Reprinted from THE AMERICAN JOURNAL OF TROPICAL MEDICINE
Vol. 16, No. 2, March, 1936

A FIFTH YEAR'S OBSERVATIONS ON MALARIA IN PANAMA, WITH REFERENCE TO THE FAILURE OF ATABRINE TO CONTROL AN EPIDEMIC[1]

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Received for publication January 25, 1936

Over a period of six years, 1930 to 1935, "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, 4). 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" (4). The impossibility of controlling mosquito production in the area without a financial outlay far in excess of the benefits to be obtained, led us to attempt malaria control measures based on individual treatment of infected persons.

The method of attack, which is economically defensible, theoretically practicable, and apparently, in the hands of others, successful, employed by us was an attempt to reduce the malaria

[1] Read at the thirty-first annual meeting of the American Society of Tropical Medicine, St. Louis, Missouri, November 20–22, 1935.

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parasite incidence in the "seed-bed" of the disease, the great reservoir of parasites in young children and adolescents, from which the disease is spread. We had always in view the economic aspect of the problem, which is the limiting factor in controlling malaria in a labor force under tropical conditions.

In our previous report (4) we outlined the methods used since the beginning of the work. To orient the reader who is not acquainted with our previous publications, it will suffice to say that we have been using as a measure of our success, blood-parasite surveys made monthly on all the inhabitants of the area, numbering somewhat over a thousand individuals. The thick-film technique of Barber and Komp (5) (6) has been used throughout the period. The drugs and combinations of drugs used over the five-year period or our research in the towns under supervised treatment were as follows:

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, 1935 inclusive.

The control towns during this period were as follows:

September, 1930 to December, 1932, 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.*

September, 1934 to August, 1935, Chilibre, unsupervised *quinine sulphate.*

During the past year, September to August, 1935, inclusive, each person in a group of four towns who was found positive for malaria parasites was treated with atabrine, gram 1.0 over a period of five days, followed by plasmochin simplex 0.2 gram over a succeeding period of five days. In another town, New San Juan, used as a partial control, no atabrine was given except to a few clinical cases, but quinine sulphate in gelatine capsules, 15 grains daily for five days, was distributed to those found positive, followed by plasmochin simplex 0.2 gram during the five days following, the latter drug being given under strict supervision. In another town, Chilibre, used as a control, neither atabrine nor plasmochin simplex was given, but here quinine sulphate in 5-grain gelatine capsules was provided, without supervision, for all those whose names were on the positive list furnished the local authorities, and who would take the trouble to apply for treatment.

Substantially the same methods outlined above had been in use since August, 1933, a fact which must be borne in mind in view of later developments.

As stated in our previous report (4), parasite rates in all the towns under treatment, including the control, fell simultaneously to very low levels in the later months of 1934, the average rate being 8.7 per cent, and the rate for the control town being 10.0, in October, 1934. Having had previous experience with the great fluctuations in the parasite rate which occur in our region, we conservatively stated that "we must continue our treatment along present lines during the coming year (1935), until in what we feel to be the normal course of events an upswing in malaria parasite rates occurs in our control town. . . . We must come to the

