:8</td>
<td></td>
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<tr>
<td>Lahore</td>
<td>3:8</td>
<td>147</td>
<td>1:3</td>
<td>Jhelum</td>
<td>34:2</td>
<td>92</td>
<td>1:08</td>
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<tr>
<td>Peshawar</td>
<td>20:9</td>
<td>147</td>
<td>8:8</td>
<td>Bannu</td>
<td>17:7</td>
<td>103</td>
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<tr>
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<td>Sialkot</td>
<td>17:1</td>
<td>58</td>
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<td>89</td>
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<td>20</td>
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<td>Quetta</td>
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<td>35</td>
<td>0:0</td>
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<tr>
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<td>82:3</td>
<td>53</td>
<td>1:8</td>
<td>Karachi</td>
<td>9:4</td>
<td>20</td>
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<tr>
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<td>11</td>
<td>0:0</td>
<td>Maymyo</td>
<td>19:0</td>
<td>136</td>
<td>10:2</td>
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<tr>
<td>Quetta</td>
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<td>88</td>
<td>2:6</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Karachi</td>
<td>18:3</td>
<td>34</td>
<td>5:3</td>
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* 35 per 1,000 were relapse cases.

The figures for the relapse-rate, although they cannot be accepted as accurate, are definitely very favourable as compared with the usual quinine treatment. In the quinine-treated control series of Sinton, Smith and Pottinger (1930) at Kasauli the relapse-rate was as high as forty-two per cent. Using the same treatment as was employed for these cases they reduced the relapse-rate to eight per cent. The relapse-rate in the present series, as applied to the total cases treated, is even lower.

**DEATHS.**

There were two deaths among the Indian cases.

The first was a sepoy, aged 32, with fifteen years' service. He was admitted with a history of rigors, pains and vomiting for two days, temperature 102° F. Spleen and liver not palpable. *P. vivax* ring forms present. Placed on plasmoquine and quinine treatment.

3rd day. Urine normal, temperature 96° F.

4th day. *P. vivax* gametocytes and *P. falciparum* crescents in blood, quinine not being excreted in urine.

5th day. *P. falciparum* crescents present, quinine demonstrated in urine.
6th day. Rigor and vomiting, temperature 102.4°F. No toxic symptoms of plasmoquine. No plasmoquine after this date.

7th day. 9 a.m. Temperature 100°F. Bile-coloured fluid vomited. Complained of pains in chest and abdomen. No signs of cyanosis present, but difficulty in breathing. Abdomen flaccid, spleen not palpable. Jaundice marked. Pulse 104, rather weak. Heart and lungs nothing abnormal. Urine bile coloured, quinine present in urine.

Note.—Patient did not look very seriously ill, but seemed uncomfortable, and got some ease from abdominal pain in a sitting position.

4.30 p.m. Condition same as in the morning and not considered serious. About fifteen minutes later the patient vomited once and was dead when the Sub-Assistant Surgeon returned.

Post-mortem examination was refused by the relatives and by the unit to which the patient belonged.

The Officer Commanding Indian Military Hospital adds a note:—

"There does not appear to be any connection between the plasmoquine treatment this case was undergoing and the symptoms and signs on the last day of his illness. The bilious vomiting, jaundice and abdominal pain were typical of the bilious remittent type of pernicious malaria. The final syncope was apparently due to cardiac dilatation."

The Medical Specialist, Baluchistan, also states:—

"I am strongly of the opinion that the plasmoquine was not the direct cause of death, but that he already had a hepatic deficiency. Whether the condition was hastened by the administration of plasmoquine it is impossible to say."

The second patient was an Indian groom. His temperature on admission was 100°F., he complained of headache and gave a history of fever for one day. He had a previous history of fever in his village one year ago. Benign tertian rings were present. He was placed on combined plasmoquine and quinine treatment.

2nd and 3rd day. Temperature normal.

4th day. Temperature 101.4°F. No abdominal pain or discomfort. Urine specific gravity 1024. No albumin or sugar present.

5th day. Temperature which had risen to 102.8°F. on the evening of the previous day came down to 99°F. No abdominal pain, but patient looked seriously ill and was passing dark-coloured urine; temperature 102°F. Plasmoquine stopped.

Evening: patient very restless, breathing shallow and rapid, looked very pale and run down, cyanosis present. Still passing dark, reddish-coloured urine resembling port wine. Specific gravity 1028, blood, bile, and urates present.

