THE PRINCIPLES GOVERNING THE CURATIVE AND THE SUPPRESSIVE TREATMENTS OF HUMAN MALARIA, WITH SPECIAL REFERENCE TO MILITARY CONDITIONS.
By Brigadier J. A. Sinton, M.D., D.Sc.
(Consultant Malarialogist to the War Office.)
[Received March 3, 1945.]

A large amount of additional knowledge about the chemotherapy of malaria has accumulated since the war started. In spite of this, there appears to exist in some quarters a failure to appreciate the basic principles of such treatment. There is also much uncertainty as to how this knowledge can be applied to the best advantage under the very varied conditions which arise during active military service.

Theoretically, it should be possible to interrupt the cycle of the human malaria parasite from mosquito to man and back again by a direct chemotherapeutic attack upon the Plasmodium in either host. In our present state of knowledge, however, this can only be attempted during the sojourn of the parasite in the human body. The whole of the plasmodial asexual cycle (schizogony) occurs in the vertebrate host, while the sexual development (sporogony) is completed in the mosquito. The only stages of the latter cycle that occur in man are (i) the forms (gametocytes) destined for the initiation of the sporogonic cycle when taken by the mosquito, and (ii) the mature products of the latter cycle (sporozoites), which may give rise to infection when inoculated into man. It is necessary, therefore, to consider in how far these stages of the sexual cycle and the various stages of the asexual one can be affected adversely by the administration of drugs to the human host.

A successful chemotherapeutic attack upon the gametocytes or upon the sporozoites in man would be in the nature of a true prophylactic action (i.e. the prevention of the transmission of infection either to the mosquito or to man respectively). On the other hand, an attack upon the different stages of the asexual cycle would be a curative action (i.e. treatment of an infection already acquired by the human host). It is convenient, therefore, to consider the use of chemotherapeutic agents in man from (i) the Prophylactic standpoint and (ii) from the Curative one.

DEFINITIONS OF THE TERMS USED TO DESCRIBE THE CHEMOTHERAPEUTIC ACTIONS OF ANTI-MALARIAL DRUGS.¹

Much confusion and controversy have resulted in the past because of varied meanings applied to the same terms in malaria therapy. It is most essential, therefore, that exact definitions should be given to the terms used.

¹ These definitions are discussed more fully by Sinton (1937) and Sinton et al. (1939).
I.—TERMS USED IN DESCRIBING CHEMOTHERAPEUTIC MEASURES AIMED AT THE TRUE PROPHYLAXIS OF MALARIAL INFECTION.

(A) Prophylaxis of the Passage of Infection from the Human to the Insect Host (Gametocyte Therapy).

(1) Direct gametocyte prophylaxis is the prevention of the development of infection in the insect vector by the direct destruction, sterilization, or devitalization of the gametocytes before they leave the human host.

(2) Indirect gametocyte prophylaxis is a reduction in the infectivity of the human host because of a temporary diminution in the number of gametocytes, or a temporary elimination of these forms from the peripheral blood, through the destructive action of anti-malarial drugs upon the asexual parasites from which they are derived.

(3) Eventual gametocyte prophylaxis is the permanent elimination of gametocytes from the peripheral blood by the complete eradication of the schizogenic forms from which they originate.

(B) Prophylaxis of the Passage of Infection from the Insect to the Vertebrate Host (True Causal Prophylaxis)

(1) True Causal Prophylaxis.—The complete prevention of the development of any schizogenic blood forms as the result of the radical destruction of all introduced sporozoites (or of any hypothetical stages between the latter and the former), i.e. the prevention of infection in man.

II.—TERMS USED IN DESCRIBING CHEMOTHERAPEUTIC MEASURES AIMED AT THE CURE OF INFECTION OR ITS MANIFESTATIONS.

(1) Suppressive Treatment.—The prevention of the development of the clinical manifestations of sub-patent infections by means of continued drug treatment.

(2) Clinical Cure. —The cure of clinical manifestations should develop.

(3) Radical Cure. —The permanent elimination of the infection by the destruction of all those forms of the parasite that are capable of continuing the asexual (pathogenic) cycle in the human host, i.e. permanent prevention of relapses, either clinical or parasitic.

1 So far as is known, gametocytes are derived primarily from the blood schizogenic forms of the Plasmodium, and are so liable to be regenerated so long as infection continues. (It is unknown what part the exo-erythrocytic stages seen in avian malaria and hypothesized in mammalian malaria play in their development.)

In the absence of radical cure, the effects of gametocytocidal drugs are only temporary, and these forms tend to reappear when the temporary action of the drug has passed off. In our present state of knowledge, there appears to be no hope of achieving a permanent disappearance of gametocytes from the peripheral blood, and so the elimination of actual and potential malaria carriers, unless at the same time the infection is eradicated.

