OBSERVATIONS ON THE TREATMENT OF MALARIA BY COMBINED PLASMOQUINE AND QUININE METHOD.

By

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H I S T O R Y.

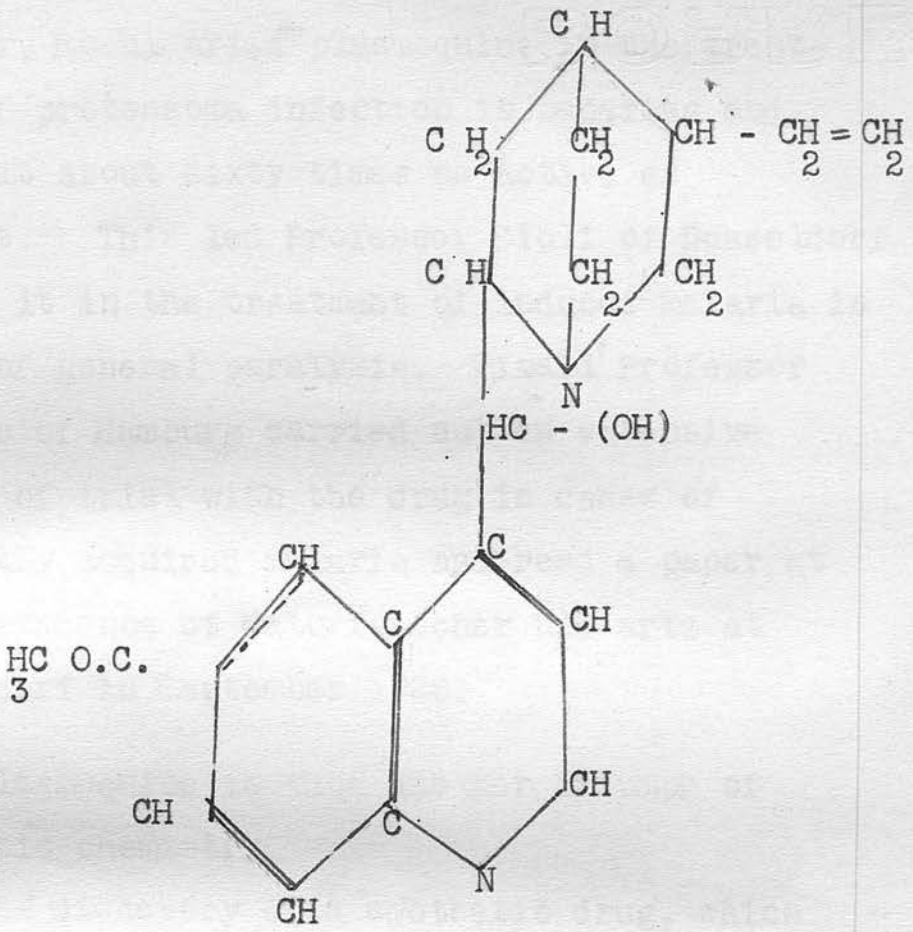
On the 25th: September, 1926, Reuter announced the discovery of Plasmoquine, a new cure for malaria.

Some confusion has been created by calling this compound variously "beprochin" later on "plasmochine" and now in English speaking countries "plasmoquine".

It is the outcome of team work by the chemico-therapeutic sections of the Eberfeld factory. Perkins in 1856, as the outcome of a study of the possibility of quinine synthesis, isolated the first coal tar dye, Mauvein. At that time it was supposed that the quinine molecule contained two chinolin rings, but in 1890 the workers at the Eberfeld factory proved that this view was wrong.

C H E M I S T R Y.

In 1907 Rabe described the chemical constitution of the quinine molecule as consisting of one chinoline ring connected by a secondary alcoholic group with the so called "loipon" portion; that is the piperidine ring with two intermediate CH radicals.



Horlien describes plasmoquine as a N-diethyl-amino isopentyl-8-amino-6- methoxyquinolin salt obtained by synthetic methods and not derivative of Quinine, thus differing from quinine principally by lack of the "loipon" portion.

Physical properties.

It is tasteless, light yellow, finely granular powder; fairly easily soluble in alcohol, soluble in water to 0.03 per cent at 20° C and rapidly converted into the hydrochloride by the hydrochloric acid of the stomach. The salt contains 10 per cent of plasmoquine base.

Dr. Roehl tried plasmoquine in the treatment of proteosoma infection in canaries and found it about sixty times as active as quinine. This led Professor Sioli of Dusseldorf to use it in the treatment of induced malaria in cases of general paralysis. Finall Professor Muhlens of Hamburg carried out an extensive series of trial with the drug in cases of naturally acquired malaria and read a paper at the conference of Naturforscher und artz at Düsseldorf in September 1926.

Plasmoquine is thus another triumph of synthetic chemistry.

The discovery of a synthetic drug, which has a marked destructive action on the malaria parasite, is a most important event and very careful tests are necessary to determine to what extent it can be used to replace the cinchona alkaloids which upto the present have proved the most useful drugs in the treatment of malaria. Apart from the possibility that it may prove more efficacious than the cinchona alkaloids, it forms a very important starting point from which to conduct further researches into synthetic drugs.

The results recorded have chiefly dealt with the effect of the drug on the clinical symptoms of the disease and upon the rate of disappearance of parasites from the peripheral

blood. No large series of cases seems to have been examined along the lines laid down by Sinton (1926 a) for testing the efficacy of a drug in producing a permanent cure of malaria, although in many instances the patients have been observed clinically for some time after the end of treatment.

Several papers have been published testifying to the value of plasmoquine as an anti-malarial drug of high potency more especially in benign tertian malaria and for the destruction of crescents in the peripheral blood. The advantages claimed for it are:-

(a) A very small dose, 1 - 1½ grains daily, is sufficient to control fever.

(b) Unlike quinine, it produces no nervous symptoms during its administration.

(c) It quickly removes the crescents from peripheral blood.

Sinton and others (1926 a) have laid down the following desiderata for an ideal treatment of malaria:-

(a) It should bring about a rapid cessation of the symptoms complained of by the patient and of any acute condition which is likely to be dangerous to his life.

(b) It should cause no harm to the patient, i.e. there should be an ample margin between the therapeutic and toxic doses to allow for individual idiocyncrasy.

(c) It should destroy all parasites in the body or at least bring about such a condition that the natural defences of the body can complete the destruction, thus preventing recurrence of symptoms with reinvasion of parasites into the peripheral blood at a later date.

(d) It should rapidly destroy all the sexual forms of the parasites in the peripheral blood and so prevent the patient becoming a "carrier" of the disease.

(e) It should, if possible, be effective against all different species of malaria parasite.

(f) It should be cheap --- not so important in the case of military population, as an expensive drug, if efficacious, proves far cheaper in the long run than numerous relapses of malaria.

Up to the present, attempts to find this ideal remedy have not been entirely successful, although in plasmoquine, especially in combination with quinine, one would appear to possess a drug which fulfils many of the above postulates. Unfortunately, as at present prepared, it offends against postulate "2" the therapeutic and toxic doses being in many cases dangerously near each other.

Benign tertian malaria would appear to be an ideal disease in which to test the efficacy of different lines of treatment.