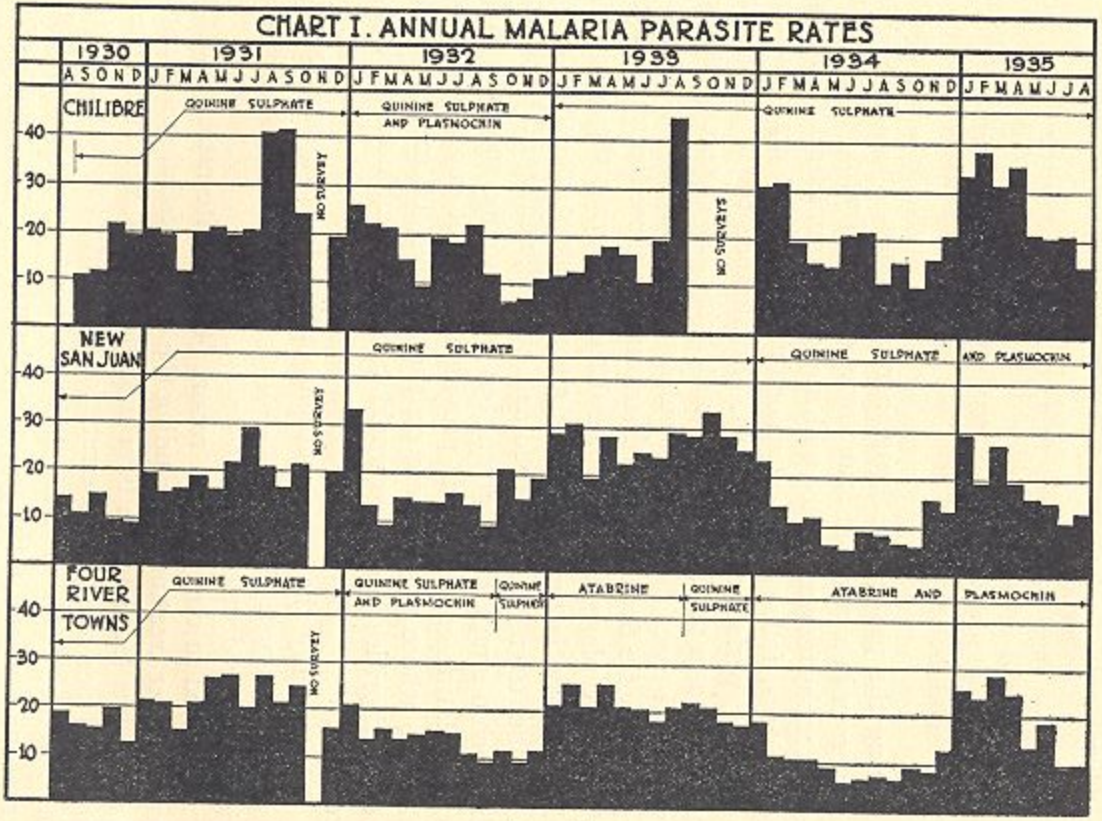
CHART I. ANNUAL MALARIA PARASITE RATES
1930
1931
1932
1933
1934
1935
A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A
CHILIBRE
QUININE SULPHATE
QUININE SULPHATE AND PLASMOCHIN
QUININE SULPHATE
NO SURVEY
NO SURVEY
NEW SAN JUAN
QUININE SULPHATE
QUININE SULPHATE
AND PLASMOCHIN
NO SURVEY
FOUR RIVER TOWNS
QUININE SULPHATE
QUININE SULPHATE AND PLASMOCHIN
QUININE SULPHATE
ATABRINE
QUININE SULPHATE
ATABRINE AND
PLASMOCHIN
NO SURVEY
40
30
20
10

CHART 1

conclusion that our present year's (1934) work is of the nature of a progress report" (4, p. 145). The material in the present paper is an account of our results obtained while continuing our methods into the succeeding year of 1935.

That our conservatism was abundantly warranted, appeared in an unexpectedly short interval after the words quoted above were written. Referring to chart 1, it will be seen that, after a period of very low parasite rates in October, 1934, the rates in all villages, treated either with atabrine-plasmochin, quinine-plasmochin, or quinine only, began to rise until, much to our disappointment, an epidemic began in January, 1935, which lasted for four months, in spite of all our efforts. The remarkable fact concerning this epidemic is that the parasite rates rose nearly simultaneously in all the towns, to approximately the same levels, although four of the towns had received atabrine-plasmochin treatment, thoroughly supervised, for two years previous to the epidemic. During the epidemic period, every person living in the 4 atabrine-plasmochin treated towns, whose blood was parasite-positive, was treated until rendered negative, as confirmed by a blood-smear at termination of treatment. Nevertheless, the parasite rates continued high during the four months of the epidemic, with many clinical cases and a great increase in heavy infections. It is logical to assume that, had we not intensively treated these four towns, the parasite rates therein would have exceeded those reached in our control town, as indeed they did in one of the towns, Guayabalito, in January, 1935, where they were 34.4 per cent, against 33.8 per cent in Chilibre, the control town. The truly epidemic character of the outbreak in the atabrine-plasmochin treated villages is shown by the experience in Gatuncillo, a town of about 100 persons, in which blood-parasite rates have always been high, in spite of continued treatment. Here during the period including December, 1934 to March, 1935, no less than 86.3 per cent of the population showed malaria parasites in the blood in at least one monthly survey. This high incidence occurred, it must be emphasized again, after two years of intensive treatment with atabrine and plasmochin, in which every positive which could be reached had been adequately treated with a potent drug.

