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A FOURTH YEAR'S OBSERVATIONS ON MALARIA IN PANAMA, WITH REFERENCE TO CONTROL WITH ATABRINE AND PLASMOCHIN[1]

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PART I

During the past five years, 1930 to 1934, an area lying in the mid-basin of the Chagres River in Panama has been observed and studied with regard to malaria, and various sorts of treatment have been given the inhabitants in an effort to control the disease. The topography, climate and other physical factors of this area have been sufficiently discussed in previous reports (1, 2, 3). The area is typical of much of the Caribbean coastal lowlands of Central America, and the population of the five river villages and of the control town 5 miles away is fairly typical of the small rural communities in this part of the world. The only marked difference lies in a somewhat stronger negroid element in these people than is usual. Taken as a whole, villages of this type form the reservoir of native labor which must be used by commercial companies in developing the resources of the country. Hence any factor which lowers the efficiency of such labor must be fought.

Malaria is the most serious cause of lowered efficiency in such a population. It cannot be entirely eliminated, but by various means it can be reduced to negligible proportions, as is witnessed by conditions in the Panama Canal Zone, which lies within 7 miles of our towns. The costly measures of control used there are not economically feasible in our area, so our efforts have been directed toward a reduction of malaria, either by direct attack on

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the parasite by drugs, or by breaking the chain of infection in the mosquito by antigametocyte treatment. Our efforts have been concentrated on the seed-bed of malaria, the young children and adolescents, in an attempt to decrease this great reservoir of infection, from which the disease is spread.

In this attempt we have used several drugs and combinations of drugs over the four-year treatment period. These various methods may be here briefly summarized:

Quinine sulphate to all positives found in monthly surveys, without adequate supervision; September, 1930 to December, 1931.

Quinine sulphate to all positives found in monthly surveys, without adequate supervision; combined with *plasmochin simplex* 0.01 gram twice weekly to all inhabitants; January, 1932 to September, 1932.

Atabrine, to a selected group, without supervision; August, 1932.

Quinine sulphate, to all positives, without adequate supervision; October, November, and December, 1932.

Atabrine, 1.0 gram over a five-day period, under strict supervision, to all positives who could be reached; January, 1933 to August, 1933 inclusive.

Atabrine, same dosage, unsupervised, to all positives; September to December, 1933.

Atabrine, 1.0 gram over a five-day period, and *plasmochin simplex*, supervised treatment, in 4 towns; *quinine sulphate* treatment, unsupervised, and *plasmochin simplex* 0.2 gram over five days, supervised, in 1 town. Both treatments over the period from January, 1934 to August, 1934 inclusive.

The control towns during this period were as follows:

September, 1930 to December, 1931, Chilibre, unsupervised *quinine sulphate.*

January, 1932 to December, 1932, New San Juan, unsupervised *quinine sulphate.*

January, 1933 to August, 1933, New San Juan, unsupervised *quinine sulphate.*

January, 1934 to August, 1934

Chilibre, unsupervised *quinine sulphate.*

New San Juan, unsupervised *quinine sulphate* (no atabrine), but with supervised *plasmochin simplex.*

The results of these efforts are here briefly summarized:

Malaria parasite surveys, using the thick-film technique, are the yard-stick by which our results are measured. These surveys are made monthly, and beginning in September, 1930 were followed by treatment with quinine sulphate supplied under the supervision of a native community nurse, who was supposed to give each adult sufficient quinine sulphate for a ten-day course using 20 grains a day. Children received proportionate doses.

Before this treatment was instituted, we had as a base-line several surveys made at various times during the previous year. These showed a rather high malaria rate. Combining the figures for the initial surveys made in each town, we find a malaria parasite rate in 599 persons of 45.6 per cent. Two later surveys, made in June and August, 1930, before treatment was started, show malaria parasite rates of only 23.0 and 18.3 per cent, in 469 and 387 persons, respectively. The comparatively low rates found in these later surveys strongly indicate that the primary survey was made at a time of unusual prevalence of malaria, probably at the crest of one of the cyclical variations in malaria rate which have occurred several times during our own work, as will be shown.

If we use the initial surveys as our base-line, our results are encouraging. But if we use the later surveys, made just before treatment was instituted, the results of a year's work are disappointing. The combined malaria parasite rate in September, 1930 was 16.2 per cent; in September, 1931 it was 23.1 per cent. A similar, but much more marked increase occurred in Chilibre, our control town, which rose from 10.1 per cent in September, 1930 to 43.1 per cent in September, 1931. The inefficacy of the treatment used was due probably to the objections of the people to quinine, with consequent failure to take enough of the drug to reduce the parasite rate. It should be mentioned that all treatment was voluntary, at that time and ever since, during all of our work.