The virulence and sympomatology of benign terian malaria remains fairly constant from year to year and from individual to individual and the causative organism is not in doubt. An excellent check on the immediate therapeutic effect of any drug is afforded by its action on pyrexia, or, better, on the parasite in the blood. Its final curative power may be accurately gauged by the relapse rate. Finally in quinine, we possess an excellent control treatment of proved value.

During the malaria epidemic which occurred in the months of July to November, 1929, in Lahore Cantonment a large number of cases were treated by Plasmoquine with quinine. At the same time more than 500 cases were treated with ordinary quinine mixture, of these only 300 cases were kept under observation as a control. Three Units, namely, 10/8th Punjab Regiment, 1/12th Frontier Force Regiment and 5th Probyns' Horse were selected for this plasmoquine treatment. All other Units were used as controls.

Procedure adopted in the treatment of each case:-

As soon as a case is received in this hospital, his blood is examined for malaria parasites, only those cases of malaria which showed malarial parasites in the blood being selected for the investigation of the drugs.

Each patient was kept in hospital for four days after his temperature became normal and not discharged until both thick and thin films were found negative to the parasites. The remaining treatment was carried out in unit lines. The result of observations are summarized under the following heads:-

1. Total number of cases treated by Plasmoquine and quinine and the mode of administration.

2. Amount of Plasmoquine given and the mode of administration.

3. Total number of cases treated by ~~Plasmoquine with quinine~~ ordinary quinine mixture, and the method of its administration.

4. Effect of combined Plasmoquine treatment and quinine treatment on

   (a) Temperature

   (b) Parasites

   (c) Spleen

5. Toxic effects of plasmoquine:-

   (a) dosage

   (b) time of appearance

   (c) If reappearing after a few days stoppage

   (d) Nature of toxic symptoms

6. Relapses after the combined plasmoquine treatment and ordinary quinine treatment -- ratio of

7. Conclusions

1. Total number of cases treated by Plasmoquine and quinine.

Malaria	B.T.	292
"	M.T.	6
	Total	298 cases

Of these, 25 stopped treatment before completion of the full courses owing to the transfer of the man to other Units or discharge from service.

Dosage.

The original dosage used, when the drug was first introduced, was in some instances as much as 0.12 to 0.20 grm daily and some workers (Hasselmann and Hasselmann-Kahlert, (1928); Krauss (1929), are apparently still using these or even larger doses, although makers and most other workers have reduced the maximum daily dose to 0.06 grm. The results recorded by many investigators indicate that equally good results can be obtained with smaller doses.

Some workers state that 0.06 grm daily is the maximum dosage which can be given without ill effects. Muhlens (1927); Schulemann and Memmi (1927); Fischer (1928); Brahmachari (1928), Cordes (1928) however who started with daily doses of 0.08 grm. reduced his dosage to 0.06 grm. and finally to 0.04 on account of ill effects and even then some of his patients developed severe toxic symptoms. Wallace (1928) found that a reduction of the dose from 0.06

to 0.04 grm daily when combined with quinine produced almost equally good results. Macphail (1928) thinks that 0.04 grm of the drug given with quinine can safely be administered under very ordinary supervision, while Fischer and Weise (1927) states that the maximum daily dose free from ill consequences is 0.03 grm.

Sinton, Smith and Pottinger (1929-30) states that combination of quinine with plasmoquine is clearly indicated. They deduce from results that when these two drugs are combined, a higher percentage of radical cures is obtained by smaller doses than when either of the drug is given separately in larger doses. They also assert that plasmoquine alone is inferior to quinine in the control of fever in benign tertian malaria, indeed some authorities recommended that the fever in malaria should first be cut short by quinine treatment before plasmoquine is started. In addition it has been asserted that Quinine tends to reduce the toxicity of the plasmoquine.

The facts that the combination of these two drugs produce better results in the radical cure of the disease, the disappearance of parasites from the peripheral blood and the cure of symptoms, suggest that each drug may be an adjuvant to the other and that it is possible that plasmoquine given in smaller non-toxic doses, although it may not kill all the parasites,

yet may so damage them that quinine can complete the destruction. This destruction may possibly be increased by larger doses of quinine or a larger duration of treatment.

The combination of plasmoquine and quinine, plasmoquine compound, issued by the makers contains the proportion of 0.01 grm. plasmoquine to 0.125 grm (2 grains) Quinine in each tablet. When these are given for treatment, if the daily dosage of plasmoquine is reduced to 0.06 grm, the dosage of quinine is only 0.75 grm (12 grains) Quinine while with 0.04 grm plasmoquine only 0.5 grm (8 grains) quinine are taken. Sinton and others (1930) consider the administration of quinine with plasmoquine in its present form of plasmoquine compound tablets unsuitable for general use for the following reasons:-

(a) If a mixed infection with P.vivax and P.falciparum is present, perhaps undetected, the amount of quinine with the smaller doses of plasmoquine is much too small for the treatment of the latter infection, or even to control malarial symptoms in some cases.

(b) The dose of quinine is too small to be optimum for the reduction of fever and the quick control of the clinical symptoms of the disease, which is what the paient expects,

(c) The use of quinine in solution gives a greater and more rapid absorption of the

drug than when it is given in solid form.

(d) The administration of tablets of ~~quinine~~ plasmoquine followed by quinine in solution is much cheaper than the use of tablets of plasmoquine compound.

(e) The issue of two strengths of plasmoquine compound tablets has led to confusion in dosage. When the drugs are given separately, such confusation is unlikely to arise.

Mode of administration.

The makers recommended the following course of treatment. The daily dose of 0.02 grm. plasmoquine 3-4-5 times, should not be given more than five days in succession. The after treatment is carried out in the same manner as that of quinine viz:

For 5 days plasmoquine
4 " rest
3 " plasmoquine
4 " rest
3 " plasmoquine
4 " rest
2 " plasmoquine
5 " rest
2 " plasmoquine
5 " rest
2 " plasmoquine
5 " rest

Precautionary measures.

When convulsive pains of the stomach or cyanosis of the lips are noticed after the administration of plasmoquine, it should immediately be stopped and only given again when symptoms have completely disappeared.

The recommended treatment therefore consisted of 17 days of treatment and 22 days of rest, a total of 39 days, provided more rest were not required on account of toxic manifestations.

The doses recommended for strong adults was 0.06 to 0.10 grm. daily.

Eichholtz (1927) as a result of animal experiment considered that quinine tended to lessen the toxic effects of plasmoquine. Manson-Bahr (1927b) and Schulemann and Memmi (1927) from their study of the use of drug on malarial patients, considered that the addition of quinine to Palsmoquine was useful in preventing the cynosis. Some times seen during treatment.

Muhlens (1926) reports a relapse of 31% after plasmoquine as compared with 59% after quinine.

Sinton and Bird (1928-1929) relapse rate 30%, but when duration of treatment was increased from 17 to 28 days, relapse rate fell from 36% to 23%. Relapse rate amongst the 86 cases treated with plasmoquine alone or combination with quinine was only 21% which is a

remarkably low rate when compared with that amongst the controls and with those of other workers on treatment with quinine (Stephens Etc. 1917-19; Acton Etc. 1921).

