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MODERN THERAPY OF BENIGN TERTIAN MALARIA

BY

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Not the least beneficial result of prosecuting a war widespread throughout highly malarious regions after being deprived of our main sources of quinine has been the impetus given to the search for the ideal antimalarial drug. A vast army maintained in the field is an excellent source of clinical material to the research worker, and has been responsible for the determination of the properties of many drugs which would have taken twice or thrice as many years of peace to elucidate partially.

At the onset of the recent war, mepacrine had the reputation of being a poor prophylactic agent and one which could not be taken in adequate dosage by the majority of persons owing to its toxic properties. This reputation had been built up during 10 years of investigation since its synthesis in 1930. Within about 12 months of its adoption in place of quinine it was established as being slightly toxic in a very small proportion of cases treated, and to be a very satisfactory suppressive agent.

At the same time it was recognized that mepacrine had many disadvantages from both the prophylactic and the therapeutic aspects. Urgent and enthusiastic research then developed with the object of discovering a drug having all the properties of an ideal antimalarial substance—namely, one which, given in infrequent and non-toxic but regular doses, would prevent the establishment of any form of plasmodial infection; and which also, when given in therapeutic doses over a short period, would produce both rapid clinical and radical cure without any unpleasant side-effects. Such an ideal has not yet been achieved, but many new and invaluable drugs have been synthesized and explored, and these have largely altered the outlook on the treatment of malaria.

In particular, the brilliant researches of Curd, Davey, and Rose¹ resulted in the synthesis of paludrine, a new antimalarial drug with exceptional properties, particularly in its action on the pre-erythrocytic stages of the malaria parasite. In America a vast co-ordinated programme of research was undertaken¹⁵ and over 14,000 synthetic drugs have been exhaustively tested for their antimalarial properties. Of the large number which were shown to have both suppressive and curative actions, two have emerged as being of great value, and have been given the non-proprietary names of chloroquine⁷ and pentaquin.⁸

The object of this paper is to review the stage at which the treatment of benign tertian (B.T.) malaria has arrived. Malignant tertian (subtertian) malaria presents difficulty only in its diagnosis, since the establishment of *Plasmodium falciparum* in the human host can be almost entirely prevented by regular dosage with almost any antimalarial drug. Its eradication is likewise easily procured if diagnosis is made early enough and there is no cerebral involvement. First relapses are very unusual after any adequate treatment, and second relapses even less common. The

treatment of benign tertian malaria, on the other hand, is concerned almost entirely with the prevention of relapses.

The following drugs will be considered: quinine (Q), a complex quinidine compound; mepacrine (M), an acridine dye; paludrine (X), a biguanide derivative; chloroquine (C), a 4-aminoquinoline derivative; pamaquin (P), an 8-aminoquinoline compound; pentaquin (SN), an 8-aminoquinoline derivative. Table I lists a series of results from the administration of a wide range of treatments for the cure of B.T. malaria.

It is emphasized that the expected relapse rates following various forms of treatment quoted elsewhere in this paper are no more than approximate estimations. Under certain circumstances the actual relapse rate may differ widely from the expected relapse rate. Sapero¹⁴ has emphasized that in interpreting the often conflicting results even of similar therapeutic regimes the percentages of medical cure obtained depend on three factors: (1) the percentage efficacy of the drugs used; (2) the percentage efficacy of the immune response; and (3) the inherent characteristics of the causative species or strain.

In endeavouring to estimate the value of the first factor, the second and third must always be taken into account. The second factor is usually difficult to assess, but the third is based on information that is more readily available. It is the difference in geographical strains which is most likely to be responsible for apparent discrepancies in the success of various therapeutic regimes. The Chesson strain, for example, used by American research workers¹⁵ originated in the South-west Pacific and is notorious for producing rapid and often-occurring relapses after antimalarial therapy. Other strains commonly met with produce relapses less frequently and at longer intervals. It is therefore also important to take into account the duration of the follow-up period when comparing relapse rates.

