MALARIA IN MACEDONIA WITH ESPECIAL REFERENCE TO THE USE OF PROPHYLACTIC QUININE.

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Between the beginning of February and the end of April, 1917, I had occasion to examine the various units of a certain Division in Macedonia with a view to determining the proportion of men on duty who were infected with malaria. Smears from 540 men were stained and searched for parasites, and the results are summarized in Table I. Plasmodia were found in over thirty per cent of the men who had been in Macedonia during the previous summer, while the altered differential leucocyte count suggested that over sixty per cent of such men were in reality infected. Had it been possible to reckon the absentees in the Malta and Salonika hospitals, the total percentage of infected men would, of course, have been much greater.

It is interesting to note that parasites were found in nearly eight per cent of men with no history of fever; if we regard the increased hyaline count as evidence of infection, their number increases to over thirty-seven per cent.

No evidence of infection being found in recent drafts, it may be assumed that the great majority if not all the men in whom parasites were present had been infected during 1916 or earlier.

Technicalities.—The average time spent over each slide was about ten minutes, and no man's blood was examined more than once. Gametes were found in over ninety per cent of the positive slides, and schizonts were also present in a large proportion. Plasmodium vivax was the common parasite found; P. falciparum was noticed on seven occasions, P. vivax being also present in four out of the seven; P. malariae was only diagnosed once. To simplify matters, P. falciparum and P. malariae have been reckoned in the table as P. vivax.

The Results of Quinine Prophylaxis.¹

Method of Administration.—The salt employed was the sulphate, the daily dose (five to thirty grains) being given either in acid solution or in the form of tablets.

Results of Analysis.—Chemical analysis showed the drug to be pure.

Results of Administration.—The men in Groups I, II and III of Table I had been taking quinine during the greater part of 1916, and I was assured by the regimental medical officers that many were taking it at the time I made the blood films. The material summarized in Table II indicates the

¹ By quinine prophylaxis is meant the regular administration of quinine with a view to preventing the development or recrudescence of clinical malaria.
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kind of evidence available. These twelve men belonged to the same brigade, the majority coming from a regiment whose medical officer had had considerable experience of malaria in the East, and who was positive that quinine was being ingested in the doses stated. The persistent slight deafness which was such a characteristic feature in half of them would seem to corroborate his statement.

### TABLE I.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Total examined</th>
<th>P. vivax present</th>
<th>Hyaline leucocytes: 15 per cent or over in men in whom no parasites were found</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.—Macedonia, during summer of 1916; fever within three months of examination</td>
<td>300</td>
<td>120 (40 per cent)</td>
<td>89, thus increasing percentage of presumably infected men to 69.6</td>
</tr>
<tr>
<td>II.—Macedonia, during summer of 1916; fever during this period but none within three months of examination</td>
<td>93</td>
<td>16 (17.2 per cent)</td>
<td>83, thus increasing percentage of presumably infected men to 52.6</td>
</tr>
<tr>
<td>III.—Macedonia, during summer of 1916; no history of fever</td>
<td>63</td>
<td>5 (7.9 per cent)</td>
<td>30, thus increasing percentage of presumably infected men to 39.6</td>
</tr>
<tr>
<td>IV.—Drafts reaching Macedonia between September 1, 1916, and December 31, 1916; never out of Britain before; no history of fever</td>
<td>40</td>
<td>3 (7.5 per cent)</td>
<td>11, thus increasing percentage of presumably infected men to 35.0</td>
</tr>
<tr>
<td>V.—Drafts reaching Macedonia in 1917; never out of Britain before; no history of fever</td>
<td>44</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE II.