Intramuscular injection of plasmoquine.

I.G. Farbenindustrie Aktiengessellschaft, the manufacturers also supply 1% aqueous solution of plasmoquine in capsules for use by intramuscular injection. The makers recommend this method of treatment in cases of tertian and quartan malaria which run a severe course accompanied by mental torpor or coma, further in cases where intestinal disturbances preclude effective oral administration and in black water fever at all stages.

The instructions for injection are as follows:-

The aqueous solution is generally injected intra muscularly but the intravenous route can also be used. The outer and upper quadrant of the gluteal region is the most satisfactory site of injection. The injections are said to be well borne and do not give rise to disturbing sequelae or prolonged pain, nor do they cause infiltration. Subcutaneous injections should be avoided, as it is followed by burning sensation at the site of injection which lasts for some hours, although it does not cause inflammation.

The dosage recommended in tertian and quartan malaria is a daily injection of 3 to 6 cc of the solution (0.03 to 0.06 grm plasmoquine) for one

week, followed by a rest of 4 days, then the treatment is resumed in the same dosage for 3 days followed by a second interval of 4 days. This after-treatment of 3 days treatment and 4 days interval is to be continued for 5 weeks.

Duration of treatment.

The results obtained by Sinton and Bird (1928-29) indicate that a continuous course of treatment produces more permanent cures in chronic benign tertian malaria than does as interrupted treatment. If the results of series Plasmoquine I and Plasmoquine compound I, both interrupted treatments be compared with the results of their present research they go to show that with the continuous course of treatment almost equally good results in the production of a permanent cure can be obtained with a smaller daily and a smaller total dosage of plasmoquine as with the interrupted course and with less danger of toxaemia.

The use of a continuous course is preferable, for it is easier to get patients to carry out a treatment if they know it will finish within a definite short period than to get them to take a treatment of longer duration, and in which they are liable to forget the dates they should attend for treatment. If a treatment is to extend over a period of say 5 weeks, patients are much more liable to be lost sight of before the treatment

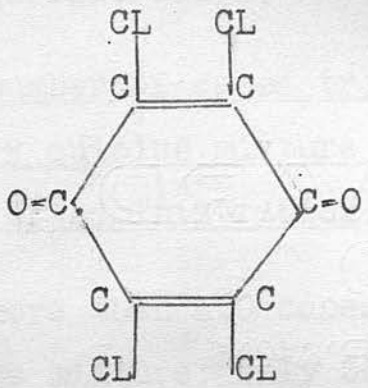
is completed, than when a course of three weeks or less is necessary. In the latter case one is in daily touch with the patients and can therefore see the progress of treatment and detect toxaemia at an early date. When the treatment is interrupted, the patient may not attend in the intervals and delayed toxic symptoms may develope during these periods.

The minimum daily treatment in relation to dosage has not been determined. Results of Sinton and others (1929-30) go to show that with daily dosage of 0.0 6 grm the maximum duration of treatment is chronic benign tertian malaria is three weeks, but the fact that many of the patients who received plasmoquine for shorter periods but who continued quinine did not relapse, suggest that probably with this daily dosage in combination with quinine a permanent cure would be obtained in a much shorter time, possibly even in 10 days, but that the chances of taxaemia with this dose are greater than with smaller doses.

Detection of Plasmoquine in urine.

Plasmoquine can be identified after medication in the urine by extracting the urine (200-300 c.c) after alkalization with ether. After adding 2% acetic acid the ether is evaporated. The residue is t aken up with glacial acetic acid and tetra-chlor-benzoquinone,

so called chlor-anil.



A bluish green or bluish color appears, according to the concentration.

Plasmoquine containing urine gives a precipitate with mercury iodide-potassium iodide, as does quinine but which persists in heating.

Plasmoquine, on the other hand, does not give the Thalleioquin reaction, which remains characteristic for quinine.

The diazo reaction is positive for plasmoquine in dilutions of 1 : 100,000.

2. Dosage administered and the mode of administration.

In every case the dose administered was .02 grm of Plasmoquine by mouth twice daily for a period of 21 days in the case of Benign tertian infection, and for a period of ten days in case of malignant tertian infection. Each dose was followed by a dose of 10 grm of quinine sulph. in citric acid (4% solution). Thus each benign tertian case received altogether 0.84 grm of Plasmoquine together with 420 grains of quinine for a full course and each Malignant tertian case received 0.4 grm of Plasmoquine with

200 grains of quinine sulph.

3. Total number of cases treated by ordinary quinine mixture and the method of administration.

Although more than 500 cases were treated by ordinary quinine mixture, only 300 cases were kept under observation as controls. The usual routine quinine mixture viz: quinine sulph. 8 grains, Acid Citric 20 grains, Tr Aurantii ½ drachm and aqua one ounce, was administered to each case three times a day. The urine of few patients was examined for quinine. Mayers reagent is added to urine containing alkaloid, a whitish apalescent cloud forms which, if due to alkaloid, disappears on heating and reappears on cooling. The density of the cloud is generally in proportion to the amount of alkaloid present in solution i.e. urine. Urine is first filtered: 10 cc is reserved as control and to another 10 cc fifteen drops of Mayers Reagent are added.

Mayers Reagent:-

Mercuric chloride	6.8 grms
Potassium iodide	24.9 "
Water	500 c.c.

The rate of absorption from the bowel and excretion in the urine of quinine, its derivatives or other alkaloids of cinchona, are both of interest in connection with treatment and checking of treatment in malaria. Quinine Hydrochloride

in powder form in doses of 5 grains given to three healthy men of different nationalities, commenced to be excreted in the urine within forty minutes and continued over a period of ten hours. (Green 1928).

To check the stated quantity of quinine in the mixture and to prevent any error in dispensing, the stock quinine solution was got frequently examined from the District Laboratory (Murree) for the actual strength of quinine present. Results were always satisfactory. It is of advantage to be able to check rapidly the stated quantity of quinine in a mixture for the prevention of fraud or error in hospitals or dispensaries. A simple method involving the dilution of the quinine mixture with water, the addition of Mayers Reagent and the use of Browns standard opacity tubes as described by Knowles is sufficiently accurate.

4. Comparative statement on the effects of Combined Plasmoquine and quinine treatment and quinine alone.

Memmi and Schulemann (1927) state that the fever in their cases disappeared one to two days with a daily dose of 0.06 grm plasmoquine. Vad and Mohile (1927) using the same daily dosage say that fever was generally controlled within 24 hours. Fletcher (1927) found with dosage that none of his 46 patients had a

temperature over 100 F after the third day and all were normal on the fourth. Macphail (1927) says the temperature of his patients became normal not later than the fourth day.

The average duration of fever vide Sinton and Eate (1926) amongst 51 patients treated with plasmoquine only was 0.8 days. Thirty eight or 74 per cent of them showed fever after the commencement of treatment, the average duration of fever in the latter cases being 1.1 days. The Maximum duration of fever in any case was 2½ days.

(A) Effects on temperature of the patients:-

From the figures below it will be seen that the average duration of temperature is 1.89 days in the case of persons treated by combined Plasmoquine and quinine method as compared with 2.85 days in those treated by quinine alone thus showing that the combined treatment brings down temperature quicker than ordinary quinine mixture.