The term "cure" is used in a very loose sense by many writers on malarial therapy. It is essential that it should always be clearly indicated whether it is intended to mean radical cure (i.e. a complete eradication of infection), or merely clinical cure (i.e. only abolition of those clinical manifestations of infection present at the time when treatment commenced). While many clinical cures may at the same time be radical ones, more especially in M.T. infections treated by modern methods, there is at present no means of determining whether the latter effect has been achieved except by prolonged post-therapeutic observation.

In the case of M.T. infections, the absence of attacks for three months after the cessation of all forms of anti-malarial treatment usually indicates a radical cure, but with B.T. the infections in some instances may remain latent and attack-free for periods of nine to twelve months in the absence of radical cure.

2 So far there is no conclusive proof that such hypothetical forms (cryptozoites) exist in the cycle of any mammalian Plasmodium. If such forms are found to occur, it may be necessary to divide "true causal prophylaxis" into two stages, (a) sporogonic causal prophylaxis, and (b) cryptozoite causal prophylaxis, for scientific convenience. Or it might be better to consider the occurrence of cryptozoites as an early stage of infection, and classify the treatment against such forms as a "curative" rather than a "prophylactic" measure. This would mean that curative methods (vide infra) would have to be divided into (a) attack on tissue forms (cryptozoites), and (b) attack on blood forms (trophozoites, etc.).

3 Relapses may be of two types—(i) Parastic ones discovered by blood examinations, and (ii) Clinical ones revealed by disease manifestations. The discovery of parasites in the peripheral blood is not always accompanied by clinical effects. The provocation of a clinical attack depends upon the number of parasites required to produce such pathogenic effects (i.e. the pyrogenic threshold of the strain or species of parasite) in the infected individual at the time of the attack. This may vary periodically in the same person. It is also influenced by certain basic factors such as (i) the natural individual or racial tolerance of the infected person (e.g. African adults appear to have a much higher tolerance than have Aryans), and (ii) the degree of immunity or tolerance acquired as the result of the present or previous infections (Sinton et al., 1931; Sinton, 1935).
If there was available any drug or combination of drugs that in non-toxic dosage was capable of producing all the therapeutic actions mentioned above, it should be possible, theoretically at least, to eradicate malaria. Unfortunately, we do not know of any such drug, or system of treatment, which can be used as a true causal prophylactic; nor do we know of one which can be guaranteed to produce by a single course a radical cure in all malarial infections, although with some types of infection a very high percentage of such cures can be obtained.

**THE PARASITICIDAL ACTION OF ANTI-MALARIAL DRUGS IN RELATION TO THE PREVENTION AND CONTROL OF MALARIA.**

Having defined the terms to be used, it is necessary to consider the various proven actions of the commonly used anti-malarial drugs in relation to their employment under military conditions. The following table gives a summary of the chief actions of the three common drugs—quinine, mepacrine (atebrin) and pamaquin (plasmoquine).

**Table showing the actions of certain anti-malarial drugs upon the blood stages of the malarial parasites.**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>B.T.</th>
<th>Ov.</th>
<th>Qt.</th>
<th>M.T.</th>
<th>B.T.</th>
<th>Ov.</th>
<th>Qt.</th>
<th>M.T.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinine</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Mepacrine</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
<tr>
<td>Pamaquin</td>
<td>x x</td>
<td>?</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
<td>x x x</td>
</tr>
</tbody>
</table>

**Notes.** — x x x indicates a very great destructive action; x x a less marked action; 0 an absence of destructive action; and ? absence of precise information.

I.—**TRUE PROPHYLACTIC ACTION OF ANTI-MALARIAL DRUGS.**

(A) **The Prevention of the Acquisition of Infection by the Mosquito (Gametocyte Prophylaxis).**

1. **Direct Gametocyte Prophylaxis.**—Both quinine and mepacrine have a direct destructive action upon the sexual forms of B.T., Qt., and ovale parasites, but none upon the gametocytes (crescents) of M.T. On the other hand, pamaquin (plasmoquine) destroys or devitalizes the gametocytes of all four forms of human malaria parasites. For these reasons, apart from any adjuvant action to the radically curative effects of the other anti-malarial drugs (vide infra), it is unnecessary to give pamaquin in infections other than M.T. if such drugs are being used. It must be remembered, however, that so long as the infection is not radically cured, these sexual forms will be liable to reappear in the peripheral blood after treatment ceases, i.e. such uncured cases will always be actual or potential gametocyte carriers, and at some later period, may spread the disease to the mosquito.

2. **Indirect Gametocyte Prophylaxis.**—Any of the anti-malarial drugs which act upon the schizonts will reduce, temporarily, the number of gametocytes being poured into the peripheral blood by destroying their precursors (i.e. the schizonts). For this reason all the ordinary curative treatments with quinine or mepacrine, have an indirect gametocyte prophylactic action, even in M.T. infections. This action is very apparent when mepacrine suppressive treatment is properly taken.