<table>
<thead>
<tr>
<th>No. of case</th>
<th>Gluchonism at time of blood examination</th>
<th>Vivax, schizonts and gametes in peripheral circulation</th>
<th>Daily dose of quinine</th>
<th>Length of time since last relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>30 gr. daily for weeks</td>
<td>1 month</td>
</tr>
<tr>
<td>2</td>
<td>Tinnitus and deafness, especially on left side</td>
<td>Yes</td>
<td></td>
<td>3 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Slight deafness</td>
<td></td>
<td></td>
<td>2 months</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>20 gr. daily for weeks</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Tinnitus and slight deafness</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>10 gr. daily for weeks</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Slight deafness</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Tinnitus and slight deafness</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>Slight deafness</td>
<td></td>
<td></td>
<td>2 weeks</td>
</tr>
<tr>
<td>11</td>
<td>Tinnitus and slight deafness</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>Slight deafness</td>
<td></td>
<td></td>
<td>1 week</td>
</tr>
</tbody>
</table>

Owing to the varying amounts of quinine ordered by the medical officers attached to the different regiments, it was possible to place 125 out of the 150 men examined during the month of February into one or other of the following groups (*vide* Table III). Whether the quinine was given in
small or large doses or not at all, seemed to make little difference either to the number of relapses or to the proportion of cases in which parasites were found; many of these men were constantly relapsing.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number of cases examined</th>
<th>Number of men in whom parasites were found</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. No quinine between attacks</td>
<td>26</td>
<td>16 (61.5 per cent)</td>
</tr>
<tr>
<td>II. 30 gr. daily</td>
<td>21</td>
<td>11 (50.2)</td>
</tr>
<tr>
<td>III. 20 ,, ,,</td>
<td>9</td>
<td>6 (66.6)</td>
</tr>
<tr>
<td>IV. 15 ,, ,,</td>
<td>6</td>
<td>4 (66.6)</td>
</tr>
<tr>
<td>V. 10 ,, ,,</td>
<td>48</td>
<td>22 (45.8)</td>
</tr>
<tr>
<td>VI. 15-30 gr. bi-weekly</td>
<td>11</td>
<td>3 (27.2)</td>
</tr>
<tr>
<td>VII. 6 gr. daily and 12 gr. bi-weekly</td>
<td>4</td>
<td>3 (75.0)</td>
</tr>
</tbody>
</table>

The evidence so far considered indicates:

(1) That despite infection, a fair proportion of the men examined had — temporarily at any rate— resisted illness or got the upper hand of the disease.

(2) That a great deal of sickness due to malaria nevertheless existed in the Division, much of it being little influenced by the administration of quinine.

The figures available from French sources show an even higher degree of infection, but entirely confirm these observations. For example Garin, although he gives no details as to the number of men examined, claims that plasmodia—usually gametes—can be found in the blood of from sixty to eighty per cent of troops returning from Macedonia without a history of malaria, while Abrami states that from eighty-five to ninety-five per cent of the French Macedonian Army was attacked by malaria in spite of early and general preventive quininisation. An early and correct solution of the following problems is therefore urgently needed:

I. Is any appreciable proportion of the Macedonian Force saved illness through the administration of prophylactic quinine? If so, what proportion?

II. Is the general course of the disease ever affected by the previous administration of prophylactic quinine? If so, is the sum of such influences favourable or the reverse?

To answer these questions as they should be answered clearly demands a very exact knowledge of the conditions upon which the usefulness of the drug, both as a prophylactic and as a curative agent, depend. Unfortunately these conditions have never been thoroughly investigated on scientific lines and large gaps in our knowledge consequently exist. In spite of these drawbacks I have been tempted to analyse and draw conclusions from the data available in the literature of the subject.

2 Garin, Presse-Médicale, June 4, 1917.
3 Abrami, P., Presse Médicale, March 22, 1917.
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I.—Is any appreciable proportion of the Macedonian Force saved illness through the administration of prophylactic quinine? If so, what proportion?

The question will be considered under the following headings:
(a) General considerations followed by an analysis of the available statistical evidence.
(b) The different methods of giving prophylactic quinine.
(c) The rôle of suggestion in quinine prophylaxis.
(d) Conclusions.

(a) General Considerations Followed by an Analysis of the Available Statistical Evidence.