Treatment adopted	No. of days after which temperature became normal.					
	1st day	2nd day	3rd day	4th day	5th day	Total
(a) Combined Plasmoquine and quinine treatment.	45	208	32	13	Nil	298
(b) Qunine treatment	38	96	132	23	11	300

The results are very similar to those of the other workers quoted above.

The consensus of opinion now is that in the case of malignant tertian malaria plasmoquine by itself has little effect on the febrile manifestations of the disease, (Sinton 1930) and that it should always be given in combination with quinine or at least one of the cinchona alkoloids when this infection is present.

(B) The effect of treatment on the duration of plasmodium vivax in the peripheral blood.

Many workers have confirmed the statement of the makers that treatment with plasmoquine causes a rapid disappearance of P. vivax from the peripheral blood. Some of the previous records may be summarised thus:-

Roehl (1926) parasites disappeared in 72 hours;

Schulemann and Memmi (1927) on 3rd to 4th days, rarely persisting till 6th;

Barmann and Smits (1927) in 3 to 80 hours average 36 hours. Pendlebury (1927) in 31 cases in only one lasted after 3rd day and none after 4th.

Manson-Bahr (1927) in 24 hours;

Vad and Mohile (1927) in 4 to 7 days.

Muhlens and Fischer (1927) in 3 to 5 days.

Sliwensky (1927a) in 2 to 7 days, and Djokic and Stambuk (1927) in 1 to 4 days. Fletcher (1927) gives an interesting table detailing the results of a dose of 0.06 grm plasmoquine daily to 46 cases. Of these 87 per cent showed parasites at the end of 24 hours, 39 per cent after 48 hours, 19.6 per cent after 72 hours, and 2 per cent after 96 hours but none later.

Roehl (1926) and Muhlens and Fischer (1927) found that the gametocytes persisted slightly longer than the schizonts and the latter authors record that doses of 0.06 - 0.15 grm daily caused a quicker disappearance than did doses 0.05 grm.

Effects of treatment on the duration of P. Falciparum in the peripheral blood.

Muhlens (1926) Muhlens and Fischer (1927) Schulemann and Memmi (1927) and Van den Braden and Henry (1927) found that plasmoquine had little effects on the sexual forms of P. falciparum. The disappearances of these forms following this treatment has been recorded, but how much to an action of the drug is doubtful. These findings may be summarised as follows:- Muhlens and Fischer (1927) say they may disappear in seven days; Fischer and Weise (1927) in 4 to 6 days; Manson Bahr (1927) inside a week; Vad and Mohile (1927) in 6-7 days; Cordes (1927) in 1 to 6 days, average 3½ days.

Fischer (1927) found that the treatment usually tended to cause a diminution in the number of the parasites but that they may disappear and reappear during treatment and may be present as long as 12 days at least in some cases. Baermann and Smits (1927) and Polychroniades (1927) had somewhat similar experiences and Muhlens (1927) also records such findings.

5. Action on crescents.

It is claimed that plasmoquine has a specific destructive action on crescents. The following are the times during which they have been recorded as persisting during treatment by different observers. Fischer and Weise (1927) about 10 days. Manson-Bahr (1927a, 1927b) 4 days. Sliwensky (1927) about 5 days, Schulemann and Memmi (1927) 6-8 days. Cherefeddin (1927) 5-6 days. Polychroniades (1927) in 103 cases 2 to 8 days. Vad and Mohile (1927) 7 to 10 days. Radojicic (1927) 4 to 7 days. Manoloff-Sliven (1927) 2 to 3 days and Pendlebury (1927) 3 to 7 days.

On the other hand, Cordes (1927) found them present from 1 to 8 days and states that he could not demonstrate that plasmoquine prevented there formation during treatment, Baermann and Smits (1927) and Macphail (1927) record the appearance of these forms during treatment.

All authorities are agreed that it has a very markedly destructive action on the crescentic gametocytes of P. falciparum, and that it constitutes a most important addition to the physicians armamentarium. Knowles and Das Gupta (1931) worked out minimum lethal dose of plasmoquine to crescents. Recent papers show that medical men are now using very much smaller doses than were first advocated by the manufacturers. Their present series here reported shows that even these doses may be unnecessarily large. Thus they have the following figures:-

Case No:	Total dose of plasmoquine that exterminated all crescents.	No: of days in which this dose was administered.
4	0.04 grm	24 hours
5	0.06 "	6 days
6	0.03 "	3 days
9	0.04 "	4 days
11	0.04 "	24 hours
12	0.05 "	5 days
13	0.18 "	3 days

They state crescents counts were very high in cases 6 and 13. In case 5 only one very degenerated crescent was seen after a total dosage of 0.04 grm in 4 days. In all cases the final proof or eradication of the infection was that a Bass culture taken with 5 c.c of the patients blood after the cessation of all treatment

remained sterile. They also state that the destructive action of plasmoquine or crescents can be studied under the miscroscope. Within 24 hours of commencing plasmoquine administration the crescents are seen to have become swollen and rounded, their outline becomes irregular; chromatin breaks up by Karyorrhexis, and the crescent stains very badly. Within 48 hours of commencing plasmoquine administration many of the crescents present in the films are almost unrecognizable as such.

Knowles and Das Gupta (1931) conclude that a total dose 0.06 grm of plasmoquine is sufficient to eradicate all crescents, even where the infestation is a very heavy one. The total dosage, they are of opinion, is probably best administered as a dose of 0.01 grm daily for six days. A total dosage of 0.04 grm spread over four days is often sufficient to eradicate all crescents.

Mixed Infection.

Fletcher W. 1927 states that twelve patients with mixed tertian malaria received a course of plasmoquine treatment. The benign tertian parasites quickly disappeared, but the sub-tertian rings persisted, and in seven instances the exhibition of quinine was necessary because parasites were still present after a week's treatment with plasmoquine. The results in sub-tertian malaria are disappointing, twenty-nine patients were given plasmoquine, but in twelve

cases it became necessary to give quinine. The drug was not altogether without effect upon the sub-tertian parasites. In almost every case they diminished during treatment and in some they disappeared altogether, but in others they increased again, although the treatment was continued and they became as numerous as they had been at the beginning.

Effect of Plasmoquine on Quartan Malaria.

Green (1928) reports the effects of plasmoquine on P. malariae as follows:-

Forty men comprising 20 Tamils, 16 Chines and 4 Sikhs who had quarten malaria were given 0.06 grm plasmoquine daily. The average weight among these cases was 48.5 kg and the average age 28.5 years. The control cases consisting of 7 Tamils and 3 Chines also with quartan malaria were given quinine gr xx daily. In this series the average weight was 46.0 kg and the average age was 30.2 years.

Among the cases treated with plasmoquine, the blood finally became negative for all forms of quartan parasite (including gametocytes) from the fourth to the ninth day of treatment with an average time of disappearance of six days.

Among the cases treated with quinine, in two of these quartan gametocytes were still present on the eleventh and sixteenth days of treatment. Among the remaining eight cases all quartan

parasites disappeared from the blood after periods of treatment varying from four to fourteen days, the average time of disappearance among the eight cases being ten days.