3. **Eventual Gametocyte Prophylaxis.**—It is only after the establishment of a radical cure by any means that the reappearance of gametocytes at a later date can be prevented after all treatment is discontinued completely.

---

1. For ease of reference in this article, benign tertian infections (P. vivax) will be indicated as "B.T.," quartan infections (P. malariae) as "Qt.," malignant tertian infections (P. falciparum) as "M.T." and ovale infections (P. ovale) as "Ov."

2. It has been reported that pamaquin (plasmoquine) in doses even as small as 0.01 gram twice weekly will suffice to reduce crescents to a very low level of infectivity among native populations not treated by other means.

The proper use of any of these methods will have an important influence on the spread of malarial infections in the field. The numbers of gametocytes developed has been found to be proportional to the intensity of schizont prevalence (see references in Sinton, 1938). The greatest numbers in B.T. and ovale infections occur during the acute attack, while with M.T. the peak is reached about seven to ten days after the maximum schizont prevalence. In the case of the former infections, adequate clinically curative and suppressive treatment will reduce the production of gametocytes to a very low and probably non-infective level, because of both direct and indirect gametocytocidal action. On the other hand, quinine or mepracrine have little or no direct action on the formed gametocytes of P. falciparum, although by their indirect action they can cause a great reduction in the numbers produced (Sinton, 1938). This is very evident with mepracrine suppressive treatment. For this reason, it may be advisable after treating an attack of M.T. malaria to give a few doses of pamaquin to cause a rapid direct destruction of any crescents which have escaped indirect effects of the clinical treatment.1

(B) The Prevention of the Acquisition of Infection by the Human Host (True Causal Prophylaxis).

So far no drug has been discovered which, in non-toxic dosage, will prevent the acquisition of infection by a susceptible human host after being bitten by an infective mosquito, i.e. no true causal prophylactic drug is known which is possible of practical application in human malaria. Some drugs, such as mepracrine, which were at one time claimed to have this property in M.T. malaria, have been shown to exert their action not upon the sporozoites (or cryptozoites), but upon the schizogenic forms which eventually develop from the former type of parasite, i.e. a curative action upon an established infection.2

II.—CURATIVE ACTION OF ANTI-MALARIAL DRUGS.

It is an axiom that unless a drug is taken, retained and absorbed, one cannot expect to get its optimal effects in the body. It is not sufficient merely to order a drug, or to hand it to the patient, asking him to take it. Steps must be taken to see that the prescribed administration is carried out. The supposed failure of proven remedies is too often due to a failure to ensure that these conditions are strictly complied with (see Sinton, 1930).

The two main drugs used in the routine therapy of malaria, whether clinical or suppressive, are quinine and mepracrine. It is necessary to know certain details about their pharmacology before one can employ them to the best advantage under different conditions.

Both drugs are rapidly absorbed when given orally, and quinine quickly reaches a high blood concentration. On the other hand, with mepracrine much of the drug is taken up by the other tissues, and it requires several days before an optimum effective blood concentration can be reached by the usual routine curative dosage.3 For this reason with such dosage the

1 A couple of daily doses of 0-02 gram of pamaquin will probably suffice for this purpose.
2 If patients already infected with P. falciparum continue to take the proper dosage of suppressive mepracrine for several weeks after the last risk of infection has passed, the majority will be radically cured, although they may never have shown any clinical signs of infection. It was this reason that caused some workers to claim that mepracrine could act as a true causal prophylactic against M.T. malaria. If, however, mepracrine is stopped within a week after infection has been acquired, attacks of the disease will occur later in most instances. It has also been shown by blood inoculation, and sometimes by blood examination, that during the early periods after the passage of infection, the blood of such persons contained asexual parasites even although mepracrine is being taken. It is evident, therefore, that although the results may simulate a true causal prophylaxis the action of the drug is upon the schizogenic forms and not upon the sporozoites or cryptozoites, i.e. it is a curative effect and not a prophylactic one. Unfortunately no such remarkable beneficial effect is produced in the case of B.T. infections, in which relatively few more are radically cured by such an extension of suppressive treatment, although large numbers may be rendered latent for several months. These undetected infections may appear at most inopportune moments and constitute a serious military problem.
3 It is on account of this slow "build-up" of blood concentration that mepracrine suppressive treatment is better started some weeks before the risk of infection occurs, or alternatively larger "loading" doses should be given a shorter time previously to achieve the same result. Similarly, to produce rapid clinical effects comparable with those caused by quinine, the dosage of mepracrine during the first two days may need to be increased to 0-6 to 0-8 gram daily, if quinine is not used.
clinical action of quinine has often been found to be more rapid than that of mepacrine.\(^1\) Quinine is, however, excreted much more rapidly than is mepacrine, so the therapeutic action of the latter drug may continue for a considerable period after the last dose. It is for this reason that, in the absence of radical cure, relapses are liable to occur sooner after the cessation of quinine treatment than after mepacrine. It has been upon such early results that some workers have reported that certain treatments with quinine and pamaquin are less effective in the radical cure of chronic B.T. infections than are mepacrine ones. More prolonged observation has in some cases shown the reverse to be true.

