THE PROPHYLAXIS OF MALARIA.

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AND

Captain J. WARNOCK.
Royal Army Medical Corps.

PART I.

By Colonel G. T. RAWNSLEY.

In the Practitioner for the month of October, 1917, the interesting statement appears that Mitzmain¹ has carried out an important investigation for the United States Public Health Service on the problem whether the mosquito or man is the winter carrier of the malaria parasite. Amongst his conclusions are:

1. Only the adult female mosquito of anopheles hibernates.
2. Anophelines were found negative for malarial parasites in winter.
3. Man was largely infected with the malaria parasite and about one-fourth (24.8 per cent) of the human carriers harboured gametocytes.
4. Three infected Anopheles quadrimaculatus were found in the houses of gametocyte carriers during May 15 to 26; previously thereto 1,189 specimens were negative.

The conclusion was thus arrived at that man is the sole winter carrier.

So far no other forms of animal life, except man and the anopheline mosquito, have been found by investigators to be carriers of the malaria parasite.

If we admit the accuracy of these statements, the lines indicated for the prophylaxis of malaria resolve themselves into the destruction of the parasite in man and the destruction of the female anopheline mosquito which alone with man is a harbouer of the malarial parasite.

It would appear therefore the best way to attain this end, as far as man is concerned, is by carrying out the necessary treatment, in a country where there is a malarial and a non-malarial season, in the winter months. The reasons which lend support to this view are:

1. There is a smaller incidence of malaria, primary cases being absent.
2. Reinfections are non-existent owing to inactivity of the mosquito.
3. If the major part of the population can be freed from the parasite, when the next malarial season starts fewer carriers of infection are present. If the treatment is begun sufficiently early relapses will indicate

who are carriers and who are not, and it should be easy in an army to
remove those who are a source of danger by sending them out of the
country before the onset of the summer and the period of renewed
mosquito activity.

The prophylactic measures adopted in this army were as follows:—

(1) In 1916:—

(a) Prophylactic quinine was given in five-grain doses twice weekly,
usually on two consecutive days. It was quite useless to prevent a very
high occurrence of malarial fever.

(b) Pieces of netting about one yard square were used to cover the face,
but not being mosquito-proof were naturally ineffectual. Subsequently
the size was increased to six feet by four feet, and in places where they
could be used hospital pattern nets were issued.

(2) In 1917:—

(a) Prophylactic quinine has been given in varying doses: ten grains
twice weekly on Thursdays and Sundays, every other day, four days
weekly and every day. In fifteen-grain doses daily and in twenty-grain
doses daily. These doses have all failed to confer prophylaxis, in fact,
I look upon the larger doses as positively dangerous. The smaller dose
probably does not as a rule check pyrexia, and so the man reports sick for
fever, his disease is recognized and he comes early under effective treat­
ment; but the larger amounts, that is a dosage of over and above ten
grains twice weekly, have in my experience in a very large number of
cases fulfilled the anti-pyretic action of the drug without destroying the
malarial parasite. In many regiments treated in this way we were lulled
into a sense of false security by the absence of pyrexia and later on many
men who had never reported sick were found with enlarged spleens,
anæmia, palpitation and all the symptoms of malarial cachexia. Thus by
these methods the men became a source of danger in spreading infection,
and the quinine instead of having a prophylactic effect had exactly the
opposite, as it failed to destroy the parasite, and so the man became
a gametocyte carrier capable of infecting mosquitoes. Many of the units
-treated with doses of quinine over ten grains twice weekly were the worst
sufferers from malaria this year. I do not consider such doses have any
effect on making the parasite quinine-resistant, but my experience is that
the strength of the quinine solution in the blood is not sufficient in the
doses aforementioned to destroy the parasite. Later on in this paper I
shall give further reasons for this opinion.

(b) A bivouac mosquito net was used. This certainly afforded large
protection and was an undisputed factor in the prevention of malaria. An
improved type is being adopted for 1918.