Treatment Involving Use of Only One Drug

Quinine

The relapse rate following treatment with quinine alone in an adequate regime averages well over 50%. A regime is considered inadequate if the daily dosage totals less than 30 gr. (2 g.) and is given for less than 10 days. In a series of cases (Q) treated by Most *et al.*¹³ the relapse rate after a 14-days course was nearly 90%. This is probably exceptionally high. When, however, as so often happens, treatment is self-administered and lasts only three to four days the relapse rate is likely to be over 90%.

When the object of treatment is the production of radical cure unaided quinine therapy is of very little value. Considering that there are more valuable methods of treatment which can produce radical cure in 8 or 9 out of every 10 cases treated, it is questionable whether there is any profit in persevering with treatment for the whole of 10 days

TABLE I.—*Comparative Relapse Rates*

Course	Reference	Geographical Strain	Dosage	Days of Treatment	Days of Follow-up	Cases Treated	Cases Relapsed	Relapse Rate %
Q	13	South Pacific	Quinine 10 gr. (0·65 g.) t.d.s.	14	120	75	67	89·4
M1a	2	Not stated	Mepacrine 0·2 g. 6-hourly for 2 days followed by mepacrine 0·1 g. t.d.s. for 10 days	12	120	650	221	34·0
M1b	5, 10	Mediterranean	Mepacrine 0·2 g. 6-hourly for 2 days followed by mepacrine 0·1 g. t.d.s. for 5 days	12	180	86	23	26·7
M2	5, 10	Mediterranean	Mepacrine 0·2 g. 6-hourly for 2 days followed by mepacrine 0·1 g. t.d.s. for 5 days	7	180	31	11	35·5
M3a	13	South Pacific	Mepacrine 2·8 g. in 7 days	7	120	69	57	84·0
M3b	5, 10	Mediterranean	Mepacrine 2·4 g. in 7 days	7	180	29	8	27·6
X1a	6	India/Burma	Paludrine 250 mg. b.d.	10	180	107	47	43·9
X1b	10	India/Burma	" " 25 mg. b.d.	10	180	24	16	66·6
X2	6	India/Burma	" " 25 mg. b.d.	10	180	108	46	42·6
C	1	*Chesson	Chloroquine 2 g. in 14 days	14	15- 89	21	14	66·6
SNa	1	*Chesson	Pentaquin 60 mg. daily	14	423	5	3	60·0
SNb	11	India/Burma	" " " " " " " " " " " "	10	180	25	3	12·0
Pa	1	*Chesson	Pamaquin 30 mg. daily	14	—	5	5	100·0
Pb	10	India/Burma	" " " " " " " " " " " "	10	180	29	8	27·6
QP _a	10	India/Burma	Quinine 10 gr. + pamaquin 10 mg. t.d.s.	10	180	168	35	20·8
QP _b	6	India/Burma	" " " " " " " " " " " "	10	180	108	17	15·6
QP _c	2	Not stated	" " " " " " " " " " " "	10	150	584	60	10·3
QP _d	5, 10	Mediterranean	" " " " " " " " " " " "	10	180	94	11	11·7
QP _e	13	South Pacific	" " " " " " " " " " " "	14	120	72	8	11·1
QP _f	4	South Pacific	" " " " " " " " " " " "	10	30-180	223	31	13·5
QP _g	1	*Chesson	" " " " " " " " " " " "	14	54-355	10	5	50·0
PX1	12	India/Burma	Paludrine 250 mg. + pamaquin 10 mg. t.d.s.	10	180	179	37	20·6
PX2	4	South Pacific	Paludrine 100 mg. + pamaquin 10 mg. t.d.s.	10	30-180	232	31	13·4
QMP	5, 10	Mediterranean	Quinine 10 gr. t.d.s. for 3 days. Mepacrine 0·1 g. t.d.s. for 5 days. Pamaquin 10 mg. t.d.s. for 3 days	11	180	29	5	17·2
QSn _a	1	*Chesson	Quinine 10 gr. + pentaquin 20 mg. t.d.s.	14	2-523	76	6	7·9
QSn _b	11	India/Burma	" " " " " " " " " " " "	10	180	26	3	11·5
Intermittent QP	5, 10	Mediterranean	Quinine 10 gr. + pamaquin 10 mg. t.d.s. in 3 courses of 7, 5, and 5 days during 31 days	31	180	45	0	Nil
Intermittent M	5, 10	Mediterranean	Mepacrine in 3 courses of 2·5, 3, and 3 g. in 5, 6, and 6 days respectively during 31 days	31	180	42	12	28·6