(A) Suppressive Treatment.

1. Quinine.—In the past it has been reported from many parts of the world that the clinical manifestations of malaria can be largely suppressed in the majority of individuals by doses of 5 to 6 grains of quinine daily.\(^2\) More recent experience tends to show that such good results can only be expected (i) when the action of the drug has been reinforced by some degree of immunity, either natural or acquired; or (ii) when the exposure to infection is not very severe or is mainly seasonal; or (iii) when the chief infection is B.T. On the other hand, it has been found that when non-immune individuals are exposed to severe malarial infections, such doses of quinine are insufficient to keep all attacks of malaria suppressed over long periods, although they will diminish the clinical severity and frequency of these attacks. The increased dosage needed to achieve the high degree of suppression produced by mepacrine (vide infra) would, in these circumstances, be too high to be tolerated by the soldier while performing his normal duties efficiently.\(^3\)

2. Mepacrine.—With mepacrine we have now a drug which in easily tolerated dosage will suppress the effects of repeated heavy infections and superinfections with either M.T. or B.T. or both. To obtain these effects, the drug should be given in a dosage of 0·1 gram every day of the week without fail. The recipient quickly becomes habituated to this amount of the drug, and it does not interfere with his normal duties, either physical or mental.

The statistics recently reported from very highly malarious areas in New Guinea show that, with the proper enforcement of such mepacrine suppression, a military force can maintain itself in the field with a very low malarial attack incidence. This is possible under conditions where, without the proper use of this drug, malaria would put the force out of action within a few weeks.

Much evidence had been accumulated in the field from all parts of the world during the past few years to indicate very strongly that, when properly and regularly taken, mepacrine would ensure a very low malarial incidence under active service conditions. Now the brilliant experiments carried out in Australia have proved conclusively that any supposed failure to suppress is mainly, probably entirely, due to a failure to carry out the routine ingestion of the drug without any intermissions. Very severe tests designed to simulate as closely as possible the conditions of heat, cold, fatigue, mental strain, poor and inadequate nourishment, etc., likely to be encountered on active service, failed to overcome the suppressive action of this drug when given in doses of 0·1 gram daily. Attacks only occur when for some reason, intentional or unintentional, there has been some interruption in the daily ingestion of the drug.\(^4\)

The occurrence of malarial attacks among groups of persons ordered routine mepacrine suppression can be regarded as prima facie evidence that the drug is not taken regularly as ordered. This failure to take mepacrine properly is sometimes due to carelessness or forgetfulness, but some individuals deliberately avoid the treatment in the hope that a resulting

---

\(^1\) The ordinary routine doses for clinical treatment are 30 grains (2 grams) of quinine daily in solution, or 0·3 gram mepacrine daily in tablet form.

\(^2\) See Sinton (1936) (pp. 134-145).

\(^3\) The question of quinine dosage is discussed by Sinton (1930).

\(^4\) The routine in the Australian Forces is that a man who, for any reason, has failed to take a tablet of mepacrine on one or more days will take an additional tablet of mepacrine on each day following, until the same total number that were missed have been taken (e.g. if three tablets are missed, two will be taken daily for the next three days).
malarial attack will secure them a period of absence from the perils and discomforts of the forward area, or even leave or invaliding outside the theatre of operations. The results of suppression in any unit depends upon the strictness with which the administration of mepacrine is supervised and enforced and, in such circumstances, a high malarial incidence is certain evidence of poor anti-malarial discipline.

As pointed out earlier, mepacrine has no true causal prophylactic action but is merely a suppressive. For this reason, if the treatment is stopped immediately after leaving a malarious area, many of the suppressed infections will soon develop into acute clinical attacks of the disease. On the other hand, it has been found that, in the absence of reinfection, if mepacrine be continued in the same dosage for about four weeks after leaving a malarious area, a radical cure will have been achieved in practically all cases of M.T. infection. It is otherwise in the case of B.T. infections. While some of the latter may be cured by suppressive treatment, a considerable number may be expected to break out after treatment is stopped. Some may appear within a few weeks, while many may remain latent for many months or even as long as a year.

The beneficial effects of mepacrine suppression may be summarized as follows:

(a) Diminution in morbidity, and so a great conservation in man-power and efficiency, both physical and mental; (b) reduction in the severity of clinical attacks, and so, (c) reduction in mortality; (d) diminution in the number of gametocyte carriers of all species of parasites and so a reduction in the source of infection to mosquitoes; (e) radical cures of many infections, especially M.T. ones, when the treatment is prolonged; (f) diminution in the tendency to blackwater fever and to post-malarial anaemia; (g) assistance to the body in building up a resistance to malaria, which will tend to diminish the frequency and intensity of clinical attacks and also help the action of anti-malarial drugs (Sinton, 1939).