In the control town, Chilibre, which received nothing but quinine, under no supervision, parasite incidence did not reach such a high level. Although the parasite rate in Chilibre was about the same during the same period (average 29.3 for Gatuncillo, against 30.0 per cent for Chilibre), only 67 per cent of the population of Chilibre had parasites during the same period of four months, in which 86.3 per cent of Gatuncillo's people were positive.

We believe that clinical attacks were more severe in the atabrine-treated towns during the recent epidemic than they were in the relatively untreated control town of Chilibre. Some exact knowledge of this condition may be obtained by comparing the number of so-called "plus" infections in the two places (a "plus" infection is one in which 1 or more parasites are present in each microscopic field of a thick blood film). In the period from January, 1935 to March, 1935 inclusive, such infections comprised 27.2 per cent of all infections in the 4 atabrine-plasmochin treated towns, while they formed only 17.0 per cent of all infections in the control town. There was no sharp increase in the percentage of heavy infections in the control town in January, 1935, as there was in the 4 treated towns at the beginning of the epidemic; the number increased by 1 in Chilibre, in a total increase of 30 positives, while it increased by 18 in a total increase of 52 positives from December to January, in the 4 treated towns. This seems to indicate that the epidemic was more severe in its effects on the individual, in the 4 treated towns, which may have been owing to a loss of tolerance or immunity caused by the previous absence of parasites in treated cases.

In making comparisons of the intensity of infections, the element of chance must be reckoned with, as we pointed out in an earlier paper (3, p. 402). Examination of the blood is made only monthly in each case, and great daily fluctuations may occur in the number of parasites found during the course of an infection. However, as the surveys are strictly comparable, and made over the same period of time, on a sufficiently large sample, errors due to chance tend to be compensated. The matter of intensity of infection will be further dealt with in a later section.

Further indication that clinical attacks were more numerous in the four atabrine-plasmochin treated towns, as compared to the control town, was obtained in April, 1935, when both authors made the blood-survey themselves in the control town. At this time, out of 222 persons whose blood was taken, only 3 showed clinical signs of malaria, and were confined to bed. Malaria parasites were found in 79 persons, a rate of 35.6 per cent. In the same month, in Guayabalito, one of the atabrine-plasmochin treated towns, 102 persons were examined, of whom 27 were positive for malaria parasites, a parasite rate of 26.5 per cent. Of the 27 positives, 8 were clinically ill, and confined to bed. The percentages of those clinically ill, among those blood-positive, were 3.8 for Chilibre, the control town, and 29.6 for Guayabalito, one of the treated towns. This seems to be unmistakable evidence that clinical malaria rates were higher in the treated towns than in the relatively untreated control town.

The assumptions based upon the foregoing facts lead us to examine carefully the factors underlying the course of events described above. Some unfavorable factor was active during the epidemic period, and we believe this to be the lowering of the natural immunity (or tolerance) of the community, caused by relative freedom from low-grade infections. In the usual course of events, as typified in the control town of Chilibre, only the clinical, disabling infections would be treated by the patients themselves, leaving the subclinical, low-grade chronic infections to smoulder untreated. We have interfered with this natural course in our treated towns, by endeavoring (with a considerable degree of success) to stamp out even the low-grade, chronic infections, particularly those which occur in young children.