* Artificially sporozoite-induced malaria.

in the absence of symptoms when there is at best only an even chance of escaping a relapse during the next few weeks. The disuse of quinine alone for the treatment of *P. vivax* infections should be recommended.

Mepacrine

* The relapse rate following treatment with mepacrine alone is rarely lower than 25%. In a series (M3a) reported by Most *et al.*¹³ the figure given is 84%. This is unusually high. It is probably true to say that on the average two out of every five cases treated relapse at some subsequent date.

The actual amount of drug administered appears to be relatively unimportant in the production of radical cure, although rapid clinical cure is more easily produced by a boosting dose at the beginning of therapy. In two parallel and strictly comparable series of cases (M2 and M3b) treated in Rome by Innes *et al.*⁵ and followed up six months later¹⁰ a larger total dosage of mepacrine produced a significantly higher relapse rate than a smaller dosage regime given over an equal period of time. An increase in the total duration of treatment also appears to have little significant effect in improving the success rate. (Compare Courses M1b and M2.)

The popularity and value of mepacrine in the treatment of *vivax* malaria from a military point of view was due to the fact that it can be given in a short course of only seven days' duration without prejudicing the final result ; and to the fact that, since it is only slowly excreted, relapses consequently rarely occur within two to three months of discontinuing treatment. At the same time there is no interference with prophylactic mepacrine. With other forms of therapy, such as quinine and pamaquin given concurrently, although the success rate is much higher, the failures that do occur relapse often within two to three weeks of discharge from hospital, and in this respect are

less welcome from a military point of view than those which relapse after two to three months.

The toxic effects of mepacrine when given in normal therapeutic dosage are negligible. Some cases, however, show an idiosyncrasy and present quite dramatic reactions to small amounts of this drug. Such reactions (mental disturbances, acute abdominal pain, etc.) should always be kept in mind when a course of therapy is started.

Paludrine

The relapse rate following treatment with paludrine alone is rarely less than 35%. In a small series of patients (X1b) from India and the Far East treated at Woolwich¹⁰ the relapse rate was 66.6%. On the average probably at least two out of every five patients treated relapse after five to six weeks or longer. The therapeutic value of paludrine alone is probably no greater than that of mepracrine.

Paludrine is remarkable in that, given in a total amount as small as 50 mg., it is capable of producing clinical cure of an overt attack of B.T. malaria. Experiments are therefore being conducted at Liverpool⁹ in order to test the curative value of paludrine given in a once-weekly dosage over a period of six or more months.

The outstanding value of paludrine is as a prophylactic or as a curative when given concurrently with pamaquin. The importance of the latter regime will be discussed later. As a prophylactic a dose as small as 100 mg. once or twice weekly is adequate to produce complete suppression of all manifestations of malaria. It does not, however, prevent the establishment of *vivax* infection, although it has been shown to inhibit to some extent the exo-erythrocytic forms which exist in the interval between the disappearance of the sporozoites from the blood and the demonstration of parasites 8 to 10 days later in the peripheral circulation.⁴ The only other drug so far demonstrated to possess this property is pamaquin.

Paludrine produces negligible toxic reactions unless given in amounts approximately twenty times the therapeutic dose. It has the advantage over mepacrine that it does not discolour the skin.