There is no doubt that mepacrine is the best drug we have at our disposal for suppressive treatment among troops. Not only is it a better suppressive than quinine, but is easier to take, does not produce cinchonism, and does not interfere with either the mental or bodily activities of the recipient.

(B) Clinical Cure.

The chief drugs of value in the cure of the clinical manifestations of malaria are quinine and mepacrine; pamaquin has no place in such treatment. With the appropriate doses of these drugs, a clinical cure is usually a relatively easy matter. This is especially the case in relapses of B.T. malaria, many of which tend to run to spontaneous recovery even in the absence of treatment. In acute attacks of M.T. malaria, it is usually necessary to give relatively larger initial doses of mepacrine than of quinine to obtain a quick result.

In ordinary cases of malaria, if the diagnosis be made early and specific treatment started promptly, the damage to the patient’s health is relatively slight; the necessary period of absence from duty should be short, unless after severe attacks of M.T. malaria or when blackwater fever or some other complication occurs. Long continued untreated or insufficiently treated malarial infections may eventually lead to considerable anaemia and debility. Such cases should be very rare or absent when proper treatment is given, and more especially when mepacrine suppression is in use.

1. See footnote 1 page 148.

2. Among troops returning from the Mediterranean area, at least 5 to 6 per cent developed subsequent attacks of B.T. malaria, often after a quiescent interval of five to six months or longer. In the tropics, where the infection rate is much higher, the incidence of such attacks will be much greater, but some reports seem to indicate that the majority of these will reveal themselves very shortly after suppression is stopped, and that relatively few will have long periods of latency.

3. In highly malarious areas during the last war from 5 to 15 per 1,000 of malaria cases admitted to hospital died, as compared with a rate of only 1 per 3,000 reported by the Australians from the S.W.P. area. Very much of this decrease is attributed to mepacrine suppression.

4. See footnote 4 on page 150.
(C) Radical Cure.

Some workers believe that malarial infections cannot be cured radically by chemotherapeutic means alone, but that, until some immunity is developed by the infected person to assist the action of the drugs, the infections will linger on and relapse for very long periods. For this reason it is sometimes recommended that the treatment of attacks should be separated from that which aims at radical cure.

While it is recognized that the presence of some degree of immunity, either natural or acquired, may be of great help in producing a radical cure, it is now proven that quite a high proportion of malarial infections can be cured radically in the absence of any appreciable degree of acquired immunity (e.g. the radical cure of early M.T. infections by mepacrine). Other factors being equal (vide infra), modern practice is to attempt to obtain both a clinical and a radical cure by the same course of a treatment of short duration.

Routine prolonged treatment which aims at the production of a very high percentage of radical cures in all cases, irrespective of the type of infection, does not appear justifiable in Army practice during war, either from the point of view of the patients, the loss of manpower involved, the expense, and the supervision required. In primary attacks the course should be as short as possible, consistent with a high radical cure rate in the predominating infection. While it is admitted that prolonged courses of treatment will produce in most cases a higher radical cure rate, the benefits derived from them are not proportionate to the loss of manpower, etc., involved in implementing them (see Sinton, 1930).

Owing to the difficulty which the clinicians may encounter in obtaining an immediate diagnosis of the species of parasite responsible for the infection and the common occurrence of undetected mixed infections, some standard course of treatment should be laid down which will produce a rapid clinical cure, and, if possible, at the same time, a radical cure of the majority of the infections encountered in the area. The short standard courses of treatment advocated in the Army have proved capable of effecting rapid clinical cures against both B.T. and M.T. malaria, and in producing a very high rate of radical cure in the latter type of infection (usually more than 90 per cent with a single course of treatment). Unfortunately, these are less successful against some types of B.T. infections in which a considerable proportion (even up to 50 per cent) may relapse later.

While such B.T. infections are very easily cured clinically, and attacks can easily be prevented by continuing suppressive treatment, a relatively high proportion relapse again when such treatment is discontinued. Such relapsing cases form a serious military problem, because no one course of any of the standard Army treatments has been found to produce a high radical cure rate. These chronic B.T. cases require special types of treatment, and although several new drugs and intensive types of treatment with mepacrine have been tried, so far they have not solved the problem. Some workers state, however, that when the action of pamaquin (plasmoquine) is combined with that of quinine or mepacrine, the relapse rates in both B.T. and M.T. malaria are reduced.

Some recent work on chronic B.T. malaria of

1 In the absence of reinfection, M.T. infections seldom relapse after one year; B.T. infections usually disappear after two to three years, but Qt. infections may persist for many years. Clinical relapses in ovale infections are practically unknown.