Altogether I had access to some two hundred original articles, reports of medical societies, etc., in which the question of quinine prophylaxis was either dealt with or discussed. Nearly all of them were written in English, French or German, and all—with one exception—were published between the discovery of the malaria parasite in 1880 and the present time. 52.2 per cent of authors gave no details of their personal experience, while only 16.9 per cent made use of controls. Table IV gives an idea of the opinions expressed by these different writers, no less than eighty per cent of whom were in favour of quinine prophylaxis.

<table>
<thead>
<tr>
<th></th>
<th>In favour of quinine</th>
<th>In favour of quinine with reservations</th>
<th>Against</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statistics</td>
<td>134</td>
<td>27</td>
<td>40</td>
<td>201</td>
</tr>
<tr>
<td>Statistics but no controls</td>
<td>65</td>
<td>21</td>
<td>20</td>
<td>106</td>
</tr>
<tr>
<td>Statistics with controls</td>
<td>26</td>
<td>6</td>
<td>8</td>
<td>34</td>
</tr>
</tbody>
</table>

The majority of these papers were, however, devoid of interest. No doubt a large number of writers were unfavourably influenced by the difficulties in the way of controlling their results and realized the impossibility of appreciably increasing our knowledge in the absence of such controls. Be this as it may, the difficulties in the way of experimental research have unfortunately brought extremists to the fore, and such statements as the following are scattered throughout the literature. "The whole trend of recent inquiry and the results of clinical experiment have been to show that at the present day more than ever before, the scientific administration of quinine is established as a measure of very great value and that it is indispensable in the general prevention of the disease." 4 "Quinine has its position in relief and cure, but in sanitary administration it has none." 5

In such controversial subjects as the one under discussion, when extreme views are expressed in the absence of adequate evidence, the truth usually lies between the two extremes. Knowing as we do that resistance to malarial disease is considerably greater in the inhabitants of malarial countries than it is in immigrants from non-malarial ones, it would seem natural to suppose that, other things being equal, the benefit derived from the use of prophylactic quinine varies directly as the resistance of the individual taking it—in other words, the greater the resistance the better the statistics.

The truth of this theory can only be tested in the present state of our knowledge by analysing the statistical evidence from different countries, taking care to differentiate between the natives of such countries and immigrants.

This has been accordingly done in Tables V to VIII.

Analysis of Statistical Evidence from 1880 to Present Time.

TABLE V.—Countries Bordering on Mediterranean Basin.

<table>
<thead>
<tr>
<th></th>
<th>In favour of quinine</th>
<th>In favour of quinine with reservations</th>
<th>Against</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistics but no controls</td>
<td>16</td>
<td>0</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Statistics with controls</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>1</td>
<td>1</td>
<td>35</td>
</tr>
</tbody>
</table>

All thirty-four papers in favour of quinine prophylaxis deal with the question in so far as it affects the permanent inhabitants of the respective countries; the single paper against deals with temporary inhabitants, viz., the French Army in Macedonia.

TABLE VI.—Africa, Excluding the Mediterranean Area.

<table>
<thead>
<tr>
<th></th>
<th>In favour of quinine</th>
<th>In favour of quinine with reservations</th>
<th>Against</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistics but no controls</td>
<td>13</td>
<td>1</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Statistics with controls</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1</td>
<td>5</td>
<td>21</td>
</tr>
</tbody>
</table>

One of the four papers in which controls were used deals with natives and is in favour of quinine prophylaxis; the remaining three deal with immigrant whites—one paper being in favour and two against.

TABLE VII.—Southern Asia.

<table>
<thead>
<tr>
<th></th>
<th>In favour of quinine</th>
<th>In favour of quinine with reservations</th>
<th>Against</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistics but no controls</td>
<td>14</td>
<td>1</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Statistics with controls</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>1</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

Three out of the nine papers in which controls were used deal with natives and are in favour of quinine prophylaxis. The remaining six deal
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either with immigrants or with partly immigrant populations such as coolies on rubber plantations; two were in favour of quinine prophylaxis, four against.