Chloroquine

This was synthesized in 1944 in the United States and has had extensive trials in America, particularly as a prophylactic agent for the suppression of malaria. It is highly active as a schizonticide in all types of plasmodial infection, but it "does not prevent relapses in *vivax* malaria even when administered in doses many times those required to terminate an acute attack." Rapid clinical cure is produced with only small amounts of the drug and in very short courses, as in the case of paludrine. Relapses, however, are very frequent, and occur several weeks after discontinuing treatment, since, like mepacrine, chloroquine is only slowly degraded in the body.

Chloroquine is an excellent prophylactic, considerably superior to mepacrine and qualitatively comparable to paludrine. Given in doses of 300 mg. once or twice weekly it has been shown to produce effective suppression of all forms of malaria. It does not, however, prevent the establishment of *vivax* infection, but merely prevents the appearance of symptoms, and does not appear to have any action upon the pre-erythrocytic forms of the parasites. On discontinuing treatment, as with mepacrine and paludrine, an overt attack of B.T. malaria will develop several weeks later. As with paludrine, there is a wide margin between the therapeutic and the toxic dose, and no discoloration of the skin is produced with prolonged dosage.

Toxic reactions following normal therapeutic or prophylactic dosage are negligible.

Pamaquin

Although pamaquin has the reputation of being of little value as a schizonticide, it is capable of producing radical cure in an easily tolerated dosage. In a small series (Pb) treated at Woolwich¹⁰ with 10 mg. t.d.s. for 10 days the relapse rate proved to be only 27.6%, comparing very favourably with a series of similar cases treated with paludrine alone. Against artificially induced infection with the Chesson strain (Pa) pamaquin proved ineffective in preventing relapses in all five cases treated.¹

Pamaquin has acquired an undeserved reputation as a most dangerous drug. It is true that there is a very small margin between a therapeutically effective dose and one that is severely toxic. The toxic symptoms, too, are somewhat dramatic. Unless, however, pentaquin is shown to produce even more encouraging results than those expected of it, pamaquin will continue to be of the greatest importance in the treatment of *vivax* malaria. Its value, which will be discussed later, lies in the fact that, given concurrently with other drug therapy, it almost invariably lowers the relapse rate. This can be clearly seen from Table II and the Chart.

TABLE II.—The Value of Pamaquin in Antimalarial Therapy

Course	Dosage Regime	Cases Treated	Relapses	Relapse Rate % of All Cases Treated	Relapse Rate % Cases Successfully Followed Up for 6 Months
QMP	Quinine 90 gr. in 3 days. Mepacrine 1.5 g. in 5 days. Pamaquin 90 mg. in 3 days	29	5	17.2	19.2
MP	Mepacrine 2.4 g. in 7 days. Pamaquin 90 mg. in 3 days	29	3	10.3	12.5
QPd	Quinine 10 gr. + pamaquin 10 mg. t.d.s. for 10 days	94	11	11.7	14.3
M1b	Mepacrine 4.6 g. in 12 days	86	23	26.7	35.0
M2	Mepacrine 3.1 g. in 7 days	31	11	35.5	44.0
M3b	Mepacrine 2.4 g. in 7 days	29	8	27.6	28.6
QM	Quinine 90 gr. in 3 days. Mepacrine 2.5 g. in 5 days	21	5	23.8	26.3

Chart showing effect of pamaquin on relapse rates.

The toxicity of pamaquin will be discussed under quinine-pamaquin therapy.

Pentaquin

The relapse rate following treatment with pentaquin alone is not yet fully established. In a small series (SNb) treated at Woolwich¹¹ the relapse rate was as low as 12%. In a series of five cases (SNa) artificially infected with the Chesson strain treated at Stateville¹ three relapsed. In a large series of cases pentaquin would probably be found to give a relapse rate of not less than 25%. Pentaquin, which is very closely related to pamaquin, was synthesized in the United States in 1945. It is a very active schizonticide which produces rapid clinical cure. The recommended dosage should not exceed 60 mg. daily for 10 to 14 days.

Toxic reactions are the same as those met with in pamaquin therapy. "At the therapeutic dose, the toxicity of pentaquin is qualitatively the same and quantitatively approximately one-half to three-fourths that of pamaquin in adult persons." In the Woolwich series of 25 cases a daily dosage of 60 mg. produced toxic reactions in over 50% of those treated.

