A REPORT ON SIX HUNDRED CASES OF MALARIA TREATED WITH PLASMOQUINE AND QUININE.

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A survey of the existing literature on plasmoquine, which was first prepared by Schulemann and his colleagues in 1924 and offered to the medical profession in 1926, is now well-nigh impossible.

The publications on the subject had reached on October 1, 1930, a total of 415, and a search through the Index Medicus up to date shows that plasmoquine appears under every aspect of the malaria problem—therapeutics, prevention, prophylaxis, blackwater fever, avian malaria, malarial treatment of G.P.I., etc.—and that almost every article on malaria that one reads has some reference to plasmoquine.

Apart from the importance of its discovery as the first synthetic preparation which was found to have a definite action in malaria, the fact that it had a specific action on certain stages in the development of the parasite in man had far reaching effects. Since then a new form of malaria therapy has arisen—the treatment of malaria by attacking the various phases of the life cycle in man, a drug for the sporozoites, a drug for the schizonts, a drug for the sexual forms. In the past, one gave quinine in as large doses as possible, as quickly as possible and for as long as possible. This resulted in a relapse rate of 50 per cent.

The present position as regards plasmoquine, as gathered from a survey of the recent literature, and especially the "Discussion on Synthetic Anti-malarial Drugs" at the Royal Society of Tropical Medicine and Hygiene (1932), is as follows:

*Plasmoquine* has a definite action on the sporozoites of *Plasmodium falciparum*, and in non-toxic doses it can be used as a prophylactic.

In *P. vivax* infections it has also a definite action on the sporozoites, and in large doses will prevent infection in 50 per cent of the cases; in the remainder, infection does not develop until six months or more.

In *P. falciparum* infections it has no effect on the schizonts, but it is extremely effective against the sexual forms.

In *P. vivax* infections it has some effect on the schizonts, not as great as quinine, but it is very effectual against the sexual forms.

It is extremely effective in treating *P. malariae* infections; no relapses are recorded.

In combination with quinine it is most effective in preventing relapses in *P. vivax* infections.

Its effect in preventing relapses is the subject of this paper. The general
consensus of opinion among tropical workers is that the treatment of benign tertian infections with a combination of plasmoquine and quinine has reduced the relapsed rate to between 5 and 7 per cent. This opinion, however, is not so enthusiastically shared by laboratory workers and clinicians in non-tropical countries. Both James and Swellengrebel (1932) at the discussion mentioned above, gave results at variance with those of tropical workers, and in the "Memoranda on Medical Diseases in Tropical and Sub-tropical Areas" (1930) it is stated that plasmoquine has not fulfilled its early promise.

This is a curious situation, for usually it is the other way about; laboratory workers and clinicians at home frequently find that remedies are excellent, whereas the tropical worker frequently finds them useless.

The discrepancy in results has given rise to much discussion and, it is suggested, may be explained by various factors: (1) That the cases in the tropics may have developed or been allowed to develop some immunity before the drug was administered. (2) That the strain of parasite, especially in India, may be very mild. (3) That the period of observation after treatment is not long enough.

These suggestions appear to be quite reasonable, and a study of the various papers relating to the treatment of British soldiers in India appears to support suggestion No. 3, in that the period of observation after treatment was not long enough. The period of observation after treatment with plasmoquine and quinine in Manifold's cases (1931) was six months, in Sinton, Smith and Pottingers' cases (1930) eight weeks, and in Jarvis' cases (1932) twelve weeks.

This paper is an attempt to form a sequel to Manifold's, in that:

(1) Cases treated with plasmoquine and quinine have been carefully observed over a period of from three and a quarter years to a minimum period of ten months.
(2) Cases have been separated into primary infections and relapses.
(3) Cases were most carefully investigated in the endeavour to find out where the infection was originally contracted and, as will be seen, many of the cases were infected, not in India, but in China, Burma, etc.