6th day. Cyanosed, jaundice marked, restless, bilious vomiting present, methaemoglobinuria.
7th day. Temperature 100.4°F. Pulse weak and irregular. Patient unconscious. Respirations 28 per minute. Marked anaemia, very restless, still passing port wine-coloured urine.
8th day. Patient restless, unconscious, bilious vomiting. Respirations 24 per minute, pulse 100 per minute, cyanosis present, methaemoglobinuria.
9th day. Patient restless and unconscious. Urine scanty, and passed in bed. Methaemoglobinuria and marked cyanosis present.
10th day. Patient died from respiratory failure at 4:00 hours.

Post-mortem report.—

**Liver,** marked fatty degeneration. Microscopical examination showed fragmentation and degeneration of lining epithelium of the tubules. Lumen of tubules filled with amorphous debris, partly derived from the lining epithelium, but chiefly composed of haemoglobin or a derivative therefrom. Melanin pigment present in considerable amount.

**Kidney,** marked fatty degeneration. Microscopical examination showed fragmentation and degeneration of lining epithelium of the tubules. Lumen of tubules filled with amorphous debris, partly derived from the lining epithelium, but chiefly composed of haemoglobin or a derivative therefrom. Melanin pigment present in considerable amount.

**Spleen.—** Melanin pigment present and pulp sinuses filled with debris of haemoglobin or its derivatives.

History of two cases of methaemoglobinuria which recovered.

**Case 1.**—Indian recruit.
1st day. Pyrexia and rigor. Blood-smear negative.
2nd day. Temperature normal.
3rd day. Pyrexia and rigor. *P. vivax* ring forms present.
5th day. Temperature 101.6°F. Plasmoquine (0.04 grammie) and quinine (grains xx) treatment commenced.
6th-8th day. Normal.
9th day. Abdominal pain and vomiting, yellow tinged conjunctiva. Plasmoquine stopped.
12 noon. Condition as above.
6 p.m. Temperature 104°F. Rigor, vomited bile-stained matter, pain in loins, lower abdomen and liver region. Jaundice marked on skin and conjunctiva, pulse rapid, blood-smear negative for malaria parasites.

Urine dark colour, albumin present. On standing separated in two layers, top of brownish colour and lower of brownish sediment. Tube casts and red blood corpuscles in sediment.
8 p.m. Epigastric pain intense, eyes sunken, face pinched, pulse rapid and thready. Frequent desire to pass urine, and passes one to two ounces of dark-coloured urine.
10th day. Condition as before. Temperature 100°F. Urine dark coloured, patient cannot retain anything.
6 p.m. Temperature 103°F. Condition as before.
11th day. Temperature 99°F. Urine dark-coloured, albumin present.
12th day. Temperature normal, urine still dark-coloured, albumin and tube casts present.
13th day. Temperature normal, urine faint dark colour, albumin and tube casts present, jaundice much less, pain in loins less.
J. A. Manifold

14th day. Temperature normal, urine much clearer, no tube casts, slight traces albumin.

15th day. Condition much improved.
The condition of this patient steadily improved, and on the 20th day he is noted as having recovered.

Case 2.—Indian groom (methæmoglobinuria).


2nd day. Temperature 100°F.

3rd day. Temperature 99°6°F.


6th day. Temperature normal. Urine less deep in colour than yesterday.

7th day. Temperature 99°F. Improved and urine less deep in colour.

10th day. Doing well. No blood or bile in urine.

Patient made an uninterrupted recovery.

The first death occurred in a case of definite mixed infection, as gametocytes of P. falciparum were present in the blood. As a post-mortem was refused, the cause of death must remain uncertain. Neither the officer commanding the hospital concerned nor the medical specialist of the district was of opinion that death could be attributed to the plasmoquine.

The total amount of plasmoquine given to the patient was 0'18 gramme, during treatment for four and a half days.

The case in which the second death occurred appears to have presented all the symptoms of a typical attack of blackwater fever. It is possible that the ring forms of malarial parasites, although described as P. vivax, may have been actually P. falciparum rings. As, contrary to instructions, the blood-films of these cases were not retained in the hospital, the original diagnosis could not be confirmed. The patient was an Indian groom, a class of individual often heavily infected with subtertian malaria from childhood, and there was a definite history of an attack of malaria while on leave in his village. The total amount of plasmoquine administered was 0'16 gramme during four days' treatment.