(c) Head net veils and gloves for men on night duty. These were not
popular; men complained of difficulty in seeing and of handling their arms
and in many cases they were discarded.

(d) Repellant ointment is undoubtedly useful if it is replaced very
frequently during the hours men are exposed on night duty.
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(e) Other anti-malarial measures having for their object the destruction of the mosquito.

In 1916, owing to the advanced state of the season, when we took over our present front little was done in this respect, but this year extensive drainage, canalization, oiling, clearing of brushwood, scrub and rank vegetation and burning of grass, etc., in the vicinity of camps, have been carried out with undoubtedly good results.

(f) Pitching camps on as high ground as possible and away from known malarial sites.

The result of these methods is shown by a comparison of the average daily sick rates for all causes per month as under for the same two Divisions. Malaria practically only affects these rates:

<table>
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<th>Month</th>
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<td>November</td>
<td>0.25</td>
<td>0.34</td>
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The slightly higher rates for October and November, 1917, are due to the fact that in 1916 all malarial cases were evacuated from the country, whereas in 1917 they have been treated here, therefore these rates include a higher proportion of relapses. But satisfactory as these results are it appeared to me that more might be done, and with this end in view I considered the advisability of putting troops on a much higher dose of daily quinine, viz., thirty grains daily. Captain D. Thomson, R.A.M.C., in his paper in the Journal of the Royal Army Medical Corps stated this should be given in hospital, keeping the man in bed the first week, up in the ward the second week, and taking gentle exercise out of doors during the third week. But hospital treatment except for men with high temperatures or otherwise needing admission would not be feasible in the case of large numbers of men suffering from chronic malaria in an army in the field. I therefore received permission to start a small camp for 100 men; these men were under ordinary conditions except that they performed no large amount of work. They went for walks and did all the fatigues of their camp. The treatment given was thirty grains of quinine in mixture daily as follows:

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B| Quinine sulph. ... ... 10 gr. or, Quinine bisulph. ... 10 gr.
| Acque ... ... ad 1 oz. Acid hydrochlor. dil. ... q.s.
| Acid sulph. dil. ... ... q.s. Acque ... ... ... ad 1 oz.
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Thrice daily, further well diluted with water, within five minutes of each meal, i.e., breakfast, dinner and tea. An iron, arsenic and quinine tabloid was also given at the same time, the composition of which is:

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B| Iron hypophosphite ... ... 2 gr.
| Acid, arsenious, B.P. ... ... ½ dr.
| Quinine bisulphate ... ... 1 dr.
| Strychnine sulphate ... ... ½ dr.
| Saccharine, B.P. ... ... ½ dr.
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G. T. Bawlsley, R. A. Cunningham and J. Waynock

The clinical results were rapid and exceeded all expectations, there were no untoward symptoms, such as deafness, altered vision, etc., and from the rapid disappearance of anaemia and the healthy colour which appeared in its place, it was easy to pick out new arrivals from those who had been some few days in camp. Even after five days the improvement was marked.

Being satisfied with the success of this treatment and that it had no ill effects on the men, it was resolved to continue treatment in other cases and under different conditions; in the one instance fifty-one men who were known to be badly infected with malaria were camped near a casualty clearing station and kept as nearly as possible under service conditions, doing route marches and fatigues, and about the same amount of work as they would have done in the front line. They lived in bivouac tents with mosquito nets, and during a great part of their stay the weather was very variable, being wet with cold winds, conditions which should have been favourable to chill and consequent malarial relapse. While here advantage was taken of the proximity of a Bacteriological Laboratory and an Ophthalmic Centre, for the purpose of carrying out observations appertaining to the state of the blood and the condition of their eyes.