The writer has been in charge of all the cases of malaria admitted to the Connaught Military Hospital, Poona, for the past four and a half years. For one and a half years over 250 cases were treated with quinine alone, and he was in a position to judge the results of the two treatments, all the other factors being the same, the only difference being the reduction in the amount of quinine given and the addition of plasmoquine. The relapse rate on quinine alone was 25 per cent. Since the commencement of plasmoquine treatment on July 7, 1929, in all 600 cases have been treated, 100 of these in 1932, and although none of these has relapsed up to October 13, 1932, they are not included in the figures for working out the relapse rate. The 600 cases included all types of malaria infection—P. vivax, P. falciparum, P. malariae, and a mixture of all three. No case of infection with P. ovale was noted. The patients included officers, other
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ranks, women and children (no non-European cases are included in the series).

All cases were diagnosed microscopically and the treatment was instituted at the earliest possible moment, often within ten minutes of admission to hospital. There was no attempt to allow a patient to develop any tolerance or immunity; on the contrary, speed in diagnosis and giving treatment was aimed at, and if an extra dose of quinine had to be given it was invariably given in the first twenty-four hours.

Almost always in primary cases a lag period was noted, in which the fever was present but parasites were not found for twenty-four to forty-eight hours. This is in keeping with James's findings.

SOURCE OF INFECTION.

The majority of cases were infected at Poona or Kirkee. Every patient was carefully questioned, and as far as possible every endeavour was made to find out where and when he had been infected.

In 1930 a new battalion arrived in Poona direct from Hong Kong where it had been heavily infected with malaria: this battalion furnished most of the relapse cases in 1930 and during the early part of 1931. In 1931 another battalion arrived from Shanghai, moderately infected; this battalion furnished most of the relapses in 1931.

In 1929 one battalion came from Quetta. There were also cases which had been infected originally in various parts of India and Burma.

RECORDS.

A careful follow-up system was employed. Every patient who had been treated with plasmoquine and was still in the station, was inspected personally every six months. In the case of patients who had left the station, a questionnaire was sent to their medical officers to find out whether they had relapsed. Ninety-five per cent of the patients treated with plasmoquine were thus traced, some three and a quarter years after treatment.

TREATMENT IN THE PRE-PLASMOQUINE PERIOD.

As mentioned before, the writer treated 250 cases of benign tertian malaria in the pre-plasmoquine period with the usual standard method as was then laid down for India, i.e., quinine sulphate 30 grains daily for about ten to fifteen days, depending on the case. This was followed by a post-hospital quinine course of 10 grains daily for two months; a tonic mixture of iron and arsenic was also given. The treatment was personally supervised and presumably efficiently carried out, but it struck the writer that the more efficiently it was done the more likely was the patient to relapse. Patients used to relapse several times during the year, sometimes during their post-hospital quinine course or immediately after it.

In 1928 ten cases were transferred to Kasauli, the Malaria Treatment Centre, as they had relapsed more than three times in the year and were
Malaria Treated with Plasmoquine and Quinine

considered to be a nidus of infection in their battalion. The relapse rate for the 250 cases treated was over 25 per cent.

Plasmoquine Period.

Numbers treated with plasmoquine and quinine from July, 1929, to October, 1932.

<table>
<thead>
<tr>
<th>Type</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.T. primary</td>
<td>263</td>
</tr>
<tr>
<td>B.T. relapse</td>
<td>141</td>
</tr>
<tr>
<td>M.T. primary</td>
<td>108</td>
</tr>
<tr>
<td>M.T. relapse</td>
<td>10</td>
</tr>
<tr>
<td>Mixed infection</td>
<td>13</td>
</tr>
<tr>
<td>Quartan</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>600</td>
</tr>
</tbody>
</table>

Note.—A primary case is one whose documents do not show evidence of a previous attack of malaria of the same type.

A relapse case is one in whose documents there was an entry for the same type of malaria within eighteen months. This period is purely arbitrary, but it is considered well within the limits of the ordinary relapse. In James's series of eighty-one controlled cases only one relapse occurred after a year, all the others occurred in under one year.

In July, 1929, treatment with plasmoquine and quinine was begun, and an interim report on the first 108 cases treated was submitted to Major Manifold in April, 1930. This report is incorporated in his article in the Journal of the Royal Army Medical Corps, 1931.

The writer's conclusions as regard the value of plasmoquine have in no way been modified by a further two and a half years' experience in the treatment of another 500 cases.

Description of the Drug (A Bayer Product).