During the three-month period between September, 1931 and January, 1932, treatment was continued on the plan outlined above; in January, 1932 the administration of plasmochin simplex

was begun in 4 of the towns, in addition to quinine sulphate. Two control towns received quinine sulphate only. The plasmochin, given for its sterilizing effect on gametocytes, and not because of its curative power, was administered by ourselves twice weekly, in doses of 0.01 gram, for a period of nine months, from January to September, 1932 inclusive, to all the inhabitants of the 4 towns who could be reached. About 390 out of 680 persons took 75 per cent of this treatment, and almost all the remainder received some plasmochin.

Again our results, as compared with parasite rates in our two control towns, were not satisfactory. Table 1 shows these rates in the quinine-plasmochin group of 4 towns, the quinine control town, and in Chilibre, a town used as a control, in which only 0.01

TABLE 1

Parasite rates in treated and control towns (1932)

	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER
Quinine-plasmochin 4 towns.....	17.9	13.7	18.7	13.2	15.2	17.3	16.4	10.6	8.9
Quinine (New San Juan).....	33.3	12.9	8.8	15.1	13.7	13.8	15.8	12.9	8.8
Quinine-plasmochin (Chilibre)...	26.8	23.2	22.3	13.9	9.0	18.6	18.0	22.2	12.3

gram of plasmochin per week for four weeks was given to all positives, in addition to quinine sulphate.

The control towns show a greater proportional reduction in malaria parasite rate than does the quinine-plasmochin treated group of 4 towns. The plasmochin apparently had some effect on the oöcyst rate in Anopheles, for in the 4 plasmochin-quinine towns, it was only half that found in New San Juan, which received no plasmochin. Apparently the effect was not great enough to show any marked decrease in malaria parasite rate. The same decrease in parasite rate occurred in Chilibre, and also to a much greater extent in New San Juan, which received no plasmochin; so it is probably unsafe to refer much of the decrease in the 4 plasmochin-quinine treated towns to the use of plasmochin.

Our control over the administration of the quinine sulphate supplied was defective, as is shown by the following figures: between January, 1932 and September, 1932, 535 persons having malaria parasites in their blood were found in our 4 plasmochin-quinine treated towns. Eighty of these could not be followed up in the succeeding month, leaving 445 whose history is known in the succeeding month; 317 of these were negative, but 138, or 30.3 per cent, were positive for two successive months, showing that they had not taken sufficient quinine sulphate, in addition to their plasmochin, to sterilize the blood. This fact helps to explain our fairly constant parasite rate throughout the first eight months of this period.

During the period from the end of September, 1932 to January, 1933, the administration of plasmochin was stopped, and quinine

TABLE 2

Malaria parasite rates in 4 towns, and in controls

	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY
4 towns	8.9	8.1	5.2	7.3	17.7
New San Juan	8.8	21.1	15.6	19.0	28.8
Chilibre	12.3	6.6	7.7	11.1	11.6

sulphate only was supplied for all those found with positive bloods, with one very important exception. In August, 1932, after the monthly survey, 32 persons who had positive blood were treated with the new synthetic drug, atabrine. Little supervision could be exercised over its administration, but evidently the drug was effective, for all persons so treated were negative at the survey made a month later. At least half of this number remained negative for the four following months. Taking this many positives out of circulation, so to speak, reduced the malaria parasite rate in our 4 treated villages during the next four months (September to December, 1932) to the lowest level it had ever attained hitherto. Table 2 gives these rates.

While the parasite rates in New San Juan, a control town receiving no atabrine, rose steadily from August, 1932 to December,

1932, the rates in Chilibre, another control town which also received no atabrine, fell nearly to the same level as did those in our 4 treated towns. So, as is quite usual in this sort of work, it is difficult to determine the exact part played by treatment in effecting this reduction in our treated towns.

In January, 1933, the reduction in rate, however it was caused, was completely cancelled, and after rising to 17.7 per cent in the 4 treated towns in January, 1933, it remained stationary for the following eight months, being 16.3 per cent in August. The parasite rates for New San Juan were consistently higher, but also stationary, ranging from 28.8 in January to 28.6 in August. During this period the senior author made a very carefully controlled study of the value of atabrine in reducing the malaria

TABLE 3

Parasite rates January to September, 1933

	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER
4 atabrine towns...	17.7	24.8	22.5	24.0	20.0	17.4	16.3	16.3	18.1
New San Juan.....	28.8	30.4	19.1	27.8	23.4	25.1	24.1	28.6	28.6
Chilibre.....	11.6	11.8	16.7	18.2	16.3	11.0	19.3	45.1	*

* No survey.

parasite rate. This drug was used in the 4 river villages, and the towns of New San Juan and Chilibre were used as controls, which received no atabrine, but were supplied with quinine sulphate for the treatment of all positives. About 400 persons whose blood showed parasites were treated in the 4 villages over a period of eight months (January to August, 1933). The dosage for adults was 0.3 gram daily for five days, and the senior author *personally administered* the drug, visiting each person treated three times daily. Contrary to our early expectations, atabrine did not reduce the malaria parasite rate, as more than half of all cases treated during the last four months were "blood positive" relapses after treatment taken during the first four months. Some of the cases showed parasites in the blood every other month during the eight-month period, having been treated at each reappearance of the parasites.