<table>
<thead>
<tr>
<th>TABLE VIII.—NORTH AND SOUTH AMERICA, INCLUDING WEST INDIES.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In favour of quinine</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Statistics but no controls</td>
</tr>
<tr>
<td>Statistics with controls</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

One out of the three papers in which controls were used deals with natives and is in favour of quinine prophylaxis; the other two deal with immigrants and are against.

A study of these tables reveals the existence of a state of affairs very different to what might have been anticipated from merely glancing over the opinions of the various writers summarized in Table IV, especially when we remember that controlled results are the only results of any scientific value. When controls were used and natives of the respective countries investigated, no less than twenty-three or 100 per cent of workers were in favour of prophylactic quinine. When controls were used and immigrants dealt with, only three out of eleven or 27·2 per cent were in its favour. The evidence available would therefore seem to justify the enunciation of the following law: “Other things being equal, the natives of malarial districts derive more benefit from quinine prophylaxis than immigrants from non-malarial ones.”

Let us now attempt to estimate the real value of quinine prophylaxis to the natives of such districts.

An attempt to estimate the real value of prophylactic quinine to the natives of malarial countries in the Mediterranean Area.—We have seen that all the available statistical evidence is in favour of administering prophylactic quinine to the inhabitants of Mediterranean districts in which malaria is endemic. What does this really amount to? Celli, one of the best known of the Italian workers, thus expresses himself: “The daily use of quinine is as necessary as daily bread during certain months.”

“He who takes quinine every day and therefore has always a supply of quinine in the blood-stream, can undergo with impunity inoculations of blood full of malarial parasites and can expose himself with little or no danger to the bites of infected mosquitoes.”

One might almost conclude from this that the Italian with a little quinine in his pocket was in a position to snap his fingers at malaria under the most unfavourable conditions. Yet a little later the following analysis of very extensive clinical material was published by the same author:

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7 Celli, cited by Henson, “Malaria,” Henry Kimpton, 1913, 186.
N.B.—This Table is reproduced by several authors.

TABLE IX. (TAKEN FROM CEILLI).

<table>
<thead>
<tr>
<th>Mosquito prophylaxis + quinine prophylaxis</th>
<th>Symptoms in 1·75 per cent of cases or 1 in 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mosquito prophylaxis only</td>
<td>2·5</td>
</tr>
<tr>
<td>Quinine prophylaxis only</td>
<td>20</td>
</tr>
<tr>
<td>No protection</td>
<td>33</td>
</tr>
</tbody>
</table>

Clearly the quinine given produced some effect, but compared with the results obtained by mosquito prophylaxis, its action was almost negligible.

The brothers Sergent, who have investigated the subject for many years in Algeria, seem less enthusiastic than they used to be. The last paper I have seen gives details of the quinine given to native children in 1910. One of their tables is reproduced, and the authors content themselves with the observation that all methods give appreciable results:

TABLE X.—TAKEN FROM SERGENT (E. AND E.).

<table>
<thead>
<tr>
<th>Dose of quinine</th>
<th>Improvement</th>
<th>No change</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>0·2 grm. daily</td>
<td>19 (5·5 per cent)</td>
<td>315 (83·5 per cent)</td>
<td>7 (2·02 per cent)</td>
</tr>
<tr>
<td>0·6 , every three days</td>
<td>38 (9·7)</td>
<td>300 (80·4)</td>
<td>16 (4·8)</td>
</tr>
<tr>
<td>0·6 , every six days</td>
<td>5 (0·8)</td>
<td>230 (90·5)</td>
<td>21 (8·7)</td>
</tr>
</tbody>
</table>

These Italian and North African results are not very impressive, especially when it be remembered that we are dealing with the only type of case in which a consideration of the general statistical evidence led us to suppose that really striking benefit would be uniformly attained, viz., natives who have presumably inherited and acquired a certain amount of immunity against the parasites of their own country.

(b) THE DIFFERENT METHODS OF GIVING PROPHYLACTIC QUININE.

The following are the two methods usually employed:

(1) A small daily dose—five grains, for example.