Plasmoquine is not synthetic quinine although the molecular weight and the chemical formula of both are remarkably alike.

Plasmoquine formula: \( C_{19}H_{29}O_{7}N_{4} \)  Synonym "plasmochin." Molecular weight: 315.

Quinine formula: \( C_{20}H_{24}O_{2}N_{2} \)  Molecular weight: 324.

Plasmoquine is known chemically as N-diethylamino-isopentyl-8 amino-6 methoxy-quinoline.

A chloral hydrate salt easily soluble forms its basis. It is a tasteless, bright yellow, and very stable powder practically insoluble in water. The contents of the tablets are hydrochlorate of plasmoquine.

In looking through the literature one is confused by the various names under which it appears. A list of the plasmoquine preparations at present in use with their plasmoquine content and doses is given for reference.

For Oral Administration.

1) Plasmoquine Simplex. 1 tablet = 0.02 grammes or \( \frac{1}{3} \) of a grain of plasmoquine.

1 tablet = 0.01 gramme (⅙ grain) plasmoquine plus 0.3 gramme (4½ grains) quinine sulphate. This name was chosen to avoid any confusion with plasmoquine simplex and plasmoquine compound.

(3) Plasmoquine Compound. Plasmoquine : quinine = 1:12.5. 1 tablet = 0.01 gramme (⅙ grain) plasmoquine plus 0.125 gramme (2 grains) quinine sulphate.

Note.—The proportion of plasmoquine to quinine is much greater in plasmoquine compound than in quino plasmoquine, otherwise they are the same.

For Intravenous or Intramuscular Injection.

(1) Plasmoquine Simplex. 1 per cent solution in ampoules. 1 cubic centimetre = 0.01 gramme or ⅙ grain of plasmoquine.

(2) Quino Plasmoquine (Quinoplasmine). Plasmoquine : quinine = 1:30 in ampoules of 2 cubic centimetres. 2 cubic centimetres = 0.02 gramme plasmoquine plus 0.6 gramme (9 grains) quinine acid hydrochlor.

The preparation used throughout this series of cases was plasmoquine simplex in doses of 0.02 gramme and 0.01 gramme.

TREATMENT OF INFECTION WITH P. vivax AND P. malariae.

The original dosage was one tablet of plasmoquine simplex 0.02 gramme with one ounce mistura quinine sulphate (10 grains to the ounce) given twice daily for twenty-one days.

The dosage of plasmoquine was reduced in September, 1930, to 0.03 gramme daily—the dose of quinine remaining the same. The dosage of plasmoquine was continued right through the series, but in September, 1931, quinine acid hydrochlor. was substituted for quinine sulphate.

The morning dose was given after breakfast, the evening dose twelve hours later. The treatment for the first ten to twelve days was given in hospital, and for the remaining period of the twenty-one days the patient attended as an out-patient twice daily.

In a few cases (8 per cent) it was found necessary to give an extra dose of quinine, usually only in the first twenty-four hours. In one case intravenous quinine was given as the patient was not absorbing quinine and the temperature was keeping up. It was at first thought to be a case of malignant tertian infection. No post-hospital quinine and arsenic course was given. All treatment ceased after the twenty-one days' course was finished.

No other medicine except calomel, magnesium sulphate, and an occasional tablet of aspirin or phenacetin was given.

All patients were kept in bed for at least four to six days after admission. They were usually kept in hospital from ten to twelve days. In the interim report it was suggested that eight days in hospital was long enough, but further experience showed that a minimum of ten days was essential.

Patients were excused duty for the remaining period of the twenty-one days necessary to complete the course; if for any reason a patient missed
a day's treatment, the period of excused duty was automatically extended. It was found absolutely necessary to keep men from doing strenuous work while they were attending for their twenty-one days' treatment.

**Toxic Effects.**

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.

A few cases complained of abdominal pain when they were asked about it. One man developed severe colic, but was removed to the operating theatre by an enthusiastic surgeon and had his appendix removed. It was never clearly proved whether his colic was due to appendicitis or plasmoquine.

One officer patient developed jaundice while attending for completion of his course on about the fifteenth day. He had no other symptoms suggestive of plasmoquine poisoning. It was never clearly explained to what his jaundice was due.