Pentaquin, as will be shown later, is of greatest value when given in conjunction with quinine.

Treatment Combining One or More Drugs

Quinine and Pamaquin

The specific action of pamaquin in reducing the relapse rate following quinine therapy was pointed out nearly 20 years ago.¹² Since that time quinine 10 gr. (0.65 g) given concurrently with pamaquin 10 mg. 8-hourly for 10 to 14 days has come to be used as the standard control course for the evaluation of other forms of treatment. Until the introduction of treatment combining paludrine with pamaquin, and pentaquin with quinine, quinine-pamaquin was the most effective of all forms of therapy for the radical cure of *vivax* infections. It is rapid in its clinical action, rarely produces symptoms of toxicity, may be given to ambulant patients on light work, and on the average produces radical cure in eight or nine out of every ten patients treated (Table I, Courses QPa-g).

The minor disadvantage that quinine is preferably administered in liquid form and has an unpleasant taste may lead to its replacement by paludrine-pamaquin treatment, since the latter has been shown to be probably as successful in producing radical cure. The final judgment on quinine-pentaquin therapy will have to await the results of wider field trials.

It is usually recommended that pamaquin administration should take place under medical supervision in hospital. Although an ideal, such precautions are unnecessary in a large majority of cases, particularly those treated with quinine and pamaquin, provided that the daily dosage of pamaquin never exceeds 30 mg. In a series (QPa) of 168 cases occurring in British troops treated at Woolwich¹⁰ only 18 showed toxic symptoms. All except one of these 18

cases required no modification of their dosage and continued to be treated ambulant for the last seven days of their 10-day course without any adverse effects. The exception developed malaria while convalescent from lobar pneumonia, and the appearance of rather more severe toxic signs in a debilitated patient made it advisable to discontinue therapy.

Cyanosis and gastric symptoms are the common manifestations, but do not in themselves indicate discontinuance of treatment, only requiring that an increase in their severity or the development of additional symptoms should be at once reported and investigated.

The premonitory general malaise and anorexia of the patient is usually a good indication of the degree of toxicity prevailing, and such symptoms require to be pronounced before discontinuation of treatment need be considered. Signs of intravascular haemolysis are a clear indication for immediate withdrawal of the drug; they occur more often in the dark-skinned races.

Paludrine and Pamaquin

Treatment with paludrine alone has been shown to give a relapse rate of 35–40%. When pamaquin is added to the regime the success rate is at once improved. Pamaquin exerts a similar specific action in lowering the relapse rate to that found when it is administered concurrently with quinine. In the two series (PX1 and PX2) shown in Table I the results were almost identical with those found in the control series treated with quinine–pamaquin (QPa and QPf respectively).

It will be noted that the total amount of paludrine in course PX1 is two and a half times that given in course PX2, and that despite this larger dosage, when compared with the control, the success rate is no higher. This is the more important since with the higher dosage of paludrine the incidence of toxic reactions was considerable, approximately 40% of cases showing cyanosis or gastric symptoms. There was also a marked anorexia and malaise in the great majority of patients which compared unfavourably with the state of well-being of the control series treated with quinine–pamaquin.¹¹ In the other series, in which the paludrine dosage was only 300 mg. daily, the toxic side-effects were negligible.⁴ This difference in toxicity of the two courses is due to the fact that, like mepacrine, paludrine is a stronger base than pamaquin and displaces it from the tissues. The toxic reactions therefore are related not to paludrine but to a high plasma pamaquin level.

The optimum eight-hourly dose of paludrine when given concurrently with 10-mg. doses of pamaquin is probably 100 mg. or less. Such a course of treatment is likely to prove at least as successful as quinine–pamaquin therapy.