(2) A larger quantity—usually fifteen grains, taken on two consecutive days at intervals of from a week to ten days.

The advocates of method No. 1 claim that quinine taken in this way is always circulating in the blood, and object to No. 2 because it leaves the individual defenceless for several days owing to the rapid excretion of the quinine absorbed.

The partisans of method No. 2 maintain that by giving quinine in this manner the curative effect of the drug is not interfered with; but that the use of No. 1 may lead to the production of quinine-proof strains of parasites. I have searched the literature but can find no evidence of one method having any appreciable advantage over the other.

It is interesting to note that in Italy, Greece, and North Africa, three
to six grains daily is the ordinary dose employed, and larger quantities are not usually supposed to give any better results. On referring to Table III we notice that, on the whole, the smallest percentage of cases was diagnosed in those who were taking least quinine. The possible significance of these facts will be considered later.

(c) The Role of Suggestion in Quinine Prophylaxis.

In quinine prophylaxis, as in all forms of medical treatment, the personality of the physician is not without influence; while the extent of his confidence in the treatment proposed can usually be gauged by the patient with considerable accuracy. These considerations explain to some extent the ephemeral success of many new drugs and methods of treatment. Traces of a similar process can be found in the history of quinine prophylaxis. Laveran,10 for example, in his book on malaria, published in 1898, comments on the fact that the English, who previously wrote so much in favour of prophylactic quinine, seem to have got tired of it.

The psychological aspect of malaria prophylaxis has received considerable attention from American writers, several of whom regard the cooperation of the public as essential, and agree that no means of stimulating its curiosity and of keeping its sympathy should be neglected.11 and 12

In Macedonia the French authorities advertise the merits of quinine by means of humorous coloured posters and picture post cards, which must go far towards reconciling the "poilu" to his daily dose. In Algeria the brothers Sergent have initiated the use of pink tablets containing three parts of sugar and two of quinine bihydrochloride, and state that these are everywhere accepted by the natives with the greatest alacrity, in marked contradistinction to their attitude towards the classical method.

These things are really worth bearing in mind, and the striking possibilities of suggestion are vividly brought home to one by the following incident, related in all seriousness by Henrot.13 "Dr. Nouat, head of the Military Hospital, Calcutta, was consulted by the Governor of Bengal as to the best way of protecting messengers against malaria. So many died from pernicious malaria as a result of the unhealthy country they had to cross, that messengers had become unobtainable. Dr. Nouat, acting on a theory prevalent at the time—that infection took place via the respiratory tract—constructed respirators containing finely divided animal charcoal, and made the messengers wear them; the effect was excellent, for the messengers, although taking exactly the same route as their predecessors, ceased being ill."

10 Laveran, Traité du Paludisme, 1898.
(d) CONCLUSIONS AS TO THE EFFECT OF QUININE IN PREVENTING CLINICAL MALARIA IN MACEDONIA.

(1) Primary Malaria.—We saw in Table I that a proportion of the men exposed to the risk of infection escaped, evidently because—(a) They had never been bitten by infected mosquitoes, or (b) if infected, their powers of resistance were equal to the occasion and no clinical symptoms ensued.

To what extent had the natural resistance of these latter been reinforced by taking quinine?

Although the drug must have been the decisive factor in a few cases, the previously considered evidence points to their number having been very limited. No matter what disease we take, a proportion of any population is always more or less refractory. Moreover, malaria may be a very chronic condition, and the presence of parasites in the blood of people who have never developed symptoms, and who have never taken quinine, is perfectly well known. As Bass says: "No doubt many people get infected without ever knowing anything about it; others infected under similar conditions may be ill and in some cases die." Further, the absence of symptoms in such apyrexial carriers is no guarantee of permanent immunity; in many cases all that is needed to produce an attack is such slight lowering of vitality as is produced for example by a chill, a surgical operation, or a broken bone.

(2) Recurrent Malaria.—I have come across no evidence which leads me to suppose that quinine is any more efficient in preventing relapse than it is in aborting the initial attack (vide Tables II and III).