Two medical officers, Captain W. H. Peacock, R.A.M.C., and Captain T. H. Comerford, R.A.M.C., gave most valuable assistance in closely watching and supervising the progress of treatment. No unfavourable symptoms were observed in any of these men by either of these officers, nor by myself as the result of frequent inspections. No defects of vision or hearing were observed. Anaemia soon vanished, the haemoglobin rose in the blood and parasites disappeared microscopically, the spleen went down in size and the men became robust, vigorous and active. Nearly all the men increased largely in weight and previous results were confirmed. These fifty-one men were given no quinine for first few days of their stay at the casualty clearing station before treatment was commenced and fifteen of the number suffered from relapses of malarial fever and in many the parasite was found in their blood during this time. They took bichloride of quinine.

In the other instance a company of a battalion was placed, at my request, on the same treatment by Lieutenant-Colonel R. A. Cunningham, R.A.M.C., whose report is added (Part II). This company remained doing full duty in the trenches, and subsequently, at the expiration of their tour there, in the support line. They took the treatment as will be seen without any unfavourable symptoms, but on the contrary with marked and beneficial results.

Two men out of the original fifty-one of the first observation had to remain on under treatment; one man still had the malignant parasite in his blood, but after a further period of treatment this had disappeared microscopically; the other man was suffering from an irregular atypical pyrexia, no parasite being found in his blood, but on the cessation of quinine
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the malignant parasite was found in moderate numbers. No other man out of this number nor amongst the cases of the second observation treated by Lieutenant-Colonel Cunningham has so far had a relapse.

Allusion may now be made to the opinion previously expressed that smaller doses of quinine up to twenty grains do not make the parasite quinine-resistant. The result of the treatment of thirty-grain doses daily was followed by immediate, very rapid and marked improvement in men well dosed the whole season with quinine; the blood tests showed by the early disappearance of the parasite and the rapid rise in the hemoglobin that no powers of quinine resistance had been conferred on the parasite when sufficient and effective doses of the drug were given, and one would not have expected to attain these results so speedily had such been the case, and the credit must be given to the production of such alterations in the blood to the activity of the drug.

The course of treatment recommended and which will be further observed is to put a company of a regiment at a time on thirty grains quinine daily for a period of twenty-four days. Men after four weeks begin to suffer from quinine intolerance.

Points to bear in mind are that the mixture should be well diluted in at least an ounce and a half of water, and administered immediately after a meal—the longer interval that elapses the more chance there is of intolerance to the drug. It should be given twice daily in fifteen-grain doses morning and evening; three minims of liquor arsenicalis hydrochloricus may be added to each dose, but Fowler's solution should not be used, as this preparation in an acid solution is liable to deposit the arsenic to the bottom of the bottle and a dangerous dose of arsenic may thus be given. The tablet of iron, arsenic and quinine is also a useful adjunct to treatment in place of the liquor arsenicalis hydrochloricus in the mixture. Another precaution is that the solution should be measured in a dispensing measure-glass, and tablespoons and other such measures not employed, as inaccuracy in dosage is bound to occur.

It has been found by Lieutenant-Colonel Cunningham, R.A.M.C., that healthy men stand this dosage as well as, if not better than, those suffering from malaria, and also in a further observation on my part; consequently the conclusion arrived at is that in very unhealthy portions of a line troops should only remain twelve days at the most and during this period should receive a daily dosage of thirty grains of quinine; this idea will be further developed during the next malarial season. Further, from a result of experience of two malarial seasons in Macedonia, my experience in West Africa, India and the West Indies is enhanced that:

1. Prophylactic quinine as now given is useless if not dangerous in the prevention of malaria, as it so frequently only masks the disease.
2. That the proper prophylactic dose is one of thirty grains daily, but this cannot be given for a longer period than four weeks.
3. That a smaller dosage of quinine does not render the parasite quinine-resistant.
Prophylaxis should aim chiefly at destroying the mosquito and its larva, and protecting man from its bites, and when man becomes infected destroying the parasite by suitable doses of quinine, especially during the post-malarial season.

In the case of troops every officer and man who has been exposed to malarial infection should undergo a winter prophylactic course. In this connexion Colonel Sir M. P. C. Holt recently told me he had the blood examined of many men in this country with no record of malarial fever and found many of them infected with the parasite.