Combinations of Quinine, Mepacrine, and Pamaquin

Quinine, mepacrine, and pamaquin have been given in various combinations for the treatment of B.T. malaria. A commonly used regime consisted of quinine 10 gr. t.d.s. for three days, followed by 1.5 g. of mepacrine, given in five days, followed by 10 mg. of pamaquin eight-hourly for three days. Good results, with moderately low relapse rates, were obtained with this course, but generally speaking it is less successful than quinine–pamaquin therapy.

Innes *et al.*⁵ treated several series of cases at Rome with different combinations of these drugs. These were followed up six or more months later,¹² with the results shown in Table II.

The significance of these figures is less in the actual relapse rates obtained than in the comparative results (see Chart). It is clearly shown that the three courses which contained pamaquin had a higher rate of success than the

other forms of treatment. The relapse rate following all therapeutic regimes containing pamaquin is 12.5%, whereas that following the four other modes of treatment which exclude pamaquin is 28.2%.

The bad reputation suffered by pamaquin should not be allowed to nullify this important conclusion. Until pentaquin is convincingly shown to be the drug of choice pamaquin should continue to be given as an essential part of any attempt to eradicate *vivax* infection, whatever course of therapy is preferred. It must be remembered that it should not be given concurrently with mepacrine, since the latter causes the plasma pamaquin level to rise considerably, resulting in serious toxic reactions. Pamaquin is undoubtedly best administered concurrently with quinine or paludrine.

Quinine and Pentaquin

Preliminary indications from America regarding this latest form of therapy indicate that it is likely to be more successful than any other treatment yet devised. Pentaquin is still under trial and not yet generally available, so that final judgment will have to be suspended until a large complete series of cases of naturally occurring *vivax* malaria has been treated and adequately followed up against standard controls.

It was probable that pentaquin, being an 8-aminoquinoline derivative closely related to pamaquin, would have a specific action in reducing the relapse rate when administered with quinine. This indeed has been the case, for, although the results from Stateville¹ are as yet incomplete, interim reports show that against the Chesson strain of *P. vivax* (QSNa) the expected relapse rate is far lower than with any other mode of treatment suggested for this severe type of malaria.

In a series of 26 cases of naturally occurring B.T. malaria (QSNb) treated at Woolwich¹¹ three cases are detailed as relapsing, but none in fact had proved infections. Two patients treated themselves with mepacrine at the onset of symptoms, which were as likely to be due to coryza as to malaria; while the third did report having symptoms suggestive of a rigor. A relapse rate nearer 5% would probably be a more accurate estimate for this series of cases.

With the recommended dosage of 60 mg. daily very few, and only mild, toxic symptoms have been reported from America.¹ These consisted of cyanosis of a mild degree and occasional abdominal pain. In the Woolwich series these symptoms and signs were encountered in over 50% of the cases treated. One patient also developed pyrexia and pain in the hepatic area, and treatment was discontinued. The general malaise and anorexia of the great majority was in marked contrast to the good health and appetite of those treated with quinine–pamaquin.

Intermittent Therapy with Quinine–Pamaquin and Mepacrine

Innes *et al.*⁵ treated a series of cases at Rome on intermittent regimes of quinine–pamaquin and mepacrine. The follow-up of these cases six months or more later showed remarkable results.¹⁰ The courses used were as follows:

Mepacrine.—An initial course of 2.5 g. in five days followed by two courses of 3 g. each given in six days, with "rest" periods of seven days between all courses.

Quinine–Pamaquin.—An initial course of quinine 10 g. plus pamaquin 10 mg. given eight-hourly for seven days, followed by two similar courses of five days each with "rest" periods of seven days between all courses.

The patients chosen were those who had experienced six or more relapses in the previous six to nine months. At the time of treatment all patients had recently concluded a

course of therapy and were consequently symptomless and parasite free. The results are summarized in Table III.

TABLE III.—Results of Intermittent Therapy

Course	Cases Treated	Cases Followed Up	Relapses	Relapse Rate of Those Successfully Followed Up for 6 Months	Relapse Rate of All Cases Treated
Intermittent mepacrine	42	66%	12	42.9%	28.6%
Intermittent quinine-pamaquin	45	62%	0	Nil	Nil

It was regrettable that more cases could not be followed up, but owing to the exigencies of war the majority of the Dominion troops could not be traced. Nevertheless the result of the intermittent quinine-pamaquin treatment is significant and in remarkable contrast to the results obtained in any other series of cases treated in the Mediterranean area.