II.—Is the general course of the disease ever affected by previous quinine prophylaxis? If so, is the sum of such influences favourable or the reverse?

The matter will be discussed under the following headings:

(a) The clinical evidence and its significance.
(b) The mode of action of quinine in malaria both as a prophylactic and as a curative agent.
(c) Conclusions.

(g) THE CLINICAL EVIDENCE AND ITS SIGNIFICANCE.

The following examples are taken from the literature of the subject:

(1) Celli states that both doctors and patients are unanimous that daily prophylactic quinine very frequently aborts primary infections, notably diminishes relapses, and prevents cachexia.

(2) So far back as the American Civil War the responsible medical authorities state that men were saved from attack and preserved in perfect health for the time being by the use of prophylactic quinine, but

16 "The Medical and Surgical History of the War of the Rebellion," 1888, iii, 165.
that the method was abandoned owing to the shortage of quinine and to the eventual sickness of such men.

(3) Neiva (Brazil) who was in charge of 3,000 men in a highly malarial district found that to obtain the same therapeutic effect, the dose of quinine had to be increased in proportion to the length of exposure to infection.\textsuperscript{17}

(4) Bell (Panama) states that men who were receiving the drug, in comparison with those who were not, under otherwise identical conditions, furnished fewer cases in the proportion of three to four; that such men were, however, more refractory to treatment, had a more prolonged convalescence and relapsed more frequently.\textsuperscript{18}

(5) Stitt\textsuperscript{19} is of the opinion that quinine in reasonable doses has little or no effect, while those who take it are less amenable to its curative action and relapse more frequently than those who only take the drug at the time of an attack; he also maintains that quinine prophylaxis does not prevent either anaemia or splenic enlargement, while Jacobson\textsuperscript{20} goes so far as to say that although symptoms may be masked for a time, the actual damage is as great as though no quinine had been given.

(6) We have seen that in Macedonia quinine alone is quite unable to prevent malaria, while very large doses have to be given in many cases to obtain clinical amelioration. Only a few weeks ago at a meeting of the Society of Tropical Medicine and Hygiene, a paper was read by Sir Ronald Ross in which details were given of various intensive forms of quinine treatment in chronic cases of malaria invalided from Macedonia. No matter how big the dose or what route was chosen for its administration, frequent relapses still occurred.

Comment: After studying this and similar evidence, we are bound to admit that the general course of the disease may be adversely influenced by the previous taking of quinine. How is such a thing possible and why do different observers get such remarkably discordant results? The answer to the last question will be considered first.

\textit{Why does Quinine give such Variable Clinical Results?} — Under ordinary circumstances the key to the problem undoubtedly lies in the constitution of the patient and in his state of health both at the time of infection and subsequently. We know that under good social conditions intermittent malaria tends to cure itself both temporarily and permanently, and that whether quinine be given or not, the temperature returns to normal in a few days. If only a little outside help is required to change the balance in favour of the patient, good hygienic conditions, an enthusi-

\textsuperscript{17} Neiva. Cited by Hudleston, \textit{Journal of the Royal Army Medical Corps}, London, 1913, xxi, 320.


astic physician, and a little quinine will suffice either to definitely cure the individual, or at any rate to prevent his relapsing for a considerable time in the absence of reinfection. If on the other hand the resistance of the patient falls short of this, no marked benefit will result.

We have just seen that clinical evidence favours the view that the course of malaria may be unfavourably affected by the previous taking of quinine. How can this occur and what is the mechanism of the process?