Methæmoglobinuria.—The first case was similar in all respects also to a case of blackwater fever, and may have been a case of mixed infection. The patient was a recruit, and in few Indian villages is it possible to escape a subtertian infection. The case also occurred in Jubbulpore, a highly malarious station, and about the same time fifty-five cases of a subtertian malaria and several cases of mixed tertian and subtertian infections were treated in the same hospital.

The second case appears to have been very much milder in type. The notes on this case are not sufficiently full to be of much value, but as the
temperature did not become normal for eight days from the onset of pyrexia, and the patient was an Indian groom, subtertian infection was probably present.

Excluding the first death as not due to plasmoquine, there have been therefore three cases of methämoglobinuria, with one death among the Indian group. All these cases were in all probability either mixed infections, or pure subtertian infections, and as quinine was administered as well as plasmoquine, it is impossible to say which drug precipitated the attack of blackwater fever.

If the methämoglobinuria and blackwater fever symptoms in general are to be attributed to the direct toxic action of plasmoquine, apart from an ordinary attack of blackwater fever, it is difficult to believe that a case would not have occurred among the British group treated (1,298 cases). It is probable that the treatment produced in the affected patients conditions which enabled an attack of blackwater fever to occur. That such conditions may be equally produced by quinine and other factors such as chill, alcohol, etc., is well known.

In all cases the symptoms appeared in the early stages of treatment, on the fourth and fifth day. As well over 1,000 cases of subtertian malaria received plasmoquine treatment in a similar daily dosage for five days in addition to the 3,213 cases receiving twenty-one days' treatment, many cases of mixed infections being undoubtedly included in the Indian group, the percentage of cases in which an attack of blackwater fever was precipitated by the plasmoquine and quinine treatment must have been very small, probably no greater than with the usual quinine treatment.

Manson Bahr (1927) (a) describes a case of methämoglobinuria in a case of mixed infection treated with plasmoquine, the daily dose of plasmoquine being 0.12 grammes; symptoms appeared after a total amount of 0.4 grammes, a much larger quantity than was given in the present series.

Various authors, Muhlens and Fischer (1927), Schnellmann and Memmi (1927), Polychroniades (1927), Talianidis (1928), report on cases of blackwater fever treated successfully with plasmoquine: which appears to indicate that the methämoglobinuria in the three cases in this series could not have been due to the direct toxic action of the small doses of plasmoquine employed. Eiselsberg (1927) however reports one case with no history of malaria, in which, after 0.2 grammes plasmoquine, symptoms similar to those of blackwater fever developed.

The question whether the symptoms in these cases can be attributed directly to plasmoquine must be considered therefore as undecided. On the whole it is thought that probably they were not so attributable.

The opinions of the medical officers who supervised the treatment in a large number of cases are given below. In certain hospitals comparatively few cases were treated, and although the impression gained was favourable medical officers naturally reserved their judgment.

Major E. B. March, M.C., R.A.M.C., Medical Specialist, Baluchistan
Plasmoquine District: "Plasmoquine is undoubtedly a dangerous drug, and unless the results of treatment are very considerably better than any other form of treatment, it is not considered a suitable drug for use in the Army, but may possibly prove useful for selected cases. The treatment was, however, considered effective."

In the British Military Hospital in Quetta forty-three cases completed treatment. No toxic symptoms of any kind are noted as occurring among the last twenty-five cases in the register. Among the first eighteen patients, toxic symptoms are recorded in six cases.

1. 4th case. Cyanosis marked, finger-nails also affected (tenth day). Did not clear up until four days, so treatment stopped.
2. 8th case. Abdominal pain and slight cyanosis (seventh day), stopped treatment three days. Symptoms reappeared on first dose, treatment discontinued.
3. 10th case. Slight giddiness (second day). Treatment stopped one day only, probably functional.
4. 13th case. Abdominal pain and vomiting (eighth day). Toxic symptoms lasted three days, treatment withheld for four days. Completed course.
5. 16th case. Cyanosis (ninth day). Plasmoquine stopped three days, cyanosis reappeared on sixteenth day, treatment discontinued.
6. 18th case. Slight abdominal pains (eighth day), lasted one day, treatment was not withheld.

In the Indian Military Hospital, Quetta, forty-two cases were treated. Toxic symptoms are recorded in three cases, and there was one death.

1. 2nd case. Epigastric pain seventh day, while attending medical inspection room for treatment. Treatment withheld, symptoms lasted seven days.
2. 4th case. Pain in lower region and diarrhoea (seventeenth day). Symptoms persisted; treatment withheld eleven days.
3. 9th case. Pain and diarrhoea (fourteenth day), symptoms persisted; treatment withheld for five days.
4. 37th case. Died on the seventh day. Case already described.