The destruction of hibernating mosquitoes. The experience here so far is that only the female hibernates.

Larvae have also been found in the winter in Macedonia beneath the ice. Measures therefore for their destruction must also be taken.

Observations as to the effect of thirty grains of quinine daily on the blood of healthy men have also been made by Captain J. Warnock, R.A.M.C., and are included in his Report (Part III).

I am indebted to Captain H. E. Smith, R.A.M.C.(T.), for the following report on the condition of the eyes and the state of vision of the fifty-one men under observation at the casualty clearing station:

"I have concluded the ophthalmic examination of the fifty-one post-malarial cases under special quinine treatment at the casualty clearing station:—

1. The visual acuity.
2. The white and colour fields.
3. Subjective symptoms, e.g., transient obscuration of vision.
4. Ophthalmoscopic examination: (a) colour of optic disc; (b) size of vessels; (c) any other abnormality.

I have to report that there was no complaint of defective sight, no objective deterioration of visual acuity, and no evidence of change in the field or fundus in any of the cases."

One half of the men who had been treated both at the casualty clearing station and by Lieutenant-Colonel Cunningham have continued quinine in fifteen-grain doses daily, the other half have had no quinine.

The men from the casualty clearing station, with two exceptions, returned to duty with their regiments on November 15, 1917, four weeks ago. A few days before leaving, a team of eleven of these men played the casualty clearing station at football and won their match by 7 goals to 2; they played with vigour and showed no signs of distress during the game.
Malaria is an infective disease which is spread from one man to another by means of anopheline mosquitoes. Reducing the number of infected persons in a community is one of the methods of lowering the incidence of the disease. Owing to the absence of the civil population, infection in the front line area is chiefly derived from the troops themselves. If, therefore, it were possible to make a large proportion of the troops non-infective before the next malarial season begins, it would greatly assist in reducing the incidence of malaria.

With this object in view, Colonel G. T. Rawnsley, D.D.M.S., of the Corps, undertook a series of observations as to the effect of the administration of thirty grains of quinine daily for a period of from three to four weeks in permanently curing the disease, and so preventing the formation of carriers. If this treatment was to be applied as a practical measure to the whole Corps, it was necessary to prove that it could be carried out whilst the men were actually engaged in their ordinary duties with their units. At his request, therefore, I carried out a course of treatment in "X" Company, the most highly infected company in a badly infected battalion. Almost every man in the company had malaria, and as it was impossible to say which men were or were not liable to relapses, all the men in the company who were present on October 10, 1917, with one or two exceptions, were put on the treatment. Each man received 30 grains quinine daily, 15 grains quinine sulphate in solution diluted to 1½ ounces being given every morning and evening after meals. During the second week two minims Fowler's solution were given with each dose, and during the fourth week three minims. As new drafts joined the company from hospital or elsewhere, they were also put on this treatment. The total number of men who received this treatment between October 10 and November 6 for at least three weeks was 104; of these eighty-eight received it for the full four weeks.

The following figures show the results of treatment:

1. Total number of men who had the treatment for at least three weeks ... 104
2. Number of men who were sent to the Field Ambulance with fever between October 10 and November 6, whilst taking 30 grains quinine daily ... 2
   These two men were sent to the Field Ambulance within the first few days after the treatment began.
3. Number of men who were sent to the Field Ambulance with fever from the rest of the battalion (numbering about 500), between October 10 and November 6... 80
   The whole of these men had been on 10 grains daily for the last three months.

In addition to the men sent to hospital during this period, October 10 to November 6, a large number of men in the rest of the battalion had mild relapses, and were treated regimentally. Among the 104 men receiving the special treatment, only six had slight rises of temperature, and this was at the very beginning of the treatment. Three officers of
G. T. Rawnsley, R. A. Cunningham and J. Warnock

"X" Company who were not on the treatment had fever between October 10 and November 6.