2 This question has been discussed more fully by Sinton (1935a, 1939).

3 Some physicians recommend that the clinical curative treatment of such cases should be followed up by a "maintenance course" of therapy. This is called "treatment to prevent relapses." It is merely a suppressive treatment, and relapses must be expected to recur when it is stopped. Although the immunity which is developing while such treatment is in progress (see Sinton, 1939) may assist in the production of a radical cure eventually, the beneficial effects produced are not sufficient to compensate for the difficulties of its strict administration under most military conditions. When given in the form of the ordinary routine suppressive treatment and not in the form of individual attempts at radical cure or suppression, such a scheme is of considerable importance under certain military conditions (vide infra).

4 Pre-war experience in India reported highly favourably upon the radically curative effects of the simultaneous administration of quinine and plasmoquine in the treatment of chronic B.T. infections (see Sinton et al., 1930; Sinton, 1930; Manifold, 1931; Dixon, 1933; Amy and Boyd, 1936; et al.). Recent controlled trials in this country tend to support this claim.

5 The reported benefits of the combined plasmoquine treatments are discussed in the 4th General Report of the Malaria Commission of the League of Nations (1937), (pp. 940-954).
Mediterranean origin supports the view that a higher radical cure rate in such infections can be produced by a combination of quinine and pamaquin than with any other form of treatment tried.¹

**THE PRACTICAL APPLICATION OF THE PRINCIPLES OF MALARIA THERAPY TO THE CONTROL OF THE DISEASE UNDER MILITARY CONDITIONS,**

The recognized actions of anti-malarial drugs must be applied differently to obtain the best effects under the varied conditions of military service.

I.—TRUE CAUSAL PROPHYLAXIS.

So far we know of no drug which it is practicable to use in non-toxic doses to produce this effect. If such a drug were available, to be satisfactory under military conditions, it should not only be a true causal prophylactic against all species and strains of parasite, but should also have a curative action to ensure that the results of any failure to take the drug in adequate dosage, with consequent contraction of infection, would be overcome by its later curative or suppressive actions.²

II.—GAMETOCYTE PROPHYLAXIS.

With the proper use of mepacrine suppressive treatment, gametocyte carriers should not be a serious problem among troops. When such treatment is not in use in a potentially malarious area, it may be advisable in M.T. infections to give a couple of small doses of pamaquin after the completion of a course of treatment to devitalize any crescents which have not been affected by the other drugs used.

Gametocyte prophylaxis may also be used in reducing the number of carriers among indigenous populations living continually in close contact with troops—a condition to be avoided. But here it is probable that the use of mepacrine suppression would be better, as it would not only act as an indirect gametocytocidal agent against crescents, but a direct one also against the gametocytes of B.T. and Qt. At the same time it would reduce the number of those acute attacks which are followed by showers of gametocytes into the peripheral blood.

III.—CURATIVE MEASURES.

1) **Suppressive Treatment.**—As emphasized above, mepacrine suppression is the most important means of controlling the results of infections in malarious, and especially highly malarious, regions. It must always be stressed that such treatment is not the solution of the problem of malaria prevention, but is only a means of controlling the ravages of the disease temporarily. When such treatment is discontinued, a large number of attacks must be expected, and these may occur at most inopportune moments thus upsetting or delaying important operational preparations. The mere fact that troops on suppressive treatment have a low malarial sick rate must never be taken as a justification for any relaxation of other measures of personal protection against the acquisition of infection (i.e. against mosquito bites). Indeed, the need for the use of suppressive treatment is a certain indication of severe risks of infection and therefore for the even stricter enforcement of all measures of personal protection.

The occurrence of numbers of malarial attacks in any unit or formation ordered mepacrine suppressive treatment is clear evidence that the drug is not being taken properly. The occurrence of a heavy malarial incidence after such treatment is stopped is definite proof that measures of personal protection have not been adequately enforced during the period of exposure to the risk of infection.

¹ See footnote ⁴ on page 153.

² An ideal prophylactic would be one in which these effects lasted for weeks or even months after a single dose or course of treatment.
(2) **Clinical Treatment.**—The treatment should be such as will produce as rapid a curative effect as possible, thus not only reducing the period of disability but also the effects of the attack upon the patient’s health. As clinical cures can be produced very rapidly in uncomplicated cases of malaria, arrangements should be made to treat all these as close to their units as possible, in order to avoid the great wastage of man-power and the prolonged periods of absence from duty which result when patients are evacuated to more distant places. The establishment of Forward Treatment Units should do much to prevent this.

If mepracrine suppressive treatment is being taken properly and attacks treated quickly when they develop, the effects upon the patient’s health should be very small and, in the absence of complications, of short duration. Few cases should require evacuation and the numbers invalided should be negligible.

(3) **Radical Curative Treatment.**—When this effect is indicated (vide infra) the course of treatment should be as short as possible consistent with a relatively high cure rate. Prolonged routine treatments in attempts to obtain a slightly higher radical cure rate are to be deprecated, save in exceptional circumstances.