No plasmochin was given as a routine during this period (January to August, 1933). During the succeeding four months, quinine sulphate was supplied to all blood positives, under inadequate supervision. The parasite rate in the 4 villages decreased from 18.1 per cent in September to 11.6 per cent in December, 1933.

Table 3 gives the parasite rates in the 4 atabrine-treated river villages, and in the two control towns.

ATABRINE-PLASMOCHIN EXPERIMENT, 1934

In view of the poor success of our attempt to reduce the parasite rate with atabrine alone, as recorded in our previous paper (3), it was hoped that the addition of plasmochin in therapeutic doses might be of aid, both because of its sterilizing effect on gametocytes, and because of its curative powers. Knowing from much previous experience the futility of attempting drug control without supervising its administration, the two drugs were dispensed personally by some responsible person. The same four villages as were used in the atabrine test were used for the atabrine-plasmochin experiment, and the same two towns, New San Juan and Chilibre, were used as controls.

In the 4 atabrine-plasmochin treated towns, treatment of all persons found blood-positive in the monthly survey was begun in January, 1934, using atabrine (1.0 gram) and plasmochin simplex (0.2 gram) over a period of five days. These drugs were personally administered to each positive case, and careful records of such treatment were made. In New San Juan, no atabrine was used, but 150 grains of quinine sulphate in capsules or tablets were distributed to each person with positive blood, immediately following the survey; 0.2 gram of plasmochin simplex was administered personally, during five days of the week following the quinine sulphate distribution. Records of this treatment were likewise carefully kept. In Chilibre, a control town, quinine sulphate (150 grains) in capsules was given to all blood-positives, to be taken without supervision, after each monthly survey.

During the first month, treatment with atabrine-plasmochin was given personally by the senior author. During the succeed-

ing seven months this treatment was supervised by an intelligent Panamanian laboratory attendant, who kept records of his treatment. He also supervised the giving of the plasmochin in New San Juan, from January to August, 1934. No supervision of any kind was given in Chilibre, where quinine sulphate alone was used, and we have good reason to believe that much of the drug was not taken.

In order to determine whether the reduction in malaria parasite rate following drug treatment is due to our efforts, we must select a datum or base-line from which to measure the amount of reduction; we must have adequate controls, which are essential in any sort of experiment; and we should have an accurate knowledge of the seasonal or yearly variations in parasite rate, in both treated population and in controls. This latter requisite is one which has often been neglected by workers in the field of malaria control, and such neglect has caused many to take undue credit for causing a reduction in parasite rate, which was not at all due to their efforts, but was simply a manifestation of a down-swing in the malaria cycle. The choosing of a proper base-line is intimately connected with this last consideration. The more observations we have made before the beginning of our work, the greater is the possibility of interpreting correctly any variation in malaria rate which may occur during the course of treatment work. Our treatment work began this year (January, 1934) at the end of a period of unusually high parasite rates, and at the beginning of a period of diminishing parasite rates. All our towns, no matter how much or how little treatment they received, participated in this reduction in rate. In 1933, on the contrary, the rates either remained stationary, at a rather high level, or increased, no matter what treatment was given. Even without this knowledge of the course of parasite rates during the previous months, the declining parasite rate in our control town, Chilibre, during 1934 shows that we must not attribute all our success in reducing the parasite rate to the treatment we used.

Putting aside for a moment the effect of seasonal variations on our rates, we shall try to measure the immediate effects of treat-

ment by noting the number of persons showing parasites in the blood in the monthly survey following treatment. In addition to this effect of treatment, we have an unique check on the amount of treatment received in the selective action of plasmochin on gametocytes, especially on the crescents of estivo-autumnal malaria. Plasmochin simplex 0.2 gram administered over five days should clear the blood of sexual parasites, so it becomes easy to determine how many persons with estivo-autumnal infections failed to take the drug. For persons showing crescents in the survey immediately following their treatment are thereby known not to have received adequate amounts of the drug. With these criteria in mind, we may examine the results of the treatments with atabrine-plasmochin and with quinine sulphate-plasmochin, in our treated towns. Taking the atabrine-plasmochin treated towns first, we treated altogether 159 cases of "parasitaemia" with atabrine and plasmochin in the dosage stated above; all these persons were surveyed in the month following treatment. Of these cases, only 4 showed asexual parasites in the following survey, and only 1, a small child, showed the presence of crescents. All the cases showing positive bloods at the survey following the treatment period occurred in one town, Gatuncillo, which consistently had the highest rate of any town in our group during the whole period of our study.

The success of the treatment in immediately ridding the blood of parasites is sufficiently evidenced by the figures given above.