From October 10 to 25 the men receiving the special treatment were in the front line, and were doing the ordinary work of the battalion—some digging, some on outpost, some wiring, etc. Two platoons were in a fort in the front line from October 14 to 25, and during this period no man in these two platoons had fever or was off duty, although each man was on outpost duty every other night, and the weather was frequently wet and cold.

On October 25 the company moved back to a camp in support, and although the day had been very wet, and the men had to bivouac on wet ground when they got to camp, no one took fever in consequence.

The men have improved very much in appearance and health, and have lost the anaemic look that they had. They are at present doing training, road making, route marching, etc., and play football with much vigour after the day's work. Many of them also took part in the regimental sports—running, jumping, tug-of-war, etc. They went back again into the front line on November 7.

During the course of treatment I saw the quinine administered, inspected every man morning and evening, felt his pulse, and inquired how he was.

In a very few cases I reduced the dose to twenty grains on account of slight buzzing and slight deafness, but it was not really necessary to have done so. In one or two cases I gave men tabloids instead of solution on account of slight indigestion. Two of the men towards the end of the fourth week of treatment complained of slight giddiness, and I stopped their quinine. Apart from these few cases all the men took the quinine without the slightest inconvenience, including fourteen men who had never had malaria.

The following are some details of the previous history of the 104 men who received the treatment:

1. Number who had been in hospital with malaria ....... 46
2. Number who had had fever, but were treated regimentally ....... 44
3. Number who had never had fever ....... 14

Total ....... 104

Details as to relapses in the ninety men who had had fever:

1. Number who had had numerous relapses previous to the commencement of the special treatment ....... 6
2. Number who had had two relapses ....... 6
3. Number who had had one relapse ....... 25
4. Number who had had no relapse ....... 53

Total ....... 90

The observation is being continued as follows:

The administration of quinine to the fourteen men who never had malaria has been stopped.

As regards the remaining 90, 2 men have gone away, which leaves 88.
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The administration of quinine to 44 of these has been stopped. The other 44 are to receive 15 grains quinine daily for one month, and then 10 grains daily for another month.

The number of relapses which occur in the first forty-four will be compared with the number occurring in the second forty-four.

A roll of the men has been made, and any case of fever which occurs among them, whether treated regimentally or admitted to field ambulance, is notified.

During the month of November seventy-two cases of malaria and N.Y.D. pyrexia were admitted to field ambulance from the rest of the battalion, and none from the men who underwent the treatment. One of the men had a slight rise of temperature on November 30, and he is being treated regimentally.

These results are exceedingly striking. In eight weeks there was practically no pyrexia among the 104 men of "X" Company, although this was the worst infected company in the battalion, while from the rest of the battalion, during the same period, nearly 150 men were admitted to hospital with malaria and N.Y.D. (pyrexia), and numerous others were treated regimentally.

There is no reason to suppose that what happened in this company as the result of the treatment would not also approximately happen in a whole battalion, a whole division, or a whole corps, if the treatment were as thoroughly and carefully carried out; and I have no doubt that if this were done the number of relapses occurring in the spring months would be immensely reduced. A roll could be kept of the men who resisted the treatment and remained carriers, and they could either be sent out of the country or kept at the base, or on the lines of communication, where the presence of carriers is not of so much importance, as there is already an infected native population there. If this were done, it would greatly reduce the number of infected anophelines in the Corps areas, and consequently lessen the incidence of malaria.

PART III.

By Captain J. Warnock.

Royal Army Medical Corps.

O. i/c Mobile Bacteriological Laboratory.

Laboratory Notes on Malaria with special reference to the treatment of a series of unselected cases.

The series of cases considered was chosen under the direction of Colonel G. T. Rawnsley. Each man had a clear past history of clinical malaria, and was so selected as to be roughly a sample of the malarially affected troops.

The treatment adopted was a continuous twenty-eight days' quinine course of thirty grains daily combined with arsenic in small increasing doses.
The usual methods of investigation have been employed throughout, and conclusions drawn from the consideration of this special series as well as from the routine examination of the many thousand specimens which the material of this army has provided.