No further toxic cases are noticed as occurring, except one case in which "splenitis" is recorded. Malaria parasites were not found, treatment was stopped for one day. The "splenitis" apparently was not considered to be due to the plasmoquine.

Captain T. J. Davidson, I.M.S., Indian Military Hospital, Sialkot (sixty-four cases): "As a routine measure I certainly do not recommend the use of plasmoquine, and so far I have not found any advantage it has over quinine, but many disadvantages, except in removing crescents from the peripheral blood in M.T. malaria."

In this hospital abdominal pain is recorded in 15 cases, cyanosis in 2, diarrhoea in 5, headache in 2. There were 5 cases of albuminuria, 1 case
of methaemoglobinuria which recovered, and 1 case of methaemoglobinuria which died.

Considering the general absence of toxic symptoms among the large number of Indian patients treated in the other Indian military hospitals, the experience of this hospital must have been singularly unfortunate. The conclusion from the British military hospital in the same station (twenty-two cases) is: "The treatment appears to be extremely efficacious and provided that the need for careful observation of patients by those carrying out the treatment is fully recognized, the general issue of plasmoquine would appear to be highly desirable."

Colonel L. T. Brassey, I.M.S., Assistant Director of Medical Services, Peshawar District: "Opinion in this district is unanimous on the value of plasmoquine treatment of benign tertian malaria as opposed to quinine alone. Its efficacy combined with simplicity of administration and shortness of course has appealed to both medical officers and troops. Toxic symptoms have been so mild that they might have passed unnoticed had not special warning been issued."

Colonel L. T. Brassey, I.M.S., Indian Military Hospital, Peshawar: "Plasmoquine was administered to 395 benign tertian cases of malaria. No serious sequela was complained of by any of the patients. One or two said they had pain in the stomach, but this soon passed off. No case of cyanosis has occurred. The opinion formed here is that plasmoquine had a very decided effect on the malaria parasite, and that it is a useful addition to the list of drugs for this condition. It is specially useful as an adjunct to quinine in the chronic relapsing case."

Lieutenant-Colonel A. F. Baboneau, C.I.E., I.M.S., Indian Military Hospital, Nowshera (144 cases): "During the experiment mild toxic symptoms were noticed in certain cases. Issue of plasmoquine as a general issue is recommended."

Major H. H. Blake, C.B.E., R.A.M.C., British Military Hospital, Nowshera: "Plasmoquine is recommended as a general issue. In this hospital 153 cases B.T. malaria were treated this year. Six have relapsed so far."

Major J. F. Bourke, M.C., R.A.M.C., British Military Hospital, Peshawar: "Total number of B.T. cases treated was 146. Eight complained of epigastric pain, and 5 displayed signs of definite so-called cyanosis. In the light of the experience gained while conducting these observations, I can now say that in no case were the signs and symptoms such as would have caused uneasiness in the mind of an experienced clinician habituated to this form of treatment. When the treatment started the evident apprehension of untoward results had a psychological effect among the patients and caused them to exaggerate minor discomfort. The treatment has definitely given a lesser incidence of relapses. It saves the soldier from a long and wearisome course of post-hospital quininization. This has made it popular with the troops in this station and has simplified
the administrative arrangements for men proceeding to England, or on school courses, leave, etc., in this country."

Major J. Bennet, R.A.M.C., British Military Hospital, Lucknow (91 cases): "In estimating the frequency of colic as a complication in the treatment of these cases, unfortunately the effect of suggestion cannot be eliminated where the symptoms have occurred once, or in cases where the patient has heard of others being affected in this way by the drug. No cases of severe dyspnœa or methemoglobinæmia occurred in the series of cases in whom the treatment was tested. The value of plasmoquine in combination with quinine in the treatment of benign tertian malaria is probably very great; and the ill-effects of its administration are slight and easily recovered from. Many cases with previous history of numerous relapses volunteer statements that they feel more physically fit under this treatment than they did when treated by previous methods."

Major V. J. Bonavia, R.A.M.C., Medical Specialist, Lahore District: "The results obtained were very satisfactory and encouraging. The treatment was simple and easy to carry out, and the toxic symptoms encountered were practically negligible, all cases having been able to complete their course. The patients were all warned what early toxic symptoms might occur, and daily asked if they felt any of these symptoms. As soon as these occurred the treatment was interrupted, to be again resumed as soon as the symptoms cleared up, usually in one or two days' time. By this simple precaution no cases causing anxiety were encountered. The second rule was not to give the plasmoquine on an empty stomach."