The immediate effect of the treatment on crescents is also quite marked, as may be shown by comparing the percentage of cases in which crescents appeared in the blood in cases treated with atabrine alone, in 1933, with the percentage of similar cases in 1934, when plasmochin was added. In 1933, 311 cases of parasitaemia caused by estivo-autumnal parasites in our 4 villages were treated with atabrine alone. At the monthly survey following treatment, 18 or 5.8 per cent showed crescents. In 1934, 158 cases were treated with atabrine-plasmochin, with only 1 case in which crescents were present at the following survey, a rate of 0.6 per cent. These results must be viewed with caution, how-

ever, as in 1933 there were many more cases with heavy infections, and hence more liable to produce crescents later, than there were in 1934.

In spite of the fact that the addition of plasmochin to the treatment with atabrine reduced the number of malaria carriers, the crude crescent rate based on all persons surveyed, whether treated or not, remained nearly as high as it was in 1933, the figures being 24.1 per cent for 1934 and 29.5 per cent for 1933, among all cases of estivo-autumnal malaria. This may be explained by the fact that many persons showed both crescents and rings at their first positive examination, although they may have been negative previously for all forms of the parasite.

The effect on the relapse rate (blood-parasite relapse only) is difficult to judge, complicated as it is with the effect of a naturally diminishing malaria parasite rate. Of the 99 cases of parasitaemia treated during the first four months of the eight-month treatment period, and who could be followed up thereafter, 39 cases again showed parasites in the blood at some time during the period following their initial treatment. This is nearly 40 per cent of all such cases. Among these 39 persons, there were 10 who, at 2 surveys, not necessarily consecutive, following their first treatment, had positive bloods. Most of these persons were treated at the second reappearance of their parasites, but showed parasites a third time, in spite of such treatment.

This is a somewhat lower rate of blood-parasite relapse than was experienced in 1933, when atabrine alone was used, but even so it does not lead us to think very favorably of the efficacy of the combination of atabrine and plasmochin in preventing blood-parasite relapse. Under the conditions of our work it is nearly impossible to obtain accurate data as to the clinical attack rate, so we are forced to depend on the blood parasite rate as our measure of efficacy of drug treatment.

During the first month of the combined atabrine-plasmochin treatment, the senior author administered the drugs personally to 15 persons who had shown malaria parasites in the blood on many occasions during the previous year, but who at the time (January, 1934) had negative bloods. Of the total of 15 who

received the two drugs, in an attempt at sterilization of the blood, 6 persons showed parasites at some time during the succeeding seven months, 2 of them in the month immediately following the treatment.

TOXICITY OF PLASMOCHIN

During the course of our previous work with atabrine (3), no toxic symptoms of any kind were noted in any of the 400 cases so treated. It was far different with plasmochin. During January, 1934, all treatments with atabrine and plasmochin were administered by the senior author. Of 25 persons so treated, 2 had severe toxic reactions, necessitating the withdrawal of the drugs. During the four months period, January to April, 1934 inclusive, in which combined atabrine-plasmochin treatment was given, we had knowledge of 13 cases showing symptoms of toxicity following such treatment. These symptoms ranged in severity from mild epigastric discomfort to the most severe gastric and abdominal pain; diarrhoea; nausea and vomiting; and headache. Some reactions were of such severity and duration as to lead the sufferers to seek medical attention. These symptoms usually set in before the five-day treatment period had ended, but sometimes they were delayed in onset until several days later. So numerous and severe were such cases that they caused alarm among our villagers, and we thought it best to discontinue the combined administration of the two drugs. So in May, 1934, atabrine alone in the same dosage (1.0 gram over five days) was given under supervision, while plasmochin simplex (0.2 gram over five days) was given, not under strict supervision, during the week following the atabrine treatment. Apparently this method of giving the drugs separately, although in the same amounts as before, reduced the number of reactions. In May, we had one of the few cases of blackwater fever we have observed in our villages, in a boy of twelve years, whose symptoms came on shortly after he had completed a course of atabrine and plasmochin, given in separate weeks. The child recovered rather promptly, and was negative for malaria parasites at the next monthly survey. We realize the loophole for error to creep into

our results in not carefully supervising the administration of plasmochin as we did the atabrine, but economic considerations overruled in the matter, as we could not afford the expense of maintaining the required supervision.

We feel that the toxicity of plasmochin renders it unsuitable for mass administration, without adequate medical supervision. This opinion is shared by many other workers (4), (5), (6), whose experience with the drug has been similar to our own.

TREATMENT WITH QUININE AND PLASMOCHIN (NEW SAN JUAN)

In our largest town, New San Juan, no atabrine was administered, but quinine sulphate in capsules (15 grains daily for five days) was given to all persons found blood-positive. The administration of this drug was not strictly supervised until the last four months of the eight month's period.

In addition to quinine sulphate, 0.04 gram of plasmochin simplex was administered to all positives during five days of the week following the quinine treatment period, under strict supervision, accurate records being kept of the amount of drug taken.