The points considered have been:
(1) Continuous clinical records of temperature, pulse, weight, etc., among the fifty-one special cases.
(2) Untoward effects of quinine, if any, such as vomiting, giddiness, deafness, defects of vision, etc.
(3) Laboratory examinations directed to the condition of the blood and the study of the malarial parasite.

Control examinations were made in a number of "healthy" men chosen so far as could be determined from amongst those who had not had malaria and who had served only for a short period with this army.

As an introduction to the detailed account, some general observations may be made on the malarial question as it arises here.

(a) The whole natural picture of malaria has been necessarily clouded by the complication of quinine treatment.
(b) Malarial patients are often much more seriously debilitated, even after a few attacks, than the blood examination would suggest, and conversely the blood will often show an enormous number of cells invaded by the parasite with no corresponding clinical gravity of effect.
(c) All three classical types of malarial parasite have been found. The quartan parasite has been extremely rare but the benign and malignant tertian parasites have been universally prevalent and a seasonal variation has been strictly observed.

In the early months of the year, benign tertian alone was seen and gamete forms were relatively frequent; with the advance of summer however the gamete forms became less and less in evidence, but again increased in proportion with the commencement of the winter.

The malignant tertian parasite appeared about mid-July and increased in prevalence through the hotter months, declining in numbers with the autumn temperature, though still accounting for most of the severe cases until toward the end of November, when the benign parasite in "relapse cases" became again the common type.

It may be added that thick-and-thin film methods of examination have been employed, and that thin films have been found most generally useful, thick films being, however, the method of choice for the discovery of pigmented, more especially the crescent, forms.

(d) Quinine treatment and diagnosis. Malarial pyrexia is so generally reduced by moderate doses of quinine, e.g., thirty grains daily, that a temperature over 99° on the fourth day is a practical exclusion of malaria.

The response, or absence of response, to quinine treatment is therefore practically decisive from the point of view of diagnosis. This statement refers to the "ordinary case," and qualifications will be dealt with later.
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(e) Quinine in moderate doses quickly banishes asexual parasites from the peripheral circulation, so that, often after one dose, and usually after three doses of ten grains, microscopic diagnosis becomes very tedious.

The gamete forms are not so influenced, but their numbers are not generally great.

Following these general statements some detailed figures may be given of the results of the inquiry into the effects of the combined quinine and arsenic treatment carried out under more or less active service conditions.

I.—Clinical Records.—These may be shortly summarized:

(a) There was no difficulty with continuous administration of quinine, and no unpleasant effects noted beyond very slight vomiting, easily corrected, which occurred in a few cases in the fourth week of treatment.

(b) All the men looked better with two exceptions; one case (malignant tertian) will be detailed later, and the other was under special vaccine treatment for boils.

(c) An average increase of weight of five pounds was recorded. In only five cases was a decrease noted; two of these were the cases mentioned above, and the decline of the others (two pounds) was so slight as to be negligible.

(d) Cardiac response to exercise was much more healthy at the end of treatment than before.

II.—Laboratory Examinations.—Attention was directed to:

(1) Discovery of the parasite and inquiry into its reaction to quinine medication.

(2) Hæmoglobin estimations.

(3) Counts of red and white blood cells.

(4) Differential counts of white cells.

(5) Inquiry into a possible fragility of the red cells of men undergoing quinine treatment and a possible hemolytic action of the serum.

(1) The malarial parasite was discovered in nineteen out of the fifty-one cases (M.T. 6, B.T. 9, ? type 4); two of these cases were continuously apyrexial and two others only once reached 99°. In general, it may be stated that benign tertian parasites are not often found in the apyrexial period during the season of prophylactic quinine.

It has been determined, however, by a commission working under the direction of Lieutenant-Colonel L. B. Dudgeon, Consulting Bacteriologist to this army, that during the winter months a careful search will reveal the parasites in apyrexial "malarial carriers" in a considerable percentage of the cases.