**IV.**—GENERAL OUTLINES OF THE PRACTICAL APPLICATION OF MALARIA THERAPY UNDER DIFFERENT CONDITIONS OF MILITARY SERVICE.

The most appropriate method for the control of malaria in the field by therapeutic measures will vary with the type of individual involved, the intensity of the malarial risk, and the probable duration of exposure to such risk.

(A) **Non-infected Individuals Coming to Reside in an Area where the Chances of Acquiring Infection are Relatively Slight.**

If local conditions are such, either naturally or as a result of anti-mosquito measures, that the individual is only likely to become infected or reinfected at long intervals, there appears to be no object in subjecting him to the tedium of suppressive treatment, nor to the discomfort of repeated attacks, in an endeavour to raise his immunity, as advocated by some workers (see Sinton, 1939, p. 209).

In such circumstances the aim of therapy should be to produce a rapid clinical cure of the attack and a radical cure of the infection at the earliest moment by as short a treatment as possible. The ordinary standard courses advocated by the Army should achieve this result in the very great majority of M.T. infections and in a large number of fresh B.T. ones. In the former type of infection it may be necessary occasionally to give a few doses of pamaquin for the direct destruction of any sexual forms not affected by the quinine or mepracrine treatment. Pamaquin is unnecessary for this purpose in B.T. or Qt. infections, although sometimes needed as an adjuvant to radically curative treatment. Relapsing infections should be specially treated along the lines advocated above.

(B) **Individuals Coming to Reside in a Non-malarious or only Slightly Malarious Area from a Highly Malarious One.**

In all cases the routine mepracrine suppressive treatment in force in the highly malarious area should be continued without intermission for at least four weeks after the last chance of acquiring infection has passed. This should eradicate most of the M.T. infections which are so dangerous to life and the protean manifestations of which are so liable to be overlooked in non-malarial areas with fatal results.

The treatment policy to be adopted will depend upon the probable duration of the sojourn of the individual or formation in the less malarious region.

(1) **Period of Absence from Heavy Risk of Infection likely to be of long Duration.**—If the absence is likely to be six months or more, suppressive treatment should be stopped in most instances. It may, however, be continued temporarily in the case of key personnel or units where the protean manifestations of which are so liable to be overlooked in non-malarial areas with fatal results.

2These factors have been discussed in greater detail by Sinton (1935a), (1937) and (1939).
among whom at the time any heavy sickness incidence would seriously interfere with military operations. Its continuation may also be needed when, in the progress of active operations, troops pass from a highly malarious area to a less malarious one, or the annual break in malarial incidence is only for a short interval.

It must be remembered, however, that there is no evidence that the prolonged continuation of suppression is likely to produce radical cures of B.T. infections (i.e. the chief relapsing disease after suppression stops) in numbers proportionate to the trouble needed to continue the treatment in non-malarious areas. The majority of persons still infected with this parasite will relapse when treatment stops, so the sooner they develop signs of infection (if this does not interfere with urgent military considerations) the sooner can appropriate radical treatment be started. So long as suppressive treatment is continued so long will the potential sick rate in the unit be masked and impossible to evaluate. Such masked infections may break out at critical moments after suppression is stopped.

(2) Period of Absence from Risk of Heavy Infection of Short Duration.—If the period of absence is likely to be of relatively short duration, as in the case of troops returning for rehabilitation, re-equipment, refresher training, etc., or if only a short interval occurs in the transmission season, the suppressive treatment should be continued without intermission as in the highly malarious area. If such treatment be stopped, the troops will be liable to develop attacks of malaria, mainly B.T., which may interfere seriously with their activities and delay their return to active field duties.

It is a waste of time to stop suppressive treatment in such circumstances, and to allow attacks to develop in order to give radical treatment, because many of these men are likely to become reinfected within a short time after their return to a dangerous malarious area, undoing the effects of radical treatment. At the same time, it is probable that the suppressed infections will help the individual to develop a considerable degree of immunity, which, with the aid of the suppressive treatment, will make him less liable to get disabling attacks in the future ("immunization without risk") (see discussion by Sinton, 1939).

Patients who develop ordinary attacks need only receive a short course of treatment sufficient to produce a rapid clinical cure, and should then immediately resume suppressive treatment without any interval between. No more prolonged treatment should be used in an attempt to produce a radical cure, because M.T. infections will be radically cured by the continued suppression and B.T. ones will be effectively suppressed. Patients who develop blackwater fever, or in whom some other serious complication develops, will require special treatment. In the former instance, at least, they should not be allowed to return to a highly malarious region.

If M.T. cases treated in a potentially malarious area show crescents after finishing curative treatment, a couple of small doses of pamaquin at the end of the course should be sufficient to render these non-effective.

(C) Individuals Exposed to Constant and Frequent Infection, and Reinfection and Superinfection.