From the fact that 9 persons out of 53 positive in January, 1934, were again found positive in February, it seems certain that many persons failed to take their quinine ration, for plasmochin simplex alone in the dosage indicated is insufficient to render parasite-free a case showing a "1 plus" infection (showing 1 parasite or more per microscope field in thick film). The record improved as more supervision was provided. Of 65 cases treated during the first four months, which could be followed up, 26 cases later showed parasites again in their blood, or 40.0 per cent, nearly exactly the same percentage as was found among the 99 persons treated and followed up during the same period, in the 4 villages in which atabrine-plasmochin was used. There were 7 cases out of the 26 blood-parasite relapses who showed parasites at 2 surveys following their first treatment.

In spite of the facts that quinine sulphate, a less potent drug than atabrine, was used in New San Juan, and that the whole project was much less closely supervised, the results of the quinine-plasmochin treatment were much similar to those attained with atabrine-plasmochin.

As in those towns, our results are likewise complicated by the fact that we did our work during a period of naturally diminishing malaria rates. A word of caution must be injected here against attributing all the improvement in blood-parasite rates to drug treatment of any sort. In the course of our work, we found during the first four months a total of 24 persons with positive blood, who for one reason or another could not be given subsequent treatment, yet who were found negative at the later surveys. In the ordinary course of events, had these persons been treated, the freeing of their blood from malaria parasites would have been attributed to the drug treatment.

TREATMENT WITH QUININE SULPHATE ALONE (CONTROL TOWN, CHILIBRE)

Chilibre is not altogether an ideal town to use as a control, as the racial composition of its population differs somewhat from that of our river towns, and the floating population, because of its accessibility by motor road to Panama City, is much greater than is found in those towns.

Most unfortunately, we have no record of the course of malaria rates in this town over the period from September, 1933 to December, 1933 inclusive. No funds were available to continue surveys and treatment during this period. We do know that the survey made in August, 1933 showed the high rate of 45.1 per cent, and that the crude rate in January, 1934, when surveys and treatment were resumed, was 30.8 per cent. Knowing the course of malaria rates in New San Juan during the period September to December, 1933, it is logical to assume that malaria rates did not materially decrease in Chilibre, but probably remained at a relatively high level.

The individual records of the inhabitants are not so complete as they are in our 5 river villages, as in many cases only two or three monthly examinations out of a possible eight, from January to August inclusive, could be made. In order to avoid either a dilution or an enrichment of malaria parasite rates, caused by the inclusion of a large floating element, the records of 334 persons present at two or more monthly surveys are used as the basis for

computing the malaria parasite rates in this town. Comparison of crude rates with rates obtained from "regular" inhabitants (those present 2 or more times out of 8 surveys) show that the crude rates are slightly lower, but never more than 3 per cent, and usually less than 1 per cent, lower than rates among the regular inhabitants.

The striking difference immediately noticeable between the individual records among the Chilibre folk, and those in our 5 river towns, lies in the far greater number of persons who remained positive over two or more months. While in our 5 river towns we have only 26 records among 910 persons who were positive for two consecutive months, *whether treated or not*, in Chilibre among 334 persons we find 34 such cases; in addition we find 8 persons positive for three successive months; 4 for four successive months, 3 for five successive months, and 1 apiece for six and seven months. No doubt many of the 34 persons positive for two successive months only would have graduated into higher classes had they been present at every monthly survey. From the standpoint of the success of quinine treatment this is a very disappointing showing, but as proving the thesis advanced that a natural reduction in malaria parasite rate was taking place, it is ideal material. In the 5 treated villages we had only 2.8 per cent of our "regular" inhabitants positive at two successive monthly surveys. In Chilibre, 51 persons out of 334 "regulars" or 15.2 per cent, were positive at two or more successive surveys. Surely these people who remained so uninterruptedly positive could not have taken a great deal of the quinine which was furnished them.

And yet in spite of this lack of treatment, the rates among our "regulars" in Chilibre fell from 34.0 per cent in January, 1934, to 13.2 per cent in August, eight months later. This reduction is nearly as great (61.2 per cent) as that which occurred in our treated towns; taking these as a whole, their parasite rate dropped from 18.4 to 8.0 (65.5 per cent) in the same period of eight months.

The reduction in malaria parasite rate followed a period of rather high rates in all towns, including the control, and descended from the high rates in a regular, orderly manner, in all towns,

including the control. At last we have attained the goal so long desired, for we now have parasite rates in our treated towns of approximately 8 per cent, which we feel is more or less of an irreducible minimum. Quite probably, judging from the data given above, a large unknown part of the reduction in rate was due to natural causes, and it is questionable whether or not in an unfavorable season, the rates can be held so low. When we view the future in the light of past experience, and note that several times since September, 1930 the parasite rates in our five villages have risen to nearly 30 per cent, and that in Chilibre they have gone over 40 per cent on three occasions, we must come to the conclusion that our present year's work is of the nature of a progress report. In order to ascertain whether it is possible, in the face of rising malaria rates elsewhere in the immediate vicinity, to keep the rates in our treated villages within bounds, by means of treatment, we must continue our treatment along present lines during the coming year, until in what we feel to be the normal course of events an upswing in malaria parasite rate occurs in our control town. There is no present indication that this has yet occurred at the time of writing, for in October, 1934, the rate in our control town dropped to 9.4 per cent, even lower than the rates in some of our treated towns.