The results of this interference developed during the epidemic period. A high infection rate, an increased number of clinical cases, and a great increase of heavy infections occurred, particularly in those towns most thoroughly treated. We have previously shown (3, p. 398; 4, p. 149) that a high crescent rate is associated with a high rate of heavy infections, especially in children, and this association likewise occurred during the epidemic period. Plasmochin, which has a definite devitalizing effect on

crescents, was of little use in controlling the high crescent rate, as in 90 per cent of the crescent-carriers in our four atabrine-plasmochin treated towns, crescents were found in the first examination in which they were parasite positive. Monthly surveys, in epidemic periods, are not frequent enough to discover all positives as they occur, and therefore many mosquito infections may result from crescent-carriers discovered too late to be treated.

The question naturally arises whether we have done more harm than good by our interference. There is little doubt in our minds that the increased severity of the disease, during the epidemic, with its concomitant result of high crescent rate, was due to decreased immunity, caused by relative freedom from parasites because of treatment.

In our third report we called attention to this possibility in the following words:

> It seems that the severity of clinical symptoms is greater in . . . "primary" cases which occur after a long period of freedom than it is in cases which increase to clinical proportions from time to time in the course of a more or less continuous latent infection. This and similar observations by other workers would lead us to believe that there is a certain element of danger in successful control of malaria to the inhabitants of any circumscribed area lying within a region of high endemicity. If continued freedom from parasites means a gradual loss of tolerance, the inhabitants of such an oasis may suffer severely from epidemics of malaria originating from introduced cases, so that their last state would be worse than their first. This possibility must always be borne in mind. . . .

A similar idea is expressed on page 189 of the Third General Report of the Malaria Commission of the League of Nations, entitled "The Therapeutics of Malaria" (7). They state "The condition of acquired immunity resulting in freedom from malarial disease after childhood is advantageous to the populations concerned, and radical interference with the process by which it comes about might be most unwise." In Part IV of their series entitled "Studies in Immunity in Malaria," Sinton and Harbaghwan (8) have analyzed the factors responsible for the production of immunity, and have systematized this knowledge; a rational

basis has been laid for the treatment or control of malaria by drugs, in populations living in areas of differing malaria endemicity. Their conclusions are in such accord with ours that we quote them extensively. In the section of their paper devoted to a consideration of the "treatment of individuals exposed to frequent and constant risk of reinfection" (the conditions under which our Chagres River village folk live), they state:

> There is much evidence to support the view that when, either by therapeutic or natural means, an individual is radically cured of an infection with one strain of plasmodium, he rapidly loses much of any acquired tolerance or premunition which he had developed to this strain as the result of his infection. The data available suggest very strongly that, to maintain any effective degree of such tolerance to the clinical effects of an infection with one strain of parasite, it is necessary for the individual to continue to harbour parasites of this strain. This means that his defensive mechanism must be continually stimulated either by the parasites of his original latent infection, or by continued re-inoculation with the same strain.
>
> If these facts be correct, and they appear to be so, the production of a radical cure of any one infection under the circumstances being discussed, would appear to be of little value, or indeed may prove harmful. If the patient be liable to frequent reinfection, homologous or heterologous, within a very short time after his radical cure, there appears to be little object in curing his infection. Such a cure would, theoretically at least, render him more liable to clinical attacks than if he continued to harbour a latent infection of the original strain, if the intervals between reinfections with the same strain were longer than the duration of his tolerance after radical cure. Even if his tolerance had persisted long enough to prevent clinical symptoms after reinfection, he would probably again acquire a chronic or sub-patent infection. In which case he would be no better off than before his radical cure.
>
> As we have not yet found a practical solution of the problem of the prevention of infection among rural populations in such hyperendemic areas (i.e., by the destruction of mosquitoes, or by other means to prevent the transmission of the disease) attempts to produce a permanent cure of infections would appear to be a waste of money, and probably even harmful in some circumstances.
>
> The provision of sufficient treatment to produce a clinical cure of any acute attacks of the disease would suggest itself as the most suitable

measure to adopt, in our present state of knowledge. Such a system of clinical cure among individuals liable to reinfection with multiple strains and at very short intervals, should not interfere radically with the development of their tolerance to the clinical manifestations of infections with the local strains, nor should it interfere seriously with any immunity already acquired or inherent. The effect of such treatment would be that the risk of a fatal result would be diminished, the severity and duration of the attack would be cut short, and the period of physical disability would be curtailed.