The rationale for such treatment was based on the discovery by Innes *et al.*⁹ that during treatment with quinine or mepacrine a drug-inhibited stage of development of the plasmodium occurred corresponding to the pre-schizont stage, and persisted for at least 12 to 24 hours in the peripheral circulation after other parasites had undergone schizogony. A tentative hypothesis¹⁰ suggests that if relapses of malaria can at all be ascribed to these drug-inhibited or retarded development forms, they may possibly persist in the host until the plasma drug level has fallen low enough for their redevelopment to take place. Such reactivity would occur during the "rest" periods of the intermittent therapy. The majority of the organisms would be destroyed by the second course of treatment and the remainder by the third course. For the success of such a regime it would be necessary to use a drug which is rapidly excreted from the body. Mepacrine is unsuccessful because it is slowly excreted, and the "rest" periods are not long enough to allow recovery of the drug-inhibited forms.

It would be of great interest to pursue such treatment in a large series of cases. The course has the disadvantage that it is lengthy, but it is also harmless and may be given without risk to patients on a full day's light work, provided they consult their medical adviser at the first suggestion of toxic symptoms. Such treatment would probably be preferable to 10-day courses for each and every relapse, and possibly more profitable than weekly doses of paludrine taken over a period of six or more months. The latter treatment, although likely to prove successful in a climate such as this country enjoys, appears somewhat too prolonged to be adhered to by the majority of patients.

Summary and Conclusions

The ideal drug for the prevention and radical cure of benign tertian malaria has yet to be discovered.

The disuse of unaided quinine therapy is recommended.

Suppressive and curative treatment with mepacrine is likely to be superseded by more recently discovered antimalarial drugs.

Paludrine and chloroquine are probably equally effective in producing complete suppression of overt attacks of malaria in once-weekly dosage. Neither is able to prevent the establishment of *P. vivax* in the human host even by daily dosage, but paludrine has some inhibitive effect on the pre-erythrocytic forms. Neither drug given alone is as successful as other forms of therapy in producing a low relapse rate.

Pamaquin is a drug which deserves greater recognition as a safe medium for the elimination of *P. vivax* infections. Given as an adjuvant in any course of antimalarial therapy it is of the greatest value in reducing the relapse rate. The toxicity of pamaquin is shown to be less formidable than is generally accepted.

No treatment so far administered to a large series of cases of naturally occurring B.T. malaria is more successful than quinine given concurrently with pamaquin. Paludrine given concurrently with pamaquin is equally successful.

Pentaquin given concurrently with quinine is likely to prove more successful in producing a lower relapse rate than any other therapeutic regime. The toxicity of pentaquin is approximately three-quarters that of pamaquin.

A 31-days intermittent course of quinine and pamaquin proved successful in the complete eradication of *P. vivax* infections in all patients followed up in a series of 45 cases. It is suggested that such a course is worth extended trials among chronic relapsing cases in a non-malarious area.

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DEMONSTRATION OF A PERSISTING EXO-ERYTHROCYTIC CYCLE IN PLASMODIUM CYNOMOLGI AND ITS BEARING ON THE PRODUCTION OF RELAPSES

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From the earliest days of the modern study of malaria the phenomenon of relapses in this disease has been invested with a mystery which has been responsible for various hypothetical solutions made in an attempt to explain the known facts.

The first of these facts is that periods of patent infection accompanied by the demonstrable presence of parasites in the peripheral blood are often succeeded by more or less prolonged periods when no such parasitaemia can be demonstrated. This condition is described as latent malaria, and it may supervene in the natural course of the disease or may be produced artificially by the use of anti-malarial therapy which destroys the erythrocytic infection. Another fact is that such relapses are often precipitated by