PART II. OBSERVATIONS ON MALARIA RATES AND ASSOCIATED PHENOMENA IN SOME NATIVE VILLAGES IN THE REPUBLIC OF PANAMA

The observations reported in this second part continue the record of surveys begun in 1930, and continued to August, 1934. The malaria parasite rates in all instances are those found in a population which was under some form of therapy for the entire period, and hence are modified by the results of such treatment.

Malaria surveys, using the thick-film technique (7), (8) were made in 5 villages lying on the banks of the Chagres River and one of its tributaries. An individual record card was kept for each individual whose blood was examined in any survey, and in this manner an accurate estimate of the numbers of permanent inhabitants could be made. This record showed a population of

910 persons in 1934. In addition, we examined at least once during the year from September, 1933 to August, 1934 inclusive, approximately 318 persons, friends, relatives, or temporary inhabitants of the 5 towns. In addition to the observations made in these 5 towns, we made exactly similar surveys and records in another town, Chilibre, lying about 5 miles away, during the eight months from January to August, 1934, inclusive. This town had a much greater floating population, as is evidenced by

TABLE 4

DATE	4 RIVER VILLAGES			NEW SAN JUAN			CHILIBRE (CONTROL)		
	Number examined	Number positive	Per cent positive	Number examined	Number positive	Per cent positive	Number examined	Number positive	Per cent positive
1933									
September	388	71	18.3	304	87	28.6			
October	363	40	11.0	246	83	33.7			
November	364	40	11.0	283	79	27.9			
December	354	41	11.6	262	27	25.6			
1934									
January	384	63	16.4	285	65	22.8	195	60	30.8
February	384	38	9.9	281	36	12.8	171	55	32.2
March	313	31	9.6	210	22	10.5	203	39	19.2
April	353	32	9.1	299	36	12.0	191	29	15.2
May	370	38	10.3	257	18	7.0	225	32	14.2
June	341	22	6.4	266	17	6.4	204	41	20.4
July	392	25	6.4	327	30	9.1	214	47	22.0
August	370	29	7.8	293	24	8.2	201	25	12.4
Total	4,376	470	10.7	3,313	564	17.0	1,604	328	20.5

the fact that we had 544 individual cards in our file, of which only 337 could be counted as permanent inhabitants. The inclusion of this floating population, both in Chilibre and in our 5 towns, in our monthly malaria parasite surveys, did not materially alter the rates as calculated upon the findings among the permanent inhabitants, so in the following tables such crude rates, including all persons surveyed, will be given. It is thought well to give separately the rates for the 4 river villages, Santa Rosa, Guayabalito, Gatuncillo and Las Guacas, for New San Juan, and for

Chilibre, because each town or group of towns received different malaria treatment. Table 4 gives the crude malaria rates in these localities for the period from September, 1933 to August, 1934.

Unfortunately, lack of funds prevented us from making surveys in Chilibre, during the four months from September to December, 1933 inclusive. However, it probably was a period of high incidence, for the survey in August, 1933 showed a rate of 45.1 per cent, and the next survey thereafter in January, 1934 showed 30.8 per cent.

The most striking single observation to be made on the above figures is the abrupt drop in parasite rate which occurred in all localities in the spring of 1934. The combined rate for the 4 villages and New San Juan fell abruptly from 19.1 to 11.1 from January to February, 1934. The surveys made in February were the first made after vigorous treatment under supervision was instituted here in January, 1934, so that doubtless a part of the decrease must be attributed to treatment. However, a similar but not so abrupt decrease occurred in Chilibre, beginning a month later here, and being spread out over two months, March and April, during which the rates dropped from 32.2 per cent (February) to 15.2 per cent (April). No change in the method of treatment was made during this period, and our records show that a great deal of the drug could not have been taken by those to whom it was distributed.

The steady decrease in parasite rate in the 4 river villages and in New San Juan, continued without a notable break from January to August. With the exception of two surveys, made in June and July, the rates in Chilibre, our control town, did likewise. Parenthetically it should be stated that this decrease continued to the time of writing (October, 1934) when the rate in Chilibre further decreased to 9.4 per cent.

From all these figures it is evident that we have just passed through one of the cyclical down-swings of the curve of malaria parasite incidence. How long this will continue, and how great its effect will be on the possibility of controlling malaria rates indefinitely, the future will disclose.