Tachycardia occurred in six cases. In all of these it was found that the men had either been put on duty or had been indulging in violent exercise while attending for treatment.

The urine of every case was fully tested and except for a few cases of transient albuminuria, nothing abnormal was found.

The dosage of 0.03 gramme plasmoquine with twenty grains of quinine sulphate or hydrochloride was sufficient in most cases to bring the temperature down on the second day. In a small percentage of cases (eight per cent) it was found necessary to give an extra dose of quinine for a few days. The dosage of plasmoquine was never increased.

**Benign Tertian Relapses.**

To avoid the criticism that cases have not been under observation for a sufficient length of time, only those cases treated up to the end of 1931 have been included in calculating the relapse rate. None of the forty-eight cases treated in 1932 had relapsed up to the end of 1932.

The nomenclature for relapses is that of James.

1. Recrudescence means a return of fever and parasites within eight weeks from the primary attack.
2. Relapse means a return of fever and parasites after eight weeks but in less than twenty-four weeks.
3. Recurrence means fever and parasites later than twenty-four weeks.
Primary Benign Tertian Cases.

Of the 215 cases of primary benign tertian malaria treated between July 12, 1929, and December 31, 1931, nine had a return of fever and parasites, i.e., 4\(^\frac{1}{15}\) per cent. Of these nine cases, none were recrudescences. Four were relapses. Five were recurrent.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Date and place of primary attack</th>
<th>Date of further attack</th>
<th>Period from end of primary attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Poona, 11.10.29</td>
<td>4.3.30</td>
<td>25 weeks, relapse</td>
</tr>
<tr>
<td>2</td>
<td>Poona, 18.10.29</td>
<td>14.7.30</td>
<td>20 weeks, recurrence</td>
</tr>
<tr>
<td>3</td>
<td>Poona, 11.12.29</td>
<td>3.4.30</td>
<td>15 weeks, relapse</td>
</tr>
<tr>
<td>4</td>
<td>Kirkee, 29.6.30</td>
<td>6.10.30</td>
<td>7 weeks, relapse</td>
</tr>
<tr>
<td>5</td>
<td>Poona, 4.9.30</td>
<td>10.3.31</td>
<td>43 weeks, recurrence</td>
</tr>
<tr>
<td>6</td>
<td>Poona, 8.7.30</td>
<td>21.1.31</td>
<td>28 weeks, recurrence</td>
</tr>
<tr>
<td>7</td>
<td>Kirkee, 18.7.31</td>
<td>6.4.32</td>
<td>38 weeks, recurrence</td>
</tr>
<tr>
<td>8</td>
<td>Quetta, 27.7.31</td>
<td>20.5.32</td>
<td>37 weeks, recurrence</td>
</tr>
<tr>
<td>9</td>
<td>Poona, 24.8.31</td>
<td>8.2.32</td>
<td>22 weeks, relapse</td>
</tr>
</tbody>
</table>

(Benign Tertian Relapses.)

These were 141 cases originally treated with quinine alone which relapsed and were then treated with plasmoquine and quinine. Of these 6 relapsed again after plasmoquine: i.e., 4\(^\frac{1}{15}\) per cent.

Of these 6—1 was a recrudescence; 1 was a recrudescence and later recurred; 3 were relapses; 2 were recurrences (includes case which recrudesced).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Date and place of primary infection</th>
<th>Relapses on quinine and dates of</th>
<th>Date of first treatment with plasmoquine</th>
<th>Date of relapse on plasmoquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>28.11.27 Hong Kong</td>
<td>8.7.28, recurrence</td>
<td>3.8.30</td>
<td>21.12.30, 19 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.11.28, relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.8.28, recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.11.28, relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.8.30, recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>19.11.28 Hong Kong</td>
<td>17.7.29, recurrence</td>
<td>29.3.30</td>
<td>8.5.30, 5 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2.30, recurrence</td>
<td></td>
<td>10.7.32, 2 years and 2 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29.3.30, recrudescence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>23.11.28 Hong Kong</td>
<td>18.3.30, recurrence</td>
<td>18.3.30</td>
<td>10.8.30, 21 weeks</td>
</tr>
<tr>
<td>13</td>
<td>1.10.29 Hong Kong</td>
<td>30.4.30, recurrence</td>
<td>30.4.30</td>
<td>14.6.30, 6 weeks</td>
</tr>
<tr>
<td>14</td>
<td>21.11.28</td>
<td>19.11.23, recurrence</td>
<td>30.4.30</td>
<td>9.10.31, 75 weeks</td>
</tr>
<tr>
<td>15</td>
<td>29.6.28 Poona</td>
<td>30.7.29, recurrence</td>
<td>30.7.29</td>
<td>11.11.29, 13 weeks</td>
</tr>
</tbody>
</table>