Discussion of the Probable Mechanism.—We have seen that under relatively favourable conditions a small daily dose of quinine tends to prevent clinical malaria or at all events to lengthen the incubation period. This, however, cuts both ways, and should an individual run the risk of being frequently infected, the tendency will be for him to receive more massive doses of sporozoites as the result of taking prophylactic quinine. Can we wonder if his malaria is of a severer type when it does develop? It is universally assumed that the sporozoites resulting from conjugation in the insect host possess a greater potential capacity for mischief in the vertebrate host than merozoites derived from many generations of asexual multiplication. We know that a European in the Tropics who stays out at night and is generally careless with regard to mosquito prophylaxis is much more likely to suffer from and to be eventually invalided home with chronic malaria than the individual who is careful in these respects. Even experimental evidence is not altogether wanting, for experiments on proteosoma infections in sparrows are said to show that the severity of the disease largely depends on the dose, that is to say on the number of sporozoites inoculated.21

We are now in a position to appreciate the inadvisability of giving prophylactic quinine over long periods, and to realize that the severity of malaria in Macedonia has been undoubtedly increased in some cases by previous quinine prophylaxis.

(b) The Probable Mode of Action of Quinine in Malaria.

(1) As a Prophylactic.—"Quinine differs from most other important alkaloids in acting not on some specialized form of living matter, but on the general nutrition of almost all forms of protoplasm. Experimental evidence indicates that a number of ferments act more vigorously in very dilute solutions of quinine, while their action is retarded by larger quantities." 22 It is possible, therefore, that the lytic action of human plasma on malarial parasites is increased when quinine is present in suitable concentration. It is equally possible that too great a concentration of quinine retards this activity; also that the long continued administration of the drug sets up a tolerance to its presence which necessitates an increase of concentration to get the original effect.

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We have previously noted that certain doctors in Mediterranean countries regard 0·2 gramme (about three grains) daily as sufficient; also that the few cases I had the opportunity of examining in Macedonia appeared to justify the view that a maximum daily dose for prophylactic quinine exists and that it is not a very big one. It is also possible that the mechanism about to be considered is not without influence.

(2) The Action of Quinine as a Curative Agent.—Barlow, as the result of experimental work, thinks that quinine in therapeutic doses does not directly destroy the plasmodium, but tends to poison infected red blood corpuscles in such a way that they are more easily acted upon by the excretory products of the parasite. This results in its liberation before segmentation has taken place and facilitates its destruction. Gametes escape because their less active metabolism does not liberate sufficient toxin to destroy even the quinine-poisoned cell.23

Comment.—This explanation is in harmony with the facts. We know, for example, that quinine given at the beginning of an attack of intermittent malaria, does not appreciably influence the train of clinical events but tends to prevent subsequent attacks. It would seem to do this by poisoning infected red corpuscles and accelerating their disintegration, thus making the conditions less favourable for the multiplication of the parasite, which is unlikely to be present in sufficient numbers to produce symptoms when the next attack is due. The functioning of this mechanism would evidently give the resisting powers of the individual time to rally. Should his vitality be insufficient to dispose of all the plasmodia the metabolism of the survivors may be assumed to slow down, and even very large doses of quinine may be unable to poison the red cells sufficiently for the parasitic toxins to destroy them with sufficient speed, the plasmodium reacting by slowing its metabolism still further. In many cases it successfully avoids extermination, and in the event of the host’s vitality being sufficiently lowered a relapse occurs.

In severe and chronic cases resulting either from massive infection or from the feeble resisting power of the individual or from a combination of the two, large doses of quinine are usually given over long periods; according to the above theory the poor results obtained would be largely due to an increased tolerance of the red cells for quinine.

(c) Conclusions.

Both clinical and theoretical considerations compel us to admit that the general course of the disease may be noticeably affected by the previous taking of quinine, and that the sum of such influences is frequently unfavourable. So far as the Allied Armies in Macedonia are concerned, there is every reason to suppose that quinine taken daily over

periods of many months has increased the severity and chronicity of the disease in a certain proportion of cases. Taking one thing with another the available evidence indicates that, in Macedonia at any rate, the disadvantages of quinine prophylaxis outweigh the advantages.

GENERAL SUMMARY OF CONCLUSIONS.

(1) Small doses of prophylactic quinine, not too long continued, are of proved utility to the natives of malarial countries, both in the absence of anti-mosquito measures, and when such measures are incomplete.