OBSERVATIONS ON TYPE OF MALARIA PARASITE, CRESCENT INCIDENCE, INTENSITY OF INFECTION, AND IMMUNITY

Table 5 shows the relative incidence of the various species of malaria parasites found during the year beginning September, 1933 and ending August, 1934. The number of positives found monthly in the 4 river villages and New San Juan are combined in this table.

TABLE 5

Species of malaria parasites in twelve monthly surveys of 5 river towns

DATE	TOTAL POSITIVES	TOTAL E.A.	TOTAL TERTIAN	TOTAL QUARTAN	PER CENT TERTIAN	PER CENT CRESCENTS IN ALL E.A. CASES
1933						
September	158	140	16	2	10.1	27.1
October	123	103	16	4	13.0	20.4
November	119	109	9	1	7.6	30.3
December	108	94	12	2	11.1	27.7
1934						
January	128	108	19	1	14.8	23.2
February	74	57	17	0	23.0	24.6
March	53	39	12	2	22.6	25.6
April	68	43	24	1	35.4	9.3
May	56	42	14	0	25.0	7.1
June	39	30	7	2	17.9	20.0
July	55	38	16	1	29.1	15.8
August	50	37	13	0	26.0	13.5
Total	1,031	840	175	16	16.9	22.8
1932–33	1,259	1,124	127	8	10.9	29.2
1931–32	956	793	136	27	14.2	13.2
1930–31	1,024	701	264	59	25.4	22.9

Table 6 shows the same data for the period from January, 1934 to August, 1934 inclusive for the control town, Chilibre. No surveys were made during the 4 months previous to January, 1934.

Several interesting comparisons may be made between table 5 and table 6. First, in our 5 river towns, as the general parasite rate decreased, the number of tertian cases increased. This did not occur in Chilibre, where there was a decrease towards the end of the year. Second, the percentage of cases harboring crescents,

among all estivo-autumnal cases, was greater in the 5 river towns, which received thorough treatment with plasmochin, than it was in Chilibre, in which no plasmochin was administered. The difference was small, but in view of the general adequacy of the plasmochin treatment, it is somewhat surprising that the drug was not more effective in reducing the crescent rate.

The crescent rate in the 5 river towns was 22.8, which is slightly lower than the rate last year, 29.2. It should be noted that in all our 5 river towns we found during the year only one person, a small girl, whom we could consider a good infector of *Anopheles*.

TABLE 6

Species of malaria parasite in eight monthly surveys, Chilibre

DATE	TOTAL POSITIVE	TOTAL FALCIP.	TOTAL VIVAX	TOTAL MALARIAE	PER CENT VIVAX	PER CENT CRESCENTS IN FALCIP. CASES
1934						
January	60	45	15	0	25.0	22.2
February	55	43	12	0	21.8	16.3
March	39	26	13	0	33.3	23.0
April	29	24	5	0	17.2	16.7
May	32	21	11	0	34.4	28.6
June	41	31	10	0	24.4	10.3
July	47	38	8	1	17.0	18.4
August	25	23	2	0	8.0	8.7
Total	328	251	76	1	23.2	17.9

This may be accounted for on the basis of the observations made on the same subject last year. We stated then "that the incidence of crescents in cases of estivo-autumnal malaria seemed to vary with the intensity of the infection. Heavy infestations, especially in children, were usually accompanied or followed by large numbers of crescents." The number of heavy infections noted in 1933–1934 was very small, as compared to those noted during the previous year. The appearance of crescents alone, without any antecedent infection to account for them, was again noted during the past year. The child mentioned above had been negative for ten months previous to the monthly survey in which she was found to have a heavy crescent infection.

INFECTION IN INFANTS

During the year from September, 1933 to August, 1934, the blood of thirty-five infants under one year of age, living in our 5 river towns, was examined for malaria parasites, on at least one occasion.

Only one child, a girl five months old, showed a heavy *falciparum* infection with crescents, on one occasion. This record is much lower than was the case in 1933, and indicates that transmission was not very active during the first eight months of 1934.

INTENSITY OF INFECTION

During the year from September, 1933 to August, 1934, out of a total of 1,031 positive bloods found in our 5 river towns, there were 155 "plus" infections (1 parasite or more to each thick-film field) or about 15.0 per cent. In Chilibre, the control town, out of 328 positive bloods there were 37 "plus" infections, or 11.25 per cent.

As mentioned in former publications, the element of chance must be reckoned with here, as the survey, made only once each month, may pick up one infection at its height, and another at a time when parasites are few in the peripheral circulation. Several more instances of the rapid rise in numbers of parasites from "negative" to "plus" infections in a few days, as noted in our previous publication, were noted.

IMMUNITY

Further work has not led us to withdraw from the position we took in our previous publication on the subject of immunity, as being a family trait. It is hoped to make this matter the subject of further study and publication, so that only two instances supporting the theory will be mentioned here.