One hundred and fifty-two cases of benign tertian malaria were treated in the British Military Hospital, Lahore. Only two cases are known to have relapsed. One relapsed twenty-three days after completing the course, and one on the day following his course. They were both put through a second course and have not relapsed since. Of the 152 cases, only 8 showed toxic symptoms which occurred from the seventh to the eighth day, and treatment was interrupted for one or two days. Six cases complained of epigastric pain. Treatment interrupted from one to two days.

One case had epigastric pain and vomiting. Treatment interrupted, two days.

One case had epigastric pain and cyanosis. Treatment interrupted one day.

Major H. G. Winter, M.C., R.A.M.C., British Military Hospital, Lahore (152 cases): "Toxic symptoms which occurred in a very few cases were of extremely mild nature. From my experience of malaria and its treatment gained in Egypt, Palestine, Cyprus, as well as in this country, I consider that the drug is a decided advance in treatment, and I recommend its general issue."

Lieutenant-Colonel S. Whitworth Jones, C.B.E., I.M.S., Indian Military Hospital, Lahore (253 cases): "It seems to me that plasmoquine has been
Plasmoquine and Quinine in the Treatment of Malaria

efficacious in reducing the number of relapses and can be recommended as a general issue."

Major S. R. Prall, I.M.S., Indian Military Hospital, Shillong (89 cases): "There were no cases exhibiting toxic symptoms. In a few individuals the pulse-rate became somewhat slow. It is considered that the treatment was highly successful, not only in the prevention of relapses, but also in diminishing enlarged spleens."

Major H. B. F. Dixon, R.A.M.C., Medical Specialist, Southern Command (108 cases): "At the beginning of the period there was a certain amount of nervousness on the part of the staff and patients on account of the warning regarding abdominal pain, and I feel sure it was suggested to the patients. However, as time went on, more confidence in the treatment was obtained and the alleged abdominal pain was not noticed. A certain amount of cyanosis was noticed in the early stages, also possibly on account of the warnings, and several patients had treatment discontinued for a few days, but as time went on the number of cases in which cyanosis was sufficient to discontinue treatment fell to almost nil.

"In my opinion cyanosis is the first evidence of toxic symptoms, and unless it is marked it is quite harmless. Discontinuance of the treatment for a few days immediately brings the patient back to normal."

"Conclusions. (1) Treatment of B.T. with plasmoquine and quinine is quite satisfactory.

"(2) The administration should be done for first seven days in hospital and then after under medical supervision, patient being excused duty for twenty-one days in all.

[General experience appears to indicate that ten days' hospital treatment is preferable to the seven-day period suggested above.]

"(3) The control of the pyrexia is more easily done than by quinine alone and the period in hospital is on the whole as short.

"(4) Toxic symptoms in order of appearance are cyanosis, abdominal pain, icterus, methemoglobinæmia.

"(5) Stopping of the drug for a few days prevents any toxic symptoms developing, soda bicarb. and glucose are recommended for cyanosis.

"(6) In the series of cases reported on the toxic symptoms were remarkably few, and in my opinion were largely the result of suggestion.

"(7) The relapse rate is strikingly low, 1'85 per cent as compared with 18'1 per cent in quinine alone taken over a period of nine months.

"(8) I strongly recommend that plasmoquine with quinine treatment be instituted as a standard treatment."

Captain S. C. H. Worseldine, I.M.S., Indian Military Hospital, Jhelum: "121 cases were placed on treatment and six showed toxic symptoms of a mild nature, so slight as not to interfere with the general use of the drug. Relapse occurred in one case only. From the small number treated the treatment would appear to be satisfactory."

Captain A. Sachs, R.A.M.C., British and Indian Military Hospital,
Jubbulpore (406 cases): "Owing to the short time of treatment it is impossible to arrive at definite conclusions. The relapse rate has certainly fallen enormously. It seems with due care that plasmoquine is a valuable adjuvant in the treatment of malaria."

Major E. Underhill, R.A.M.C., Specialist in Medicine, Mhow District: "Two points appear worthy of note: (1) The mildness of toxic symptoms; (2) the small number of relapses after treatment.