As Sinton and Harbaghwan state, and as our field experiment confirms, no practicable method now exists of preventing infections, and consequent epidemics, in such hyperendemic regions as the Chagres River area.

It is galling to make a confession of failure, but our recent experience, and the deductions of other workers, lead us to believe that, under our local conditions, it is to the people's best interests (and ours) to interfere as little as possible with the course of their malaria infections. Our main object, increasing the efficiency of native labor, may be accomplished by treating only those actively ill among the adults, and allowing the children to build up an immunity through repeated attacks of the disease. Treatment of clinical attacks in adults is a relatively simple and inexpensive measure, applicable to commercial organizations operating in the tropics. Such treatment can be entrusted to an intelligent native "practicante," and may be instituted without the necessity for time-consuming expensive blood-surveys. For such treatment, atabrine would seem to be the drug of choice, because of its lack of toxicity, ease of administration, and rapid curative effect.

THE USE OF PLASMOCHIN WITH ATABRINE

We followed the same plan of administration of plasmochin as was used during our previous year's work, namely giving a five-day course totalling 0.2 gram, in the week following the usual course of atabrine. We continued to have toxic reactions from plasmochin, but their number and severity were apparently reduced by not giving the two drugs simultaneously. We were

successful in reducing the number of crescent-carriers usually to be found after atabrine treatment alone, for during the year, out of 166 crescent-carriers among the "regular" inhabitants of our 4 atabrine-plasmochin treated towns, only 17, or 10.2 per cent, showed crescents at the blood survey in the month following plasmochin treatment.

However, we believe that there is very little use in administering plasmochin in therapeutic doses for the purpose of destroying crescents, for the great bulk (90 per cent) of the crescent-carriers showed crescents together with trophozoites at the first appearance of parasites in their blood. These crescents may have been present for a period before treatment began sufficient to allow the infection of many mosquitoes. This, together with the increased supervision required for treatment (the treatment period is doubled in length), and the severe toxic effects sometimes associated with its use, lead us to believe that no results can be obtained sufficient to warrant the use of this costly drug.

INEFFICACY OF QUININE WITHOUT SUPERVISION OF TREATMENT

If our statements regarding the inadvisability of attempting a radical cure of malaria infections in our locality are correct, then the type of treatment self-administered by the inhabitants of Chilibre, the control town, is the sort indicated. It will be remembered that here we merely provided quinine sulphate to the inhabitants, leaving it to them as to whether they would take it or not. Our results show without question that merely the provision of an adequate supply of quinine to an ignorant native population has little or no demonstrable effect on the malaria parasite rate. This can be shown by comparing the number of persons positive over many months, in the control town, with the number similarly positive in the towns in which treatment with atabrine was adequately supervised. In Chilibre, the quinine control town, among a total of 252 "permanent" inhabitants examined at least 4 times in 12 months, there were 33 persons positive for 2 successive months, 23 for 3 months, 10 for 4 months, 2 for 5 months, and 1 apiece for 6, 7, and 9 successive

months. In contrast to this record, out of a total of 478 persons in our 4 atabrine-treated towns, in which treatment was supervised, only 23 were positive for asexual parasites for 2 successive months, and only 4 were positive for 3 successive months. No person was positive for more than 3 successive months. Many of these successive positives were found positive in the intervals between surveys, and hence too late to receive full treatment. Expressed in percentages, only 5.6 per cent of 478 persons in the atabrine-treated towns were positive for 2 or 3 successive months, while 22.2 per cent of 252 persons were positive for 2 or more months (up to 9 successive months), in Chilibre, which received quinine only, without supervision of treatment. In practice, this means that quinine provided without supervision of treatment, in the expectation that such a measure will reduce the malaria parasite rate among a native population, is a delusion, and an indefensible waste of money.