Plasmoquine thus appears to bring about a more rapid reduction in the number of quartan parasites and its gametocidal action appeared to be somewhat greater than that of quinine.

The effect on parasites on cases under treatment:-

Nature of infection	Effect of combined Plasmoquine and quinine treatment	Effect of ordinary quinine treatment
B.T.(Fresh) infection.	After 2 days no parasites were detected in the peripheral blood	Ditto
M.T.(Fresh) infection	100% of parasites disappeared after 2nd day.	93% of parasites disappeared after 2nd day and the remainder after third day.
B.T. (Relapse)	No gametocytes found in peripheral blood after 4 days.	In 86% of the case Gametocytes disappeared after 4th day and the remainder after 6th day.
M.T. (Relapse)	Out of 6 cases treated in 2, gametocytes disappeared after 5th day in two, after 8th day, and in 2 persisted even after the 10th day.	No effect on Crescents

N.B. Fresh infection:- When no gametocytes found in peripheral blood within 7 days of onset, no enlarged spleen, no previous history of malaria within 1 year.

It will be seen:-

(i) Combined Plasmoquine and quinine treatment has no advantage over quinine alone in destroying the parasites in benign tertian cases (Fresh infection).

(ii) Combined Plasmoquine and quinine treatment causes an earlier and more complete disappearance of the parasites in malignant terian cases than quinine (Fresh infection).

(iii) Plasmoquine is of greater value in eradicating gametocytes from blood in benign tertian cases than quinine treatment alone.

(iv) Plasmoquine is of value in the destruction of malarial crescents which ordinary quinine absolutely fails to touch but the results claimed for this method by other observers have not been confirmed in our cases, as gametocytes (M.T.) have been found as late as the 10th day of treatment.

(C) The effects of treatment on Splenic Enlargement.

Schulemann and Memmi (1927), Manson-Bahr (1927) and Brosius (1927) all lay emphasis on a very rapid decrease in the degree of splenic enlargement in patient treated with this drug, and Macphail (1927) records a similar reduction in children. Manson-Bahr (1927) thinks that the epigastric pain complained of by some patients may be due to the rapid decrease in size of this organ. Baermann and Smits (1927), Sliwensky (1927) and Polychroniades (1927) also report beneficial effects on enlarged spleen.

The degree of splenic enlargement.

The examinations were made in the recumbent position and the results recorded in finger-breadths below the costal margin. The size of the average spleen and of the average enlarged spleen were calculated by giving a value of 0 to non-palpable spleens, a value of 1 to spleens which were palpable but not enlarged below the costal margin, a value of 2 to spleens extending one finger-breadth below the costal margin and so on.

In case of Benign tertian (Fresh infection) with palpable spleen the effect of combined Plasmoquine and quinine treatment is practically the same as that of the ordinary quinine treatment, the spleen getting to normal size within 7-10 days after temperature has come down to normal.

With regard to the chronic cases with enlarged spleen (P2 or more) no marked effect has been noticed with either treatment. 46 cases were kept under observation for 1 month without marked improvement, but on being subsequently put on spleen mixture in 22 cases, spleen was completely reduced to normal size in 21 days while 24 cases showed improvement.

On account of the high cure rate produced by the drug one would not be surprised to get the very rapid reduction in size of the enlarged spleen reported by other workers. It has not, however, been my experience that the reduction in size of the enlarged spleen in benign tertian malaria is more marked or more rapid than after treatment with the quinine.

The routine spleen mixture is made up as follows:-

Quinine Sulph.	--------	gr 5
Ferri Sulph.	--------	gr 3
Mag Sulph.	--------	dr 1
Acid Sulph. Dil	--------	M 10
Aqua ad	--------	Oz 1

Black Water Fever.

It is also of interest that, although plasmoquine as compared with quinine has been vaunted as the treatment of choice in black water fever, yet several workers have recorded the occurrence of Haemoglobinura commencing during treatment with this drug.

5. - Toxic effects of Palmoquine.

A considerable volume of literature has appeared during the past years dealing with treatment by plasmoquine, and whilst all appear in agreement concerning its valuable therapeutic action, there is fortunately a corresponding unanimity of opinion regarding the toxic effects produced in a certain percentage of cases; at least two deaths directly attributable to its use have been recorded recently, and probably other similar fatalities have occurred which have gone unrecorded.

The chief toxic effects reported as attributable to plasmoquine have been gastric pain and distress, ashy-grey cyanosis of the lips, gums and finger nails, headaches, dizziness and in a few more serious cases exacerbations of above symptoms accompanied by vomitting haemoglobinuria, Jaundice, and haemorrhagic nephritis. The cyanosis has been shown by spectroscopic tests of the blood to be due to true methaemoglobinaemia.

Eichholtz (1927) and le Heux and Wyngaarden (1927) have tested the toxicity of this drug on animals and found that in toxic doses it gives rise to cardiac irregularity, slow and irregular action of the heart marked cynosis, dyspnoea and in some cases convulsions. The recovery was usually rapid, if a fatal result

did not ensue. The effects varied in different animals and in cats the cynosis was accompanied by Methaemoglobinaemia.

Discussing toxaemia, Sinton and Bird (1928-29) report that it was seen under the conditions of their experiments that in the interrupted series toxic symptoms were more common during the first week than the subsequent ones, but that no such differences could be established in the continuous treatment. The statements of some workers would seem to imply that after the first week of treatment a certain degree of tolerance to the drug was acquired, but this has not been their experience. One would expect in the interrupted courses given by other workers that fewer toxic symptoms would be observed after the first week, because rests were given and the duration of each course of treatment was decreased, while the length of the rests was increased. The chances of the drug accumulating in the body would under these conditions be diminished after the first week. In continuous treatment there would be no such diminution in the chances and this would account for the symptoms of taxaemia being more evenly scattered over the whole course of treatment. It seems to them, therefore, that there was no evidence to show that any marked degree of tolerance to the drug was acquired and that the supposed tolerance was simply due to a diminution

in the amount of the drug given and increasee in the number and duration of the rests.

Le Heux and Van Wyngaarden (1927) found that some animals developed toxic symptoms much more readily than others when given equal doses per kilogram of body weight and thought that in the former cases this was due to a much less rapid destruction of the drug inside the body, resulting in an accumulation and thus toxic symptoms. Manson Bahr (1927b) found that toxic symptoms might occur after comparatively small doses in susceptible patients and Fischer and Weise (1927) could only explain some of their results on the assumption that there was a personnel idiosyncrasy to the drug in some instances. Sinton and Bird (1928-29) confirm the idea that some patients are more susceptible than others.

Some observers consider that the occurrence of cynosis and abdominal pains are of little importance while others think them to be danger signals rather than actual evidence of toxiaemia.

In consideration of the findings of different workers, these symptoms are undoubtedly due to toxic effects and should be taken as a warning to diminish the dosage of plasmoquine or to stop temporarily at least, the administration of the drug. Although the addition of quinine to plasmoquine seems to have some effect in diminishing the toxicity of the drug, it does not

appear to have the very marked action which some would lead one to believe.

Signs of Plasmoquine Taxaemia.