In one of the fifty-one cases crescents were found up to fourteen days after commencement of quinine treatment; such a discovery of crescent parasites after the period of treatment with thirty grains daily has been a common observation.

In a second case crescents, in small numbers, were demonstrated up to forty-six days' treatment.
In no case were asexual parasites found after three days' treatment. The effect of quinine treatment in the pyrexia of malaria has already been referred to and a general diagnostic rule laid down.

Qualifications of this rule must be made, however, in the many severe cases of malignant tertian malaria which have been, throughout the autumn, far from uncommon.

Fever of four, five, or six days' duration, with occasional irregular slight rise of temperature afterwards, is a common occurrence as an almost typical eight days' chart of a "moderately severe" case here presented would show.

In addition to these more usual types of case, rarer cases of more or less continued slight pyrexia occur on which quinine treatment would appear to have very little influence.

One such case occurred amongst the special series of post-malarial cases dealt with, and a chart with details is given. In this case no parasite was discovered, in spite of very many repeated examinations both at the beginning and during the progress of treatment.

This negative consideration, and also the absence of a palpable spleen and the existence of a high leucocytic count (9,000 to 13,000), combined with the irregular pyrexia, led to the alternative suggestions of oral sepsis, enterica and tuberculosis, for all of which hypotheses diagnostic procedures were employed with negative results.

After six weeks' continuous treatment (thirty grains daily) quinine was abandoned and in five days numerous malignant tertian rings appeared in the peripheral circulation coincident with a "bilious" vomiting and a typical attack of malignant tertian fever. Quinine was then again resumed in larger doses (forty-five grains daily), the first dose being intramuscular owing to the vomiting; the condition, however, seems to have been more or less controlled, but not shortened by the treatment.

(2) Haemoglobin estimates: Figures here are restricted to the small
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series of fifty-one selected cases and the results have been extremely striking. A rapid rise in haemoglobin value was immediately obvious, corresponding with the improved general appearance and physical fitness of the men.

CHART OF CASE 26.

The average increase was fourteen per cent at the end of treatment, but the closest grouping of figures approximated to 17.5 per cent, and this may be taken as what might be termed the "expectation of improvement."

Extreme cases of thirty per cent and forty per cent increase were recorded.
Comment may be made on the fact that most of the cases at first had haemoglobin estimations of 70 to 75 per cent, while a series of normal men gave values 85 to 90 per cent.

This difference in oxygen-carrying capacity of the blood is not enough to account for the obvious physical unfitness affecting nearly the whole series examined and would suggest that the malarial organism produces its effects more by a general toxæmia than by a limited destruction of the red blood cells. That this is so is evident from the intense tissue destruction found post mortem in practically all the fatal cases, even when macroscopically, beyond enlargement in the spleen, there may be no obvious disease or cause of death.

(3) Red counts: In the special series considered, an increase parallel to the increase in haemoglobin was observed. The average increase was fourteen per cent.

White cell counts: Observations were, for the sake of comparison, made always at the same time of the day, but owing to the known normal variations actual figures are of little value. Hence general conclusions may be given to which it was found that the small special series also conformed.

In the apyrexial period counts below 3,000 or above 9,000 are not common, while 4,000 to 6,000 would appear to be the general rule.

During an "attack," a more marked leucopenia is often found, but the exceptions are so common that this can scarcely be accepted as a rule; it would appear that very low counts only occur if there is marked anaemia, while if the attack is resistant or severe a high count is more likely to be found.

(4) Differential counts of white blood cells: These estimations again made over a large number of cases have given interesting results.

The figures may be best presented by considering definite illustrative series. Only three cell types for the moment are considered.