Plasmodium falciparum Infections.

There were 178 cases; of these 52 were treated in 1932.

The treatment for P. falciparum infections was with quinine acid hydrochlor. alone for the first four or five days, 10 grains, t.d.s. Plasmoquine simplex 0.04 gramme or 0.03 gramme was given for five days prior to discharge from hospital.

These patients were attended by their regimental medical officer for ten days after discharge and received quinine acid hydrochlor. 10 grains daily with mistura ferric arsenic.

The type of P. falciparum on the whole was very mild and in only
fifteen cases was it found necessary to give intravenous quinine. Crescents were never found in any case treated with plasmoquine. There were three deaths, all from *P. falciparum* infection; all the men were transferred from out stations and died shortly after admission.

The relapse rate was very small, two per cent in 126 cases. One case recurred three times. No appreciable difference was noted between the relapse rate on plasmoquine and that on quinine alone.

**Quartan Infection.**

The treatment was the same as for benign tertian infections. There were no relapses.

**Mixed Infections *P. vivax* and *P. falciparum.***

These were treated as for malignant tertian infections. There were no relapses of a mixed infection, but in several cases the patient was re-admitted for *P. vivax* infection and was treated with a full course of plasmoquine and quinine. These did not relapse.

Women and children take plasmoquine well. There was no evidence of intolerance or idiosyncrasy.

Two cases of accidental overdose of plasmoquine with definite symptoms of plasmoquine poisoning occurred in 1928. Two patients, both chronic relapsing infections with *P. falciparum*, received plasmoquine simplex 0.32 gramme or 5.13 grains for two days before the error was discovered. On the third day it was noticed that both of them were very cyanosed: face, ears, lips, fingers and neck. Neither of them complained until the fourth day, when Case "A" developed incessant vomiting with epigastric pain. On this day he had a slight rise in temperature, and on the fifth day he appeared to have a transient attack of nephritis. The urine contained casts, granular and hyaline, with albumin in large quantities, no red blood-corpuscles, but much hemoglobin. The amount of urine passed was much reduced. On the sixth day the urine was normal except for the presence of leucin and tyrocin crystals. On the seventh day the patient was less cyanosed, but jaundice was well marked. On the eighth day he improved and gradually recovered. There were no leucocytes throughout. The clinical symptoms suggested blackwater fever. The treatment given was intravenous glucose and saline. The second patient, except for extreme cyanosis, presented no symptoms.

It is interesting to note that both cases recurred several times later with malignant tertian infection.

**Summary.**

(1) Six hundred cases of malaria were treated in three and a half years with plasmoquine and quinine with practically no toxic effects.

(2) In 215 cases of *P. vivax* primary infections were observed over an average period of two years; the relapse rate was 4.1 per cent. In 141 cases of *P. vivax* relapse cases the relapse rate was 4.7 per cent.
(3) The dose of 0.03 grammes plasmoquine with 20 grains of quinine acid hydrochlor. daily for twenty-one days was found to be very satisfactory for \textit{P. vivax} and \textit{P. malariae} infections.

(4) A hundred and twenty-six tertian cases were treated with quinine acid hydrochlor. 30 grains daily for twelve days, plus plasmoquine 0.03 grammes daily for five days prior to discharge from hospital, followed by a course of ten days quinine acid hydrochlor. 10 grains. The relapse rate was 2 per cent.

These results go to confirm those obtained by Manifold, Sinton, Jarvis and other workers, that is, that a combination of plasmoquine and quinine is effective in reducing the relapse rate in \textit{P. vivax} infections among British troops in India.

REFERENCES.


