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The Intermittent
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The Intermittent Administration of Quinine in Malaria, with the Temperature as a Guide.

In the vicinity of Boston, as well as in the city itself, most physicians have observed, during the past summer, an unusual increase in the cases of malaria. It is, however, a disease of the country rather than of the city, and especially affects those who have to do with the soil. I desire to call attention to some of the points that are of practical interest in the treatment of this disease, especially to the intermittent method of administering quinine, with the temperature as a guide, and not the chill, that I have had the pleasure of introducing into this community. The bearing of this method will be made more clear if I first recall some points relating to the parasite of this disease, but I shall not attempt to consider here the various types of malaria nor the differing views of Laveran and of the Italian school concerning the parasites. More than ten years ago Laveran, then a French army surgeon in Algiers, discovered the parasite of malaria and years of careful study on his part, together with that of many other observers in various and widely-separated parts of the world, have confirmed and extended his first observations. Laveran's hæmatozoon, more generally known as the plasmodium malariae, has never been found in any other disease. It is not a bacterium, but, according to Bütschli's classification, belongs to the group of Gregarinida, order of Sporozoa, class of Protozoa. The history of these primitive animals outside of the body is at present unknown. A warm, moist soil, such as would be found in hot seasons after a rain, is followed by an increase in the number of cases of malaria, but where the marshy areas are completely submerged, there seems to be much less danger. It is thought to be carried to man both by



the air and by water. Many facts point to the latter as one source of infection.

Inside the body these haematozoa find their homes and food in the blood. According to Laveran, their minimum period of incubation is from six to ten days. They have a cycle of development and at certain stages of their growth are more and at others less susceptible to the action of quinine. Most observers think that—they penetrate the red corpuscles of the blood in which at first they occupy but a small space; they gradually enlarge, however, at the expense of the hæmoglobin until they have absorbed the endoglobular substance; segmentation takes place and the spores break out into the blood serum: the presence of large numbers of spores in the blood produces an attack of the fever; the maturing of different generations of parasites the return of the fever.

The successive development of the parasites indicates successive treatment, so timed as to anticipate the recurrence. Laveran compares such a method of giving quinine to the way in which liquids are rendered sterile by boiling. The first boiling is sufficient to kill most of the bacteria, but some spores remain. If, however, the boiling is repeated on the following day the spores, then having developed into bacteria, are destroyed. If the water is boiled a third time after an interval of twenty-four hours it is made sterile.

When an enemy such as the hæmatozoa, however, attacks the organism, it is not wholly indefensible; there are bodies normally present known as phagocytes which are capable of overcoming the enemy if it is not too numerous. To assist nature in this encounter, we should place the system in as good a condition as possible, and some cases recover after rest in bed, aided by good food. The mortality from malaria in Southern India is aggravated by the system of starvation to which the inhabitants subject themselves when suffering from this disease. But if, on the contrary, the parasites have the upper hand, rest alone is not sufficient, we must have recourse to quinine. It is a serious matter to have the blood deteriorated by the loss of an element that carries oxygen to every part of the body, and in severe cases there may be a great diminution in the number of red corpuscles within two or three days.

Dock, in his article on malarial diseases, dwells at some length upon the proper time for the administration of quinine and finally suggests the following plan "for the routine treatment of simple cases." First day, in the decline, 20 grains of quinine; second day, if necessary, 10 grains; seventh day, 20 grains; fifteenth day, 20 grains; twenty-second day, 20 grains. He also states that

instead of one large dose, three or four 5-grain doses may be given at intervals of two hours during the decline.

The result of the intermittent method of using quinine with the temperature as a guide, and not the chill, in such cases of malaria as came into my service at the Boston City Hospital last summer, will be seen below. There were eighteen cases in all, twelve tertians, five quotidians, and one of irregular type. In some instances the diagnosis was established by finding the parasites in the blood. One of the cases is interesting in this connection, as the patient was sent to the hospital with the diagnosis of typhoid fever, but an examination of the blood showed the presence of parasites and proved it to be a case of malaria. In treating these cases I gave 20 grains of sulphate of quinine in solution, when the temperature began to fall, without reference to the chill. With this treatment it is of course necessary to have the temperature taken at frequent intervals, and this was done in most of the cases every four hours. On leaving the hospital, the patients were given a prescription and directed to take the medicine on the seventh, fifteenth and twenty-second days. It was not found necessary to give quinine on the second day (see the preceding paragraph), as there was no chill after the first dose of quinine was administered, except in two cases, No. 3 and No. 15, the charts of which are not given. In these cases the fever returned on the second day, but in No. 3 the dose given on the first day was not administered at the right time; in No. 15 it is possible that this was also the case. The patients had no cinchonism while in the hospital. The intermittent method of administering quinine seems to lessen the risk of the cinchonism that is apt to follow after continuous doses; further, it leaves the beds in the hospital free, earlier for other patients and saves quinine, much less being used than in the continuous method.