The first concerns the relation of several "positive" families in one town (Gatuncillo) to the consistently high malaria rate in that town. There are 3 families there totalling 16 individuals, in whom malaria seems to be intractable, as parasites reappear at intervals in their blood in spite of continued and repeated treat-

ment. Judged by negative blood-films at the termination of treatment, this was sufficient to sterilize the peripheral blood. There are 92 permanent inhabitants of this town in which these 16 individuals live. Subtracting 16 from 92 leaves 76 persons, among whom during twelve months 634 blood-examinations were made. The rate among these 76 persons was 14.2 per cent, while in 159 examinations made among the 16 individuals, the rate was 32.7 per cent. This means that the 16 individuals had 2.3 times the number of positive blood-examinations per person as did the other 76 inhabitants, and accounted for 35.0 per cent of all the positive examinations made.

One of our towns, Las Guacas, offers an extreme contrast to conditions in Gatuncillo, in that it has had consistently the lowest parasite rate of all our towns, during the entire period of our work. Thinking that the low rate might be explained on the basis of a different age-grouping in Las Guacas, the inhabitants were classified as to age, and it was found that the proportion of children fourteen years of age and under was practically the same in both Las Guacas and in Gatuncillo, being 30.0 and 30.4 per cent respectively. Yet in Las Guacas 28 children from birth to fourteen years of age had 20 cases of positive blood during the year, or 0.7 per child, while in Gatuncillo 40 children from birth to fourteen years old had 82 cases, or 2.05 per child. So the difference in rate is not due to a difference in age-grouping, but to the presence in Gatuncillo of a group of persons who continued to retain their parasites, in spite of all treatment. There are in Las Guacas, several families with numbers of small children, one with 6, another with 5, and two with 3 children apiece. Yet in 168 examinations made during the year among these 17 children, only 10 proved to be positive, and these were found in 5 of the children. Contrast these with the record of 11 children in 3 families in Gatuncillo, all fourteen years old or less, who in 118 examinations made during the year, at monthly intervals, showed 39 positive, or 33 per cent of all examinations, and in which only 1 child of the 11 did not show parasites at some time during the year.

Las Guacas is slightly more accessible from the highway to

Panama City than is Gatuncillo, so that visitors are possibly more frequent, so that infected persons among them might serve as foci. And, too, Las Guacas, surrounded as it is on three sides by shallow, vegetation-covered lagoons, has a much higher Anopheline density than does any other town on the river, as was noted in previous reports. Yet its rate continues low in spite of both these unfavorable factors.

We are inclined to believe that the difference between the two towns is due to the presence in Gatuncillo of certain families which lack specific immunity to malaria infection, and to the presence in Las Guacas of families which possess this immunity, which is seemingly a family trait. Whitmore (9) noted similar family incidence in his studies of blackwater fever. Simmons and St. John (10) in the Philippines, noted that malaria was mostly confined to certain families, which could be readily discovered by spleen examination. It is planned to investigate all our material obtained over the last four years, with reference to the theory of family immunity and its converse, for it may prove to be an important factor in the problem of malaria control by drug treatment.

SUMMARY AND CONCLUSIONS

The present paper reports four year's work with drug control of malaria, in an unsanitated area in Panama. Various combinations of anti-malarial drugs were used including quinine sulphate alone or with plasmochin, and atabrine alone or with plasmochin. None of the methods used were particularly successful in reducing the malaria rate, except possibly the combination of atabrine and plasmochin. Monthly surveys over four years indicate the presence of cyclical variations in malaria parasite rate extending over several years. If treatment of any sort happens to be given during a down-swing in rate, success is nearly sure to follow; but if it is given on an upswing in rate, apparently nothing can stop the natural course of the cycle. Even atabrine, the most useful drug we have to date, was unable in 1933 to reduce materially the parasite rate during a period of eight months.

The effect of the addition of plasmochin to atabrine and to

quinine in 1934 is obscured by the greater effect of the naturally decreasing malaria rate, as evidenced by comparative rates in our control town. It will be necessary to continue the administration of both drugs during the next up-swing of the parasite rate, in order to ascertain its effect.

Although we feel that the recent improvement in malaria parasite rate is not due solely to our efforts, we have no doubt but that the general health of our villagers is much improved over its condition in 1929, before our work started. At that time there was much more evidence, in the form of anemia, cachexia and other indications of malarial infection, of the ravages of the disease. By continued work we have reduced the numbers of chronic infections, and have taught the people to apply for drug treatment for their fevers, and have effected a consequent material improvement in general health conditions which may enable them to resist successfully the next onslaught of the disease.

Part II of the paper summarizes the malaria parasite rates found in twelve monthly surveys in 5 towns in the valley of the Chagres River, and compares the percentages with those found in previous years. The evidence of our control town indicates that 1934 was a year of naturally declining parasite rates. The possibility that immunity is a family trait is discussed, and several illustrations are given in support of the theory.

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