THE VALUE OF ATABRINE FOR TREATMENT OF MALARIA

We do not wish to give the impression that, because of our failure to prevent an epidemic, atabrine is of no value in the treatment of clinical malaria. The figures just given above show that atabrine was markedly successful in eliminating parasites and alleviating clinical symptoms.

During the course of our 3 years' experience with the drug, we have observed no toxic effects, nor any contra-indications to its use. It has proved capable of eliminating asexual parasites from the peripheral blood with a 5-day treatment, using a total for adults of 1 gram of the drug. It has no effect upon the crescents of subtertian malaria, to destroy which plasmochin must be used. Unfortunately, in our hands atabrine has been much less successful than was hoped in preventing relapses, especially in young children. We believe that it is the drug of choice in treating clinical malaria in a native population, because of the short treatment period, and lack of unpleasant by-effects, which prejudice natives against any form of quinine. The ease of administration of atabrine is a distinct advantage, as many persons who would avoid quinine treatment willingly present themselves for treatment with atabrine.

II. Observations of Type of Malaria Parasite, Crescent Incidence, Intensity of Infection, Relapse, and Immunity

Part II continues the record of surveys begun in 1930 and continued to August, 1935. The populations surveyed during this period were all under some form of antimalaria treatment, and the rates are somewhat modified by the results of such treatment. The parasite rates for the group of four villages under

TABLE 1

Parasite rates in towns in the Chagres River area, 1934–1935

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
1934									
September	363	22	6.1	281	18	6.4	186	28	15.0
October	376	37	9.0	271	16	5.9	242	24	10.0
November	401	32	8.0	278	42	15.1	223	36	16.1
December	404	52	12.9	276	38	13.8	232	48	20.7
1935									
January	412	104	25.3	295	77	29.5	231	78	33.8
February	400	95	23.8	282	54	19.1	139	53	38.1
March	374	108	28.8	289	78	27.0	175	55	31.4
April	358	87	24.3	256	51	19.5	222	79	35.6
May	376	51	13.3	261	42	16.1	205	44	21.5
June	340	63	18.5	273	41	15.0	206	42	20.4
July	379	36	9.5	286	32	11.2	238	49	20.6
August	368	37	10.0	272	37	13.2	231	34	14.7
Totals	4,551	724	15.9	3,320	526	15.8	2,530	570	22.5
1933–34	4,376	470	10.7	3,313	564	17.0	1,604	328	20.5

atabrine-plasmochin treatment during the past year (September, 1934 to August, 1935) and for New San Juan, under quinine-plasmochin treatment, are given separately, as are the rates for Chilibre, the control town, which was under voluntary quinine treatment only. Table 1 gives the crude parasite rates by months for the past year.

The abrupt increase in parasite rates which ushered in the epidemic period is shown in all towns for January, 1935. After

passing through a season of abnormally low rates in October, 1934, even in the relatively untreated control town, the rates rose simultaneously in all towns in January, and remained high during the following three months. A decrease in rates in all towns was noted in May, 1935, which continued until the end of the year of observation, in August, 1935. At the time of writing (October, 1935), the low rates have continued, being comparable to those found in October, 1934.

The epidemic which occurred in the late winter and spring months of 1935 is a manifestation of one of the great cyclical swings of the malaria parasite curve which occur in our locality. Its occurrence was predicted by us in our previous report (4, p. 145), but we did not expect such high rates as actually occurred. The reasons for these high rates have been previously discussed. If history repeats itself, we may have another increase in parasite rates during the winter and spring of 1936, but it is hoped that an epidemic of such proportions as the last will not occur again.