The charts are numbered in the order in which the patients were received at the hospital, and I give on pages 7 and 8 the even-numbered ones, omitting, however, No. 18, as it was a very mild case. The odd-numbered charts are of the same character, but the average time in the hospital, of the patients there described, was about two days less, and the average temperature rather higher, than in the even-numbered cases. All cases were given 20 grains of sulphate of quinine in solution when the temperature was falling, without reference to the chill, and the dose was repeated on the seventh, fifteenth and twenty-second days. When this rule was followed, there was no chill after the first dose was administered while the patients were in the hospital, except in case No. 15

referred to above, nor after they were discharged, so far as I am aware. In view of further experience, it seems to me that in the forms of malaria most common here, a smaller amount of quinine, fifteen grains or less, would answer, or where it seems probable that the patient may be especially susceptible, 5-grain doses repeated once, or if no symptoms are produced, twice, at intervals of two hours, may be sufficient.

Charts 4, 6, 8, 12, 14, 16, on page 7, and charts 2 and 10 on page 8, show the effect of a *single* dose of quinine given on the decline of the temperature.

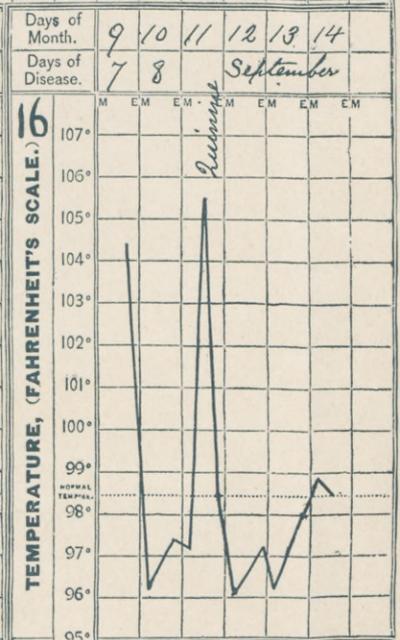
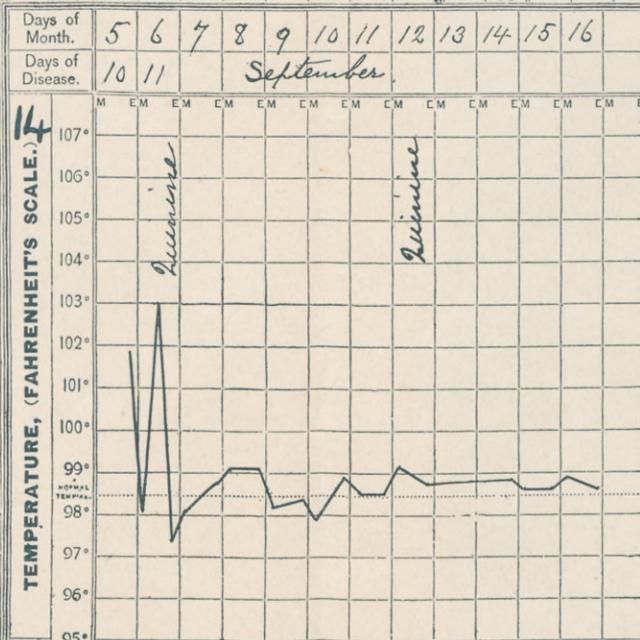
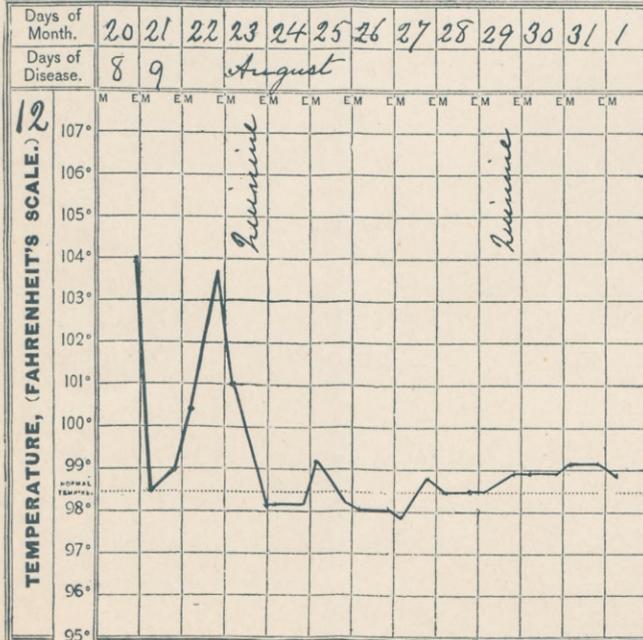
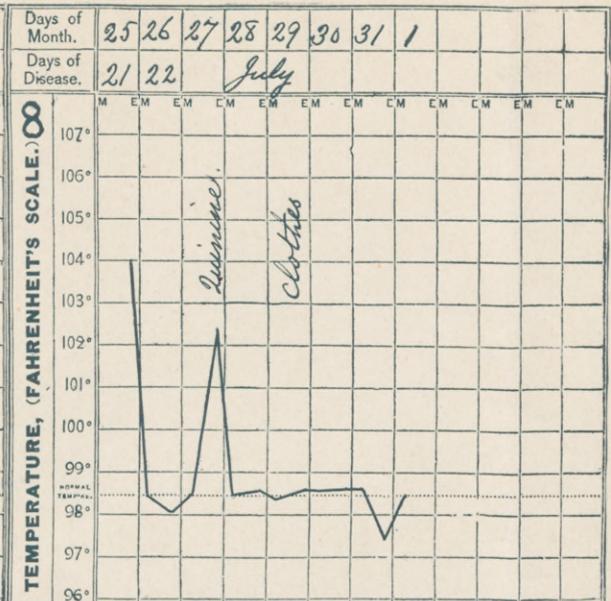
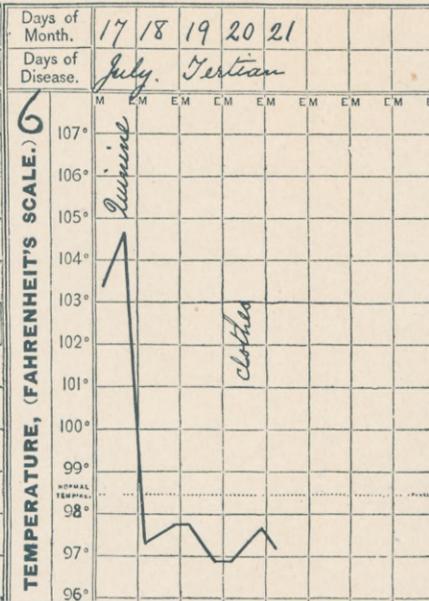
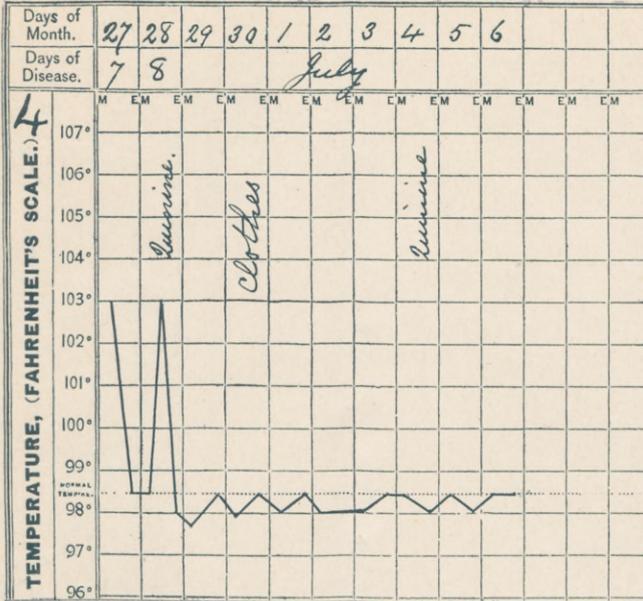
Chart 8, page 7, illustrates especially the advantage of consulting the temperature in administering the quinine, as this patient had no chill while in the hospital. He was given quinine on July 27 while the temperature was falling.