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<th>Lymphocytes</th>
<th>Large hyalines</th>
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<td>Fifty cases of benign tertian fever during an attack and before commencement of quinine treatment</td>
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<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Series 2.</td>
<td>Fifteen cases of malignant tertian, also during attack and before quinine</td>
<td>44</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Series 3.</td>
<td>Twenty-five cases of unverified malaria, during attack and before quinine</td>
<td>58</td>
<td>24</td>
<td>16</td>
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<tr>
<td>Series 4.</td>
<td>Fifty cases of afrebrile &quot;post-malaria&quot; cases during treatment with quinine</td>
<td>45</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>Series 5.</td>
<td>Fifteen cases where malaria could be practically excluded</td>
<td>48</td>
<td>42</td>
<td>10</td>
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</tbody>
</table>
Comment on these figures as regards the deviation from the normal is unnecessary, except for the inclusion of the last series, which was strictly chosen to exclude malaria but to include men who had served for at least one summer in this country.

It will at once appear that an increased percentage of large hyaline cells is of little diagnostic value in malaria; since a similar phenomenon appears to be produced by climatic or other causes amongst healthy troops serving with this force.

The numerical differences above detailed are not the only deviations from the normal, for not only is the total mononuclear count increased, but the type of cell differs widely from that found in health. Typical lymphocytes and large hyaline cells are found, but there are also present types not seen in normal blood, but occurring in the bone marrow and the spleen. Typical myelocytes are sometimes found and large finely granular mononuclear cells suggesting gradations between true myelocytes on the one hand and polymorphonuclear cells and large hyaline leucocytes on the other. The number of these cells varies and appears to have some relation to the severity of the case. The actual number has not been noted above five per cent of the total white cell count.

A further malarial abnormality is the presence of the characteristic pigment in the large hyaline and polymorphonuclear cells. This occurrence has been looked for over a series of several thousand specimens, and while pigment in both types of cell has been occasionally seen the examples have been so extremely rare that the observation can have no value in the diagnostic sense. The conclusion, therefore, drawn from this method of inquiry has been that a microscopic diagnosis of malaria must, for all practical purposes, be based entirely on the discovery of the parasite.

(5) Inquiry into a possible quinine-induced fragility of red blood cells or haemolytic action of the serum.

That quinine treatment may damage the red cells in ordinary cases and even under special circumstances predispose to, or cause, blackwater fever has been often stated. Barret and Yorke have proved that quinine in dilution approximating to that ordinarily present in the circulating blood after administration has no haemolytic action on washed red cells.

Sampson and Edie have, in a short series of men and animals, determined the total excretion of urobilin and have hence deduced a probable haemolytic power. Their series, however, has been so short and the results so varying, that any conclusions must be uncertain.

Our examinations have been limited to thirty cases. A small but almost constant difference has been found amounting to 0.025 per cent in the strength of saline which just produced haemolysis, to this extent the series treated having less fragile cells than the series of "controls," and in the same sense the serum observations have discovered no haemolytic action, the deviations from control figures in the few cases which occurred being in the direction of protection of the cells. The numbers, however,
so far examined have been too small from which to draw definite conclusions, beyond the fact that any untoward influence of quinine in the blood, if present, must be very slight, and is probably more than counterbalanced by the conjunction of arsenic.

Summary.

For the sake of clearness, conclusions may be summarized regarding the possibilities of the standard quinine treatment.

(1) No deafness, visual defects or other disadvantages are likely to accompany or follow the administration of quinine thirty grains daily for three to four weeks.

(2) The general health and physical fitness of malarial cases so treated will markedly improve under treatment.

(3) Arsenic is a valuable adjunct to quinine in the treatment of malaria.

(4) Few relapses are likely to occur and fresh infections can be dealt with as they arise (no relapse, excluding one uncured resistant case, occurred amongst the special series treated, after four weeks of very severe weather since cessation of the treatment).

(5) The malignant tertian parasite would appear to be the most resistant type. Relapse cases occurring in the early months of the year are generally benign tertian; it is probable, therefore, that a three to four weeks' course of thirty grains daily will cure a considerable proportion of the men so treated.

(6) A possible difference in the parasite found in this country from that seen elsewhere has been often mentioned. It would seem probable, however, that the different effects produced may be due to indefinite and irregular quinine administration.

(To be continued.)