The commonest indications of commencing taxeamia with plasmoquine are cynosis, or slight gastro-intestinal disturbances or the two conditions together. The rapidity with which these conditions disappear without leaving any apparent ill effects in the majority of instances when treatment is stopped make them seem usually of trivial import, so some workers only cease treatment when more severe symptoms have arisen. Schiasi and Merighi (1928) state that the occurrence of even these slight toxic symptoms cannot be disregarded as evidence of over dosage, and think as remarked by Cordes (1928) that the onset of such symptoms indicate that toxaemia is already fully established without any noticeable premonitary sign or symptoms. Cordes (1928), Roskoff and Seno (1928), Sinton (1929-30) record such cases. In these patients there is probably some cumulative action of the drug for the signs of toxaemia only develope 2-3 days after the cessation of treatment and similar cases have been noted by Macphail (1928) and M'Hutchinson and Duff (1928). If treatment was continued in such cases, severe toxaemia might be expected to occur.

Cardiac disturbances of various kinds have been reported, although Muhlens (1927) states he

found none in his Cyanotic cases. Schulemann and Memmi (1927) reported arrhythmia, but as similar cardiac disturbances have been recorded in malaria per se, they were uncertain as to whether these could be attributed to plasmoquine. Tachycardia was noted by Van den Braden and Henry (1927) and also by Morishita and Namikawa (1928). Bradycardia is considered by M'Hutchinson and Duff (1928) as an additional sign of toxaemia. This condition has also been reported by Baermann and Smits (1929), and Sinton and Bird (1928-29) noted in one of their toxic cases. It would, therefore, appear that any abnormal disturbances of the heart, greater than can be accounted for by the malarious condition of the patient, should always be considered as an indication for caution in treatment. Severe blood destruction and leucocytosis have been observed in some severe cases of toxaemia, and Muhlens and Weise (1927) in their experiments found that Methaemoglobinaemia was more likely to occur in anaemic cases.

All are agreed that immediate cessation of treatment is necessary when toxic symptoms occur and that treatment with plasmoquine should not be recommended until some days after the symptoms have disappeared.

Records by previous observers.

Milder manifestations. Muhlens (1926) and Memmi and Schulemann (1927) have suggested that

the symptoms were not due to an intoxication with the drug, but to vaso-motor disturbances in nervous patients. Unofrtunately, in the light of more recent work this theory cannot be accepted.

Eichholtz (1927) and Le Heux and Van Wyngaarden (1927) have tested the toxicity of this drug on animals and found that in toxic doses it gives rise to cardiac irregularity , slow and irregular action of the heart, marked cynosis, dyspnoea and in some cases convulsions. The recoverywas usually rapid, if a fatal result did not ensue. The effects varied in different animals and in cats the cynosis was accompanied by mathaemoglobinaemia.

Sioli (1927) and Manson-Bahr (1927) report that, in those of their patients who had marked cynosis, methaemoglobinaemia was also present.

Fischer and Weise (1927) made an extensive investigation into the cause of the cynosis during plasmoquine treatment. They found that methaemoglobinaemia could always be detected in the blood of 25 out of 26 patients a few days after the commencement of treatment, while treatment was continued and for some time afterwards. They could discover no relationship between the dosage of plasmoquine and the amount of methaemoglobin ××××× in the blood, but a marked one between the dosage and the time of appearance and duration of this condition. As a rule, the

intensity and duration increased with prolonged administration. The intensity with the same dosage usually varied inversely with the number of red blood cells, so that the greater the degree of anaemia the greater the amount of methaemoglobinaemia.

The condition remained within certain limits with the ordinary doses and they think it is of no importance. They were unable to find any sign of severe general disturbance related to any particular organ. Some of their findings showed such striking variations that they could only explain these as personal idiosyncrasies.

These workers concluded that it was the alkylamino group which was responsible for the causation of the methaemoglobinaemia, as in the case of acetanilid and phenacetin poisonings, but that with plasmoquine one did not get the unpleasant symptoms found with these drugs.

Sioli (1927) reports a case of methaemoglobinaemia and seven case where the daily dose of 0.01 grm was exceeded in which cynosis was present accompanied in two instances by jaundice. This worker and Muhlens (1927) say that daily doses larger than this amount give rise to toxic manifestations. Manson-Bahr (1927a, 1927b) also notes that with doses of 0.06 grm daily, cyanosis may occur which is undoubtedly toxic and due to methaemoglobinaemia.

Polychroniades (1927) records cyanosis in 8 out of 46 patients with doses of 0.06 grm. daily.

Muhlens and Fischer (1927) find cyanosis rare with daily doses of 0.04 grm; but say they occur with doses greater than 0.10 grm daily. Schulemann and Memmi also record cyanosis, which they consider probably due to methaemoglobinaemia and thought that it was a danger signal rather than actual evidence of poisoning. Several other workers have also recorded cyanosis.

Local epigastric tenderness and loss of appetite have been reported about the 4th or 5th day of treatment, but the makers state that these symptoms disappeared on withdrawing plasmoquine and did not as a rule recur when treatment was recommended, so their presence did not constitute a definite contra-indication to the drug.

Schulemann and Memmi (1927) state that abdominal pains may occur when large doses are given on empty stomach, but seldom if a dose of 0.06 grm daily is not exceeded. Polychroniades (1927) found that colic occurred about the 5th or 6th day of treatment and rarely after 13th. Amongst 46 patients treated with plasmoquine he records colic in eight, while with plasmoquine compound 16 out of 142 developed this complaint between the 3rd and 6th days and five others between the 7th and 12th days, a total of 14.7 per cent. He says that trivial incidents like

cyanosis and colic were present in 23 per cent of his patients.

Manson-Bahr (1927) noted abdominal pains which he thought might be due to rapid contraction of the spleen. Manoloff-Sliven (1927) says that sometimes abdominal pains and diarrhoea occur and Vad and Mohile (1927) record pains in a few cases but state they did not occur if the drug was given after meals.

Although cardiac symptoms are one of the signs of toxic action in animals, yet they seem to be rare or slight in the human subject. Fischer and Weise (1927) in their investigation of the toxicity of the drug found no such symptoms. Polychrochroniades (1927) found no change in blood pressure during treatment. Van den Braden and Henry (1927), however, record a case of tachycardia and Baermann and Smits (1927) found a slowing of the pulse after 5 to 7 days of treatment.

Albuminuria has been recorded, especially in those cases in which cyanosis was severe and methaemoglobinuria was present.

Serious complications. -

Cordes (1927) records a case of malignant tertian malaria with jaundice which received 0.08 grm Plasmoquine and 1.9 grm quinine daily, on the 5th day the jaundice increased, vomiting occurred and somnolence was marked symptom.

There was a drop of 35 per cent in the haemoglobin of the blood. This patient died on post mortem a commencing necrosis of the liver cells was found. Similar symptoms but in a milder degree were encountered in three other patients.

Baermann and Smits (1927) gave a patient 0.08 grm plasmoquine daily and on the 3rd day he developed cyanosis with a temperature of 102.5 F and became unconscious. The urine contained albumin and the patient died next day. On post mortem some necrosis of the liver was found.

Vad and Mohile (1927) report that one of their cases died of pneumonia on the 5th day of treatment and Colonel S. P. James in the discussion at the 7th Congress of the Far Eastern Association of Tropical medicine mentioned that he knew of another death following plasmoquine treatment.