(2) Quinine may be given with advantage to immigrants under the following conditions: (a) During short journeys when conditions with regard to mosquito prophylaxis are less favourable than usual. (b) An occasional dose after an unusually tiring day. (c) Nervous people may be advised to take an occasional course as an additional precaution in spite of efficient mosquito prophylaxis.

Speaking generally, it may be stated that quinine prophylaxis is usually a bad investment for immigrants in the absence of protection against mosquito bites; taking one thing with another, the practice would in their case seem to be little more than a pious fraud which has been perpetuated from one generation to the next, simply because public opinion throughout the world has never been sufficiently enlightened to encourage the working out of the problem on scientific lines. A few well planned experiments, carefully and simultaneously conducted in several countries, and these conclusions might have been reached many years ago. We know the experimental method to be at the bottom of all scientific and industrial progress, yet we refuse to admit its very obvious utility in Preventive Medicine. The following observation applies only too literally to the subject under discussion: "En dehors des sujets dont le contrôle expérimentale est facile, bien peu d'opinions s'appuient sur la logique rationnelle. Sur l'interprétation de faits au fond assez clairs, mais que n'étaient pas des expériences suffisamment tangibles, le désaccord est complet." 24 Surely this lamentable state of affairs cannot continue much longer? The experimental evidence exists, but unfortunately its neglected fragments lie embedded in a very extensive literature, much of which is of little value owing to lack of detail and to the impressions of the writers being uncontrolled by clinical experiment.

APPENDIX.

Although the difficulties in the way of efficient mosquito prophylaxis in non-immune armies operating in highly malarial countries are undoubtedly very great, the failure of quinine prophylaxis shows that more serious efforts will have to be made in order to overcome them. A few methods of procedure are therefore mentioned and their value briefly discussed.

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A.—The Destruction of Mosquito Larvae.

(1) Subsoil Drainage.—Everyone agrees that this is the ideal method. Unfortunately finance and labour difficulties militate against its general adoption. In Panama, where both money and labour were available, this method was little used, owing to the engineering works constantly interfering with the drains.

(2) The Oiling of Surface Water.—In Panama, the system of oiling seems to have been perfect, the whole area for about half a mile round all dwelling places being oiled once a week so thoroughly that all mosquito larvae were killed. The method is obviously a good one when sufficient oil can be obtained.

(3) The Piping of Streams.—In ravine country when mosquitoes breed in the pools, associated with fast running but temporary streams, such streams may be piped with advantage within half a mile of camps.

B.—Mechanical Prophylaxis Against Mosquito Bites.

In countries where the reduction of mosquito larvae is difficult, the importance of mechanical prophylaxis can hardly be exaggerated. The question will be briefly considered under the following headings.

(1) The Screening of Dwellings.—In the Canal Zone, all houses occupied by Americans had double doors, the windows being protected with copper-bronze screens, eighteen mesh to the inch. Crenstein concludes that properly screened dwellings alone can be depended upon to reduce by at least one-third the malaria incidence in a locality where malaria is endemic.

(2) Net Prophylaxis.—Stott and others have emphasized the great value of supervised net prophylaxis for soldiers.

(3) Veils and Gloves with Gauntlets.—These have been employed on sentry duty, etc. If properly used such methods should be fairly effective, but adequate supervision is obviously difficult or impossible.

(4) Essential Oils.—Oil of citronella, etc., either pure or in the form of ointment, has been tried for men on night duty, but without much success. According to Celli and others such methods have a very restricted action.

(5) The employment of African or Greek troops for sentry duty and all forms of night work during the summer and autumn months would seem to be worthy of serious consideration. After going carefully into the matter, the advantages might be found to outweigh the disadvantages.

(6) The last but certainly not least important method is the education of officers and men, as to the habits of the mosquito, and the means of avoiding infection. Pamphlets, posters, lectures, lantern slides, cinema films, all have their place according to circumstance and opportunity.

In conclusion I should like to thank my brother, Captain H. A. Treadgold, R.A.M.C., for valuable assistance.

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1 All these writers give some account of their experience with prophylactie quinine.
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