In cases 2 and 10, page 8, the intermittent method of treatment was not fully carried out, and they therefore illustrate well the importance of following the first dose by a dose on the seventh, fifteenth and twenty-second days, respectively.

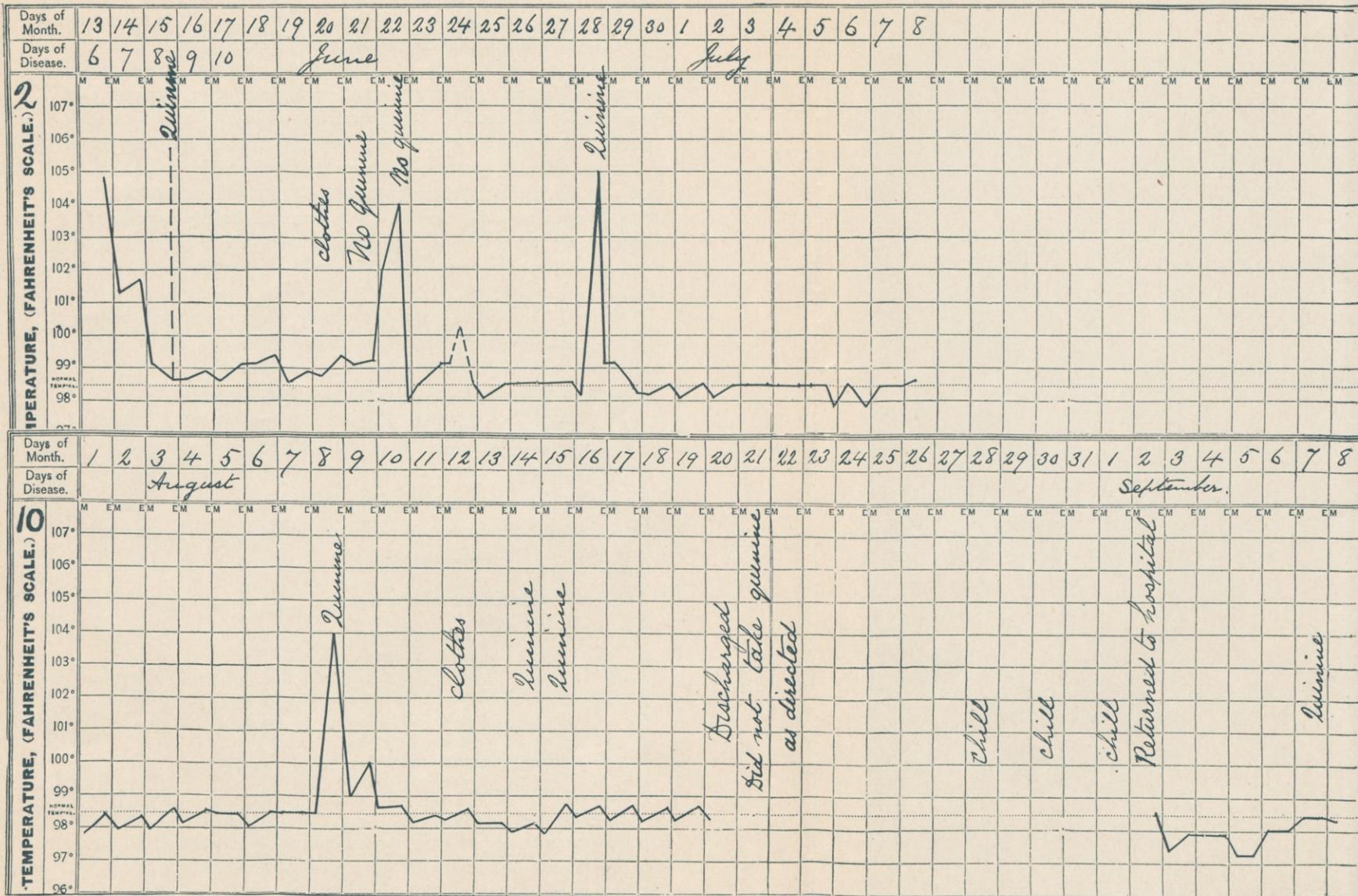
Case 2, page 8, entered the hospital June 13, 1892, and on June 15, when the temperature began to fall, quinine was administered. On June 21 the patient did not take the quinine, as she should have done, and the fever returned. On June 28 another dose of quinine was given and there were no more chills.