Eiselberg (1927) records that he saw a patient who had received a total of 0.2 grm. plasmoquine during three days and then complained of much epigastric pain. After taking the last pill he vomited and lost consciousness. On the next day he was still vomiting, his liver was tender, his urine contained much albumin and there was a great fall in the number of red blood cells. This case recovered.

A patient treated by Sioli (1927) with 0.06 grm daily complained on the 8th day of hepatic

pain and weakness. He was cyanosed, he had methaemoglobinaemia and collapsed when he attempted to leave bed. With a daily dosage of 0.06 grm plasmoquine, two of the cases recorded by Fletcher (1927) became alarmingly ill with a rise of temperature, cyanosis, vomiting and collapse.

Manson-Bahr (1927a, 1927b) records three cases with toxic symptoms. One case had received a total of 0.40 grm of plasmoquine in daily doses of 0.12 grm when he developed cyanosis with clammy sweats and abdominal pains. There are methaemoglobinuria and albuminuria. During the attack there was a mild blackwater fever which ran a favourable course. The second case had pains in the abdomen and back, nausea and cyanosis after 0.08 grm daily for 3 days. The third case had slight cyanosis, but marked abdominal pain after a dosage similar to that in the first case.

D E A T H S.

Cordes (1928) records deaths certainly due to this drug. Hulshoff (1928) had 3 deaths during treatment, one of which was probably due to plasmoquine. Brosius (1928) records that five of his cases died during treatment. The post mortem appearances found in most of these suggest that death was due to causes other than plasmoquine poisoning. Yet it seems possible that the fatal issue may have to some extent been accelerated by the drug.

The POST MORTEM findings in fatal cases of plasmoquine poisoning indicate that the brunt of the toxaemia seems to be borne by the liver, and Hulshoff (1928) points out that any indication of liver insufficiency should be considered as a contra-indication to the use of the drug. Muhlens (1927) advises that for the present plasmoquine should not be administered to patients with damaged livers, definite nephritis and cardiach leisons.

Microscope examination on fatal case.

Mallory (1928) reports on one death that occurred in Preston, and quoted in full on account of its importance.

"The patient was a male Negro, 35 years of age. He was admitted suffering from a severe attack of aestivo-autumnal malaria and was treated with the new drug, plasmoquine compound. On the 4th day of his treatment, after the fever had disappeared and the blood film was negative for malarial parasites, he developed a profound anaemia, leucocytosis, jaundice, Nausea, vomiting and somnolence. The urine was negative for haemoglobinuria. He died within 48 hours after the onset of this sudden attack. The toxic influence of plasmoquine compound was suspected to have played an important role in the cause of death.

Miscroscopic

Microscopic.

Heart negative.

Spleen-numerous lymphocytes and plasma cells in the pulp; many endothelial leucocytes in the blood sinuses containing red blood corpuscles, often in great numbers (10 to 20 and more). Malarial pigment occurred occasionally in the red blood corpuscles both free and in phagocytes.

Liver Endothelial cells lining sinusoids were prominent, occasionally phogocytic and some contained pigment. Some of the liver cells in the centres of the lobules contained vacuoles in which were dots and occasionally threads of fibrin (hydropic degeneration). Rarely a liver cell was necrotic and was being invaded by endothlial leucocytes. There was slight lymphatic infiltration of periportal connective tissue.

Kidney. Moderate ordema of the tubules.

Cerebrum. Negative.

Microscopic diagnosis.

Malarial infection of the spleen.

Marked phagocytosis of red blood corpuscles in the spleen.

Early stage of central necrosis of the liver.

Remarks.

No bone narrow was included with the other tissues. The anaemia may have been due to

destruction of red blood corpuscles by the malarial infection. The phagocytosis in the spleen would seem to indicate this. The beginning necrosis of liver cells is probably due to the toxic action of the plasmoquine, but it is not nearly so active as chloroform or carbon-tetrachloride. Possibly plasmoquine has a destructive effect on the red blood corpuscles.

Susceptibility to Plasmoquine.

Drugs such as acetanilid and phenacetin, which also contain an alkyl-amino group, have been responsible for a Methaemoglobinaemia similar to that in plasmoquine poisoning and idiosyncrasies to these drugs have frequently been noted.

Fischer and Weise (1927) explain the occurrence of cyanosis during plasmoquine treatment as possibly being dependent on some personal idiosyncrasy of the patient. Brahmchari (1928), Namikawa (1928) and several other workers have also taken this view. McPhail (1928) thinks that the complete absence of symptoms in some patients while others receiving the same dosage of the drug develope severe toxaemia suggests such an idiosyncrasy, and Cordes (1928) from his experience of the sudden development of severe toxic manifestations without previous warning, holds the same opinion, Krauss (1929) recommends that on account of the very great variation in susceptibility plasmoquine prescriptions should

be bearing the legend in large type or red ink. "Nil repetantur".

The question now arises as to the possible explanation of the incidence of such an idiosyncrasy. Menk (1928) states that it has been the experience in Cuba that Haitian Negroes cannot tolerate as large doses of plasmoquine as other races. Hasselmann and Hasselmann Kahlert (1928) do not believe that the tolerance of the Filipinos to this drug is any greater than in the Europeans. Does a race susceptibility exist?

Sinton and others (1929-30) observe that the number of severe cases of toxaemia seen during their researches seemed to be higher than those recorded in many instances by other workers using the same dosage. The population in their researches was an usually healthy one, and except for occasional relapses of chronic malaria the majority were apparently quite fit in the intervals, so the toxaemia could not be accounted for by any evident physical weakness. Their patients were all of Northern Europe origin, as were also the severe cases of toxaemia reported by Wade (1929), Ashley (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 grm given by some workers to the inhabitants of Southern Europe and of the tropics with few or no recorded severe

ill effects, while severe toxaemia and even death has been recorded in other places after doses as low as 0.06 grm daily, one is tempted to think that such a racial suspectibility may exist and that possibly it may occur more commonly in persons of Northern Europe origin among others.

Apart from any factor of individual or racial idiosyncrasy to the drug, the susceptibility of some persons may possibly be explained as due to some temporary organic disturbance of the system which was not apparent before treatment commenced. Such as liver insufficiency, lowering of the alkali reserve, etc. The fact that most of the fatal cases show marked degeneration of the liver post mortem, and that many of the most severe cases of toxaemia have occurred in patients suffering from malignant tertian malaria, in which disease the effects on the system are more marked than in either quartan or benign tertian fevers, would tend to support such a view. On the other hand, Sinton and Bird (1928-29) were not able to obtain any certain evidence that the administration of glucose and alkali as prophylactic measures against damage to the liver and a lowering of alkali reserve, caused any decrease in the incidence of toxic symptoms. Brahmchari (1928), however, recommend alkali treatment to ease the abdominal pains and Manson-Bahr (1928) uses glucose for the treatment of toxic manifestations.