"(1) As regards toxic symptoms the majority of cases treated showed none. In one case only were toxic symptoms severe, and in one case marked; cyanosis being noted in both of these. In the remainder abdominal discomfort or slight cyanosis only was observed. In no cases did the occurrence of toxic symptoms prevent the eventual completion of treatment.

"(2) Two cases only were admitted to hospital for a second attack of malaria after completion of treatment. In both cases the second admission was for M.T. malaria, the first being B.T. In view of the foregoing and with due allowance for the smallness of this experience with the drug, I am definitely of opinion that this line of treatment is a distinct advance in the treatment and control of malaria. I consider, however, that the treatment should continue to be accompanied by careful supervision of the patients, and that before it is universally adopted the disadvantages should be clearly understood by all medical officers undertaking the treatment."

In conclusion the objects of the investigation may be reconsidered, with a view to ascertaining whether answers to the questions at issue have been arrived at.

(1) Whether the treatment may safely be given to all classes of patients whatever their physique may be?

The answer as far as the British soldier in India is concerned appears to be definitely "yes." As regards the Indian sepoy and follower the answer appears to be also in the affirmative for the great majority of cases. In a small minority, about 0.1 per cent, it is possible that an attack of blackwater fever may be precipitated in individuals who have suffered from many attacks of subtertian malaria. The percentage is probably even smaller than appears from the results in this series of cases, as plasmoquine in larger daily doses, and over a period of five to twelve days, has been used to destroy the gametocytes of P. falciparum in most tropical countries. The number of cases treated must by now be very large, and instances of methaemoglobinuria occurring after treatment seem practically negligible from the literature available. As in both British and Indian cases there appears to be a small percentage with a definite idiosyncrasy to the toxic action of plasmoquine, patients will require to be kept under observation, and should be excused duty during the three weeks' treatment. While keeping the symptoms of
the toxic effects in mind great care is obviously necessary to avoid the effect of suggestion on the minds of patients with regard to these symptoms.

It also appears that minor manifestations may, as long as a watchful attitude is adopted on the part of the physician, be disregarded in the large majority of cases and treatment not withheld.

(2) Whether such toxic effects were observed more frequently in the British or Indian group?

The answer appears to be that epigastric pain, cyanosis, etc., were less frequent among Indian cases, but that the difference in the incidence was probably largely due to colour, and to the different mentality in the two groups. If the later cases in the registers of both groups are compared, there is little difference in the incidence of toxic symptoms.

(3) The incidence and importance of toxic manifestations. These are fully discussed in the body of this report. The incidence is low, and would certainly be lower in any future series of cases treated by the same medical officers. Toxic symptoms are of importance only in a very few cases with special idiosyncrasy, and as long as a look-out is kept for the possible occurrence of such cases, after a temporary cessation for a day or two the treatment may safely be continued in the great majority of cases.

(4) Was the treatment efficacious in preventing relapses? There is no doubt that it is most efficacious and a great advance on the ordinary quinine treatment. By its introduction, post-hospital courses of quinine can be abolished and the relapse rate reduced to a very low figure, thus benefiting not only the health of a large number of patients, but at the same time causing a saving to the State by diminishing the number of readmissions to hospitals annually.

(5) Can plasmoquine be safely issued to patients not under medical supervision? Although not of great importance as regards the Army in India, in which treatment can always be controlled, the question of whether the drug can be safely issued to patients not under medical supervision is constantly being referred to in the literature. From the results obtained in the present series of cases with a continuous daily dose of 0.04 gramme plasmoquine for twenty-one days, the answer would appear to be definitely in the negative. Good results might be met with in ninety-nine cases, but disaster might occur in the hundredth case.

If the margin of safety can be made greater, and good results obtained by utilizing 0.03 gramme plasmoquine as the daily dose plus quinine 20 grains for twenty-one days, a definite advance would be made.

Investigations on these lines are being carried out at the Malaria Treatment Centre, Kasauli. Major A. E. Richmond, O.B.E., R.A.M.C., reports that up to date 57 cases have been treated. Toxic symptoms have been non-existent, and the patients have been able to pursue their normal avocations in the depot, including an occasional game of hockey or football. Four cases (7 per cent), however, have relapsed after treatment, and 20 of the 57 cases have not yet completed eight weeks' observation.
Thanks must be given to the medical officers of the R.A.M.C. and I.M.S. who undertook this investigation in the various hospitals. It is considered that the results obtained are of great interest and that they afford valuable information for medical officers undertaking the treatment in future.

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