Case 10, page 8. J. K., 38 years old, entered the hospital August 1, 1892. History of slight malaria the preceding year and of chills every second day since July 4 of this year. From August 1 to 7, temperature normal. An examination of the blood on August 7 showed 2,880,000 red corpuscles and 40,000 microcytes, and diminished tendency to rouleaux. Hæmoglobin, 60%. Iron given. August 8, quinine was administered during the decline of the temperature, likewise on August 14 and 15. August 18, the blood was again examined and there were 3,340,000 red corpuscles and 10,000 white corpuscles. No abnormal sizes seen. Hæmoglobin, 90%. The patient was discharged August 20. After leaving the hospital he did not take the quinine on August 22, as directed. Returned September 2 and reported having had chills on August 28 and 30 and September 1. Quinine was administered on September 7; the patient was discharged September 8 and given a prescription for quinine to be taken September 15 and 22. This was the only case that returned to the hospital.

Case 2 shows that when the quinine was not administered on the seventh day, the fever returned. Case 10 shows that when it



CHARTS 2 AND 10.



was not administered on the fifteenth day, as well as on the first and seventh days, the fever returned.

It is known that there is no definite relation between the time of the chill and that of the maximum temperature. In my 18 cases the time both of the chill and of the maximum temperature, before quinine was given, was noted in 5 cases only. In one case the chill followed the rise in temperature and in four cases preceded the rise in temperature, coming in the first three of the four cases, six hours, three hours and thirteen hours, respectively, before the rise. In the fourth case, the time both of the chill and of the maximum temperature was noted three times, and in this case the chill preceded the rise in temperature seven hours, eight hours and one hour, respectively. In case No. 8, as already stated, there was no chill.

Charts I. and II., page 10, which the courtesy of another physician permits me to use, show what may happen under another method of administering quinine in cases similar to mine.

Case I. entered the hospital July 11, and was given

July 13, 10 grains of quinine.

July 14, 16 grains of quinine (4 at 4 A.M., 8 at 8 A.M., 4 at 8 P.M.)

July 15, 30 grains of quinine (10 grains at 4, 6 and 8 P.M.)

and this dose seems to have been continued on July 16, 17 and 18. In spite of the 30 grains of quinine given on July 15, the patient had a chill on July 16.

Case II. entered the hospital June 1, and was given

June 5, 12 grains of quinine.

June 6, 4 grains of quinine at 6 P.M.

June 7, 16 grains of quinine (8 at 6 A.M. and 8 at 10 A.M.)

June 8, 4 grains of quinine.

June 9, 16 grains of quinine.

June 10, 4 grains of quinine.

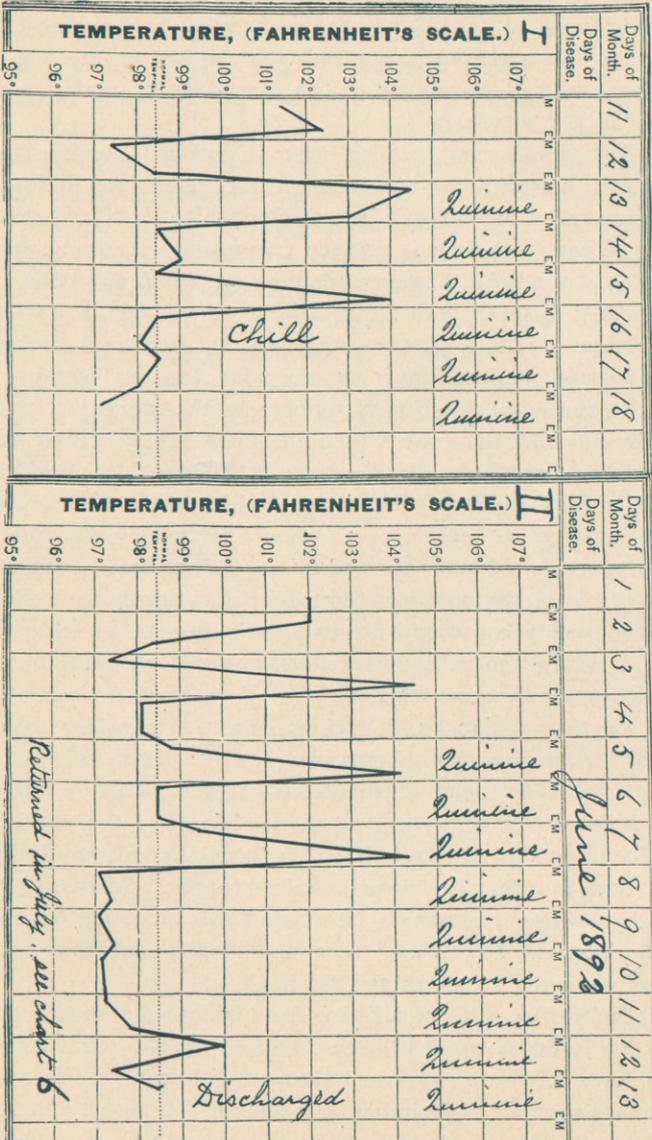
June 11, 16 grains of quinine.