One must also think of the possibility of a deterioration of the drug under certain conditions as a cause of the greater incidence of toxaemia in certain series of patients. Squires (1928) reports that a supply of the drug received by him seemed to give to a greater number of toxic cases than the previous supply used. Sinton and others (1929-30) report that in their record of the toxic symptoms observed in 1929-30 researches, a supply obtained by them was of about the same time as that received by Squires, seemed to have similar toxic effect. Although a sample from their stock when submitted to the makers was reported to show no increased toxicity, still they think the possibility of increased toxicity should be borne in mind, especially as it is well established that samples of some other synthetic drugs, such as salvarsan, may show an increased toxicity under certain conditions.

The view that many complaints of toxic symptoms are due to auto-suggestion, resulting from the fact that other patients in the same ward or party have complained of such symptoms, seems a possible explanation in some instances, when one considers that mental depression may be one of the features of the toxaemia. The observations that many of the patients who complain of such slight symptoms may later

develop several days after the cessation of treatment is against the view that auto-suggestion is a very common cause of such complaints.

Some observers state that abdominal symptoms are likely to occur if plasmoquine is given on an empty stomach, or if not followed by a drink of water. Sinton and others (1929-30) gave all their cases fluid to wash down the tablets and the morning doses were given after breakfast.

The toxic symptoms noticed were

1. Gastralgia
2. Abdominal pain
3. Vomiting
4. Diarrhoea
5. Dysenteric Symptoms
6. Cyanosis.
7. Paleness of the skin and general discomfort.

Toxic symptoms	Day of appearance													Remarks
	1	2	3	4	5	6	7	8	9	10	11	12	Total	
Gastralgia and Abdominal pain and discomfort	7	14	1	3	-	-	-	1	-	-	-	-	26	Treatment stopped for 2 days and subsequently renewed.
Cyanosis	-	2	-	1	-	-	-	-	-	-	-	-	3	Treatment stopped completely.
Diarrhoea and Dysenteric symptoms	-	-	-	-	-	-	-	-	-	1	-	1	2	" " "
Giddiness and General discomfort with paleness on the skin.	-	-	-	-	-	1	-	-	-	-	-	-	1	" " "
T o t a l.	7	16	1	4	-	1	-	1	-	1	-	1	32	

Of the 26 cases showing abdominal pain and discomfort, 2 had subsequent recurrence of symptoms, one on the 8th and the 2nd on the 17th day of renewal of treatment even after the treatment had been stopped for 2 days after the first appearance of the symptoms.

It was noticed that those who complained of the most severe effects produced by plasmoquine were not heavy smokers. Some patients, who developed toxic symptoms, were Sikh sepoys with whom smoking is forbidden by religion. It is interesting in view of the fact that Sinton and others (1929-30) noticed that plasmoquine produced severe toxic symptoms on heavy smokers.

The cause of the epigastric pain is most probably gastro-enteritis, because in few cases it was accompanied by vomiting and diarrohoea. The pain is usually described as heavy and constant, situated horizontally right across the mid-epigastrium. It has been much the most common toxic symptom complained of and has invariably ceased after a few days withdrawal of the drug. Readministration of plasmoquine after cessation of the pain has in all but a few cases been unattended by recurrence of symptoms. This is opposed to the theory that the drug has any marked cumulative action and suggests that most patients are able, after a few days, to take the drug without toxic effects. It will appear from

the above statement that toxic symptoms appeared on an average after dosage of 0.117 grm and in the majority of the cases these symptoms appeared 48 hours after the administration of plasmoquin. We observed that after 6-9 days treatment. Out of 298 cases placed under plasmoquine treatment 32 showed toxic symptoms i.e. 10.7%

Relapse. - Most observers have found that while plasmoquine produced very beneficial effects in benign tertian malaria, its action is much less marked in the malignant type of fever.

Sliwensky (1927) reports 50% of relapse, after plasmoquine treatment (22 patients) and 30.4% after the compound (125 patients).

Sinton and Bird (1928-29) report a total of 14 cases suffering from malignant tertian malaria treated with plasmoquine alone or in combination with quinine 10 or 71% relapses due to P. falciparum. Amongst seven control cases treated with quinine and Alkali the rate was 14%.

The results in the plasmoquine compound series observed by Sinton (1926) were better than those in the plasmoquine series but the number of cases is too few to generalise upon and in neither cases do they compare favourably with the quinine and Alkali treatment.

Statement of relapses after

(i) Combined plasmoquine and quinine treatment.

(ii) Quinine treatment.

(i) Of 267 cases of B.T. kept under observation for 5 months, 31, i.e. 11.6% relapsed. Out of these 27 relapsed only once, 3 twice and one thrice. 4 cases acquired fresh B.T. infection while under treatment, i.e. 1.5%.

(ii) Of 452 cases kept under observation for six months under ordinary quinine treatment, 81, i.e. 17.6% showed relapse. Among these 64 cases relapsed only once, 12 twice, 3 thrice, and 1 four times. Among these cases 11 were re-admitted for fresh infection by M.T. parasites while under treatment, i.e. 2.4%.

Note. 1

Four cases, which acquired fresh infection, while under combined plasmoquine and quinine treatment cannot be attributed to the provocative action of plasmoquinine on double infection as 11 cases of fresh infection also occurred among the series treated by quinine. This may throw some light on the value of plasmoquine as a provocative agent but further experience is necessary before any conclusion can be arrived at.

The use of plasmoquine outside hospital.

Practice.

There are apparently two diametrically opposite schools of opinion on the question as

to whether plasmoquine should be used under conditions which are not under strict medical control.

Nutter (1927) Schulemann and Memmi (1927), Krauss (1928), Barber (1929) etc. state that there can be no objection to issuing plasmoquine compound for treatment outside hospital. While Sinton and Bird (1928), Oliver and Hulshoff (1927), Brosius (1928), Phelps (1928) etc. believe that the drug is still in the experimental stage and should only be under strict medical supervision.

7. Conclusions.-

(i) The combined plasmoquine and quinine treatment is definitely superior to simple quinine treatment in the following respects:-

(a) In producing a definite reduction in the duration of the temperature in the individual.

(b) In the destruction of gametocytes especially in the case of M.T. infection where it has a definite effect but not to the extent claimed by the manufacturers.

(ii) No appreciable advantage can be claimed by this treatment in the reduction of splenic enlargement.

(iii) Toxic symptoms were manifested in 10.7% of cases treated and appeared after the administration of an average dose of 0.12 gram approximately.

The majority of these cases showed these symptoms after 48 hours of administration.

(iv) Toxic symptoms noted are Gastralgia, abdominal pain, vomiting, diarrhoea, dysenteric symptoms, cyanosis and paleness of the skin and general discomfort.

(v) Cyanosis or methaemoglobinaemia was not noticed in these cases as by other observers, as all the cases which were treated have dark skins, and lesser degrees of cyanosis cannot be detected without spectroscopic blood examinations which were not carried out.

(vi) The toxic effects of plasmoquine require careful watching and medical supervision is at all times indispensable.

Dosage recommended 0.02 gram, twice a day for twenty-one days seems to be a safe one.

(vii) The provocative effect of plasmoquine in case of double infection has not been proved.

(viii) Prophylactic use of plasmoquine as a routine antimalarial measure is not advisable.

(ix) Considering all these points it is not desirable to recommend this method of treatment as a universal routine measure, but with proper safeguard this treatment may be adopted in B.T. infection and in the cases of crescents.

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