It is well known that the indigenous inhabitants of highly malarious regions, especially those of aboriginal and not of immigrant stock, have often developed a high degree of tolerance to the effects of malarial infection by the time they have arrived at adult age. Apart from any natural immunity, much of this has been acquired as the result of repeated infections lasting over very many years. Even this high degree of tolerance may be broken to some extent when the individuals are translated to new environments, where they are attacked by different strains and species of parasite. In the latter circumstances, however, the effects of

---

1 Individuals who under these conditions develop repeated attacks of malaria, should be strongly suspected of avoiding routine suppressive treatment, and, whether officer or man, should be placed under strict supervision and observation to ensure that the drug is taken and retained.

2 See footnote 1 on page 151.

3 See footnote 3 on page 150.

4 The question of treatment in such indigenous populations is more fully discussed by Sinton and Harihagwan (1935) and Sinton (1935).
malaria are usually very much less severe than in non-immune individuals, and a substantial degree of tolerance to the new strains is developed relatively rapidly. It is otherwise in the case of non-immune populations coming from areas where malaria is absent or much less severe. In the case of troops it is necessary to differentiate these two types of individuals.

(1) **Immune or Salted Populations.**—While African and other aboriginal troops from highly malarious regions may have a high degree of tolerance to the effects of their own local strains of parasite, malarial sickness may become much more evident when such people are transferred to a foreign environment. Any increase usually appears shortly after exposure to the new infecting strains. Smaller doses of mepacrine (say a total of 0–4 gram weekly) will probably suffice to reduce attack incidence to reasonable levels, should the increase be of such magnitude as to justify its use. After such troops have become aclimatized to local conditions, suppressive treatment is usually no longer necessary. Any clinical attacks of the disease that develop are usually mild in character and their treatment should aim at a rapid clinical cure not a radical one. A radical cure will tend to diminish the beneficial immunity enjoyed because it will tend to eradicate the stimulus of continued infection which is necessary to maintain this at a high level (Sinton, 1939).

(2) **Non-immune or Semi-immune Troops.**—Such troops always suffer very severely when introduced into highly malarious areas. For therapeutic malarial control, these individuals should be given full doses of suppressive mepacrine during the whole period of residence in the dangerous region and for four weeks after leaving. If the malaria is seasonal there should be no break in the continuity of suppressive treatment, unless the intermission in the period of malarial transmission lasts more than six months.

Attacks should be treated to produce as rapid a clinical cure as possible, followed by an immediate resumption of suppressive mepacrine. As such individuals are exposed to the continued risk of early and frequent reinfection, attempts at radical cure by more prolonged treatment are a waste of time so long as they continue to reside under these conditions. The later treatment of such infections has been discussed above.

**SUMMARY OF THE APPLICATIONS OF THE PRINCIPLES OF MALARIA THERAPY UNDER DIFFERENT CONDITIONS OF MILITARY SERVICE.**

A. **Non-infected Individuals Coming to Reside in an Area where the Chances of Acquiring Malarial Infection are slight.**
   
   (1) No suppressive treatment.
   
   (2) Primary acute attacks—rapid clinical cure combined with radical treatment of short duration; occasionally gametocyte therapy for M.T. infections.
   
   (3) Relapsing Infections—(a) Repeat standard course; (b) chronic B.T.—special treatment.

B. **Individuals Coming to Reside in a Non-malarious or Slightly Malarious Region from a Highly Malarious One.**
   
   (1) **If the Period of Absence from Heavy Risk of Infection is likely to be of Long Duration.**
      
      (a) Stop suppressive treatment after four weeks (except perhaps among certain special personnel).
      
      (b) Primary acute attacks—not only rapid clinical cure but especially a radical one.
      
      (c) Relapsing infections—(i) Repeat standard treatment (no maintenance); (ii) chronic B.T. infections—special treatment.

*While continued suppression may be no longer necessary to preserve the health of such troops, it must be remembered that suppressive mepacrine will tend to keep the number of gametocyte carriers at a very low level. This may be important when these troops are residing in an area near non-immune troops.*
(2) If the Period of Absence from Heavy Risk of Infection is likely to be of Short Duration.
   (a) Continue suppressive treatment without any cessation.
   (b) Attacks treated to produce a rapid clinical cure and this treatment followed by suppression without any interval (i.e. maintenance of treatment).

C. Individuals Exposed to Constant and Frequent Infections, Reinfections and Superinfections:
(1) Immune or Salted Populations.
   (a) If much malarial sickness occurs, start moderate dosage of mepracrine suppression (this can often be stopped after a few months).
   (b) Attacks treated to produce a rapid clinical cure not a radical one.
   (c) Gametocyte therapy or light suppressive treatment sometimes necessary to prevent spread of infection to adjacent non-immune troops.

(2) Non-immune or Semi-immune Troops.
   (a) Continuous suppressive mepracrine in full doses, even if there is a break in the malaria transmission season (vide B(2)).
   (b) Attacks—Short intensive treatment to produce a rapid clinical cure, followed on immediately by continuation of full doses of suppressive treatment.

REFERENCES.