June 12, 4 grains of quinine.

Notwithstanding this, the chills returned in about four weeks, and this patient entered my service July 17, as it happened during a chill and just before the temperature had reached the maximum. He had one dose of quinine when the temperature began to fall. There were no more chills. See Chart 6, page 7.

The intermittent method of giving quinine applies, according to Plehn's experience, to prevention as well as to cure. Plehn, a surgeon on board a Dutch vessel, found that, in spite of daily doses

CHARTS I AND II.



of 3 to 5 grains of quinine, malaria appeared regularly among those under his charge while about the coast of Java. He then tried giving quinine in 15-grain doses, at intervals of seven days, to 73 persons, 40% of whom were old sufferers from malaria. To their astonishment, of the 73 persons so treated, only one had malaria, and this was a rudimentary attack *ten* days after the last dose of quinine; he had previously shown symptoms of malarial cachexia from an old attack.

In severe forms, such as occur in warmer climates, one does not wait, however, for intermissions or remissions before giving quinine, and if the stomach be intolerant, high rectal injections may be used, and when there is urgency, it should be given subcutaneously. This latter method, however, requires special precautions. Bacelli found that in severe forms, especially the pernicious, 9 to 10½ grains of quinine injected *intravenously* was not sufficient to make it a sure parasiticide, but that it was necessary to give 15 grains.

In the administration of quinine by the mouth, which is ordinarily sufficient, there are simple precautions to be taken which are too often overlooked. As the taste is disagreeable, physicians seek to disguise it by giving the drug in pills. This method ought not to be employed; quinine pills should be wholly discarded; they are frequently old and hard and in many cases are not absorbed but carried off in the stools. A case in point is that of one of my patients who, contrary to my directions, was given quinine in pills. Of the ten pills taken, nine were subsequently found in the discharges. To avoid this element of uncertainty, quinine should be given in solution, or, if it is important to consider the taste, it may be given in powder or capsule.

It has been found advantageous to give a cathartic with quinine and it has occurred to me that the usefulness of the cathartic may be due in part to the fact that it reduces the volume of the blood and thus in effect the dose is made stronger. Warburg's tincture, which experience shows to be a good way of giving quinine, acts both upon the bowels and as a diaphoretic, and thus withdraws water from the blood in two ways.

In treating patients suffering from malaria we should not overlook the anæmia which is often produced by the parasites, nor fail to relieve it by appropriate treatment with iron, or in some cases with arsenic. It is desirable to examine the blood with Fleischl's hæmometer, in order to determine the presence and extent of the anæmia.

The increase of malaria in this vicinity, and the presence of

fever
 certain forms of malaria which are not easily recognized by the older methods, prompt me to emphasize the importance of examining the blood for purposes of diagnosis in suspicious cases. Such examinations are of great importance when we remember that we may have malaria without intermittence and also that we may have forms which intermit that are not of malarial origin. A very small drop of fresh blood may be examined at the bedside, or, if more convenient, the blood may be spread very thin on a glass slide, dried by treating it with equal parts of ether and alcohol and studied later after being colored with methyl blue. Laveran warns against negative results, and in these cases advocates repeated examinations, for experience shows that in pernicious forms, for instance, the parasites may be abundant in the viscera, although they may not be found in the blood of the finger. Councilman and Golgi have found them especially abundant in the spleen.

It gives me pleasure to recognize here the interest shown by the senior house officer, Dr. E. G. Bryant, in carrying out my directions in the cases here described.

SUMMARY.

The important points to be borne in mind are :

1. In treating malaria quinine should be given when the temperature falls. The temperature should be the guide, and not the chill which may come before or after the rise in temperature.
2. Quinine should be given at intervals rather than continuously.
3. Quinine should be given in such a way that its absorption is assured.