OBSERVATIONS ON TYPES OF MALARIA PARASITES, CRESCENT INCIDENCE, INTENSITY OF INFECTION, AND IMMUNITY

Table 2 shows the incidence of the various species of malaria parasites found during the year of September, 1934 to August, 1935 inclusive. The number of positives found monthly in the four river villages and in New San Juan are combined in this table.

The same table gives the same data for the same period for the control town of Chilibre.

As in the previous year, as the total parasite rate decreased, the number of tertian positives increased in all towns, both relatively and absolutely. In other words, the epidemic was an epidemic caused by estivo-autumnal (subtertian) parasites.

As also occurred during the previous year, the percentage of cases showing crescents, among all the subtertian cases, was higher in the four atabrine-plasmochin treated towns and New San Juan, than it was in Chilibre, the relatively untreated control town. This may be partially explained by the somewhat greater number of heavy infections encountered in the treated towns, as

these tend to be followed by heavy crescent infections, as mentioned above. As most of the crescent infections were found on the first positive examination, before plasmochin could be given, the drug could have little effect on the crescent rate.

TABLE 2

Species of malaria parasites in 12 monthly surveys in 5 treated towns and in control town

DATE	FIVE RIVER TOWNS						CHILIBRE					
	Total positives	Total E. A.	Total tertian	Total quartan	Per cent tertian	Per cent crescents in all E. A. cases	Total positives	Total E. A.	Total tertian	Total quartan	Per cent tertian	Per cent crescents in all E. A. cases
1934												
September	40	28	11	1	27.5	23.3	28	24	4	0	14.3	16.6
October	53	43	8	2	15.1	20.0	24	14	9	1	37.5	25.6
November	74	58	14	2	18.9	23.0	36	26	8	2	22.2	14.3
December	90	74	16	0	17.8	29.8	48	31	15	2	31.2	27.3
1935												
January	181	164	14	3	7.7	42.0	78	60	16	2	20.5	16.1
February	149	137	12	0	8.1	25.5	53	45	7	1	13.2	28.3
March	186	171	12	3	6.5	34.6	55	44	9	2	16.3	14.5
April	138	128	9	1	6.5	27.3	79	68	9	2	11.4	17.8
May	93	75	17	1	18.3	22.4	44	31	12	1	27.3	12.5
June	104	82	21	1	20.2	15.9	42	34	5	3	11.9	2.7
July	68	54	14	0	20.6	29.6	49	30	17	2	34.7	12.5
August	74	62	10	2	13.5	9.4	34	24	9	1	26.4	8.0
Total	1,250	1,076	158	16	12.6	28.2	570	431	120	19	21.1	25.3
1933–34	1,031	840	175	16	16.9	22.8	328	251	76	1	23.2	17.9
1932–33	1,259	1,124	127	8	10.9	29.2	Data incomplete					
1931–32	956	793	136	27	14.2	13.2						
1930–31	1,024	701	264	59	25.4	22.9						

The crescent rate in the five river towns was 28.2, somewhat higher than that of the preceding year, 22.8. The number of heavy infestations with crescents was greater during 1934–1935 than in the previous year, thus increasing the possibility of mosquito infection. This also was undoubtedly owing to the greater

number of heavy infections encountered during the epidemic. As in past years, crescents appeared on the first positive examination in cases giving no indication of antecedent infection over a lengthy period.

INFECTION IN INFANTS

During the year September, 1934 to August, 1935, 28 infants born during the year, and ranging in age from 2 to 12 months, were examined an average of five times. Of these, 7 were found positive, giving an annual rate of 25.0 per cent. Three had tertian and four had estivo-autumnal infections. The youngest age at which infection was found was three months. Two infants of this age were found positive, one with a tertian infection and the other with a slight ring-form infection, probably estivo-autumnal. Crescents in small numbers were found in two of the four estivo-autumnal infections. One infant showed a "plus" tertian infection at the age of five months.

INTENSITY OF INFECTION

During the year September, 1934 to August, 1935, in a total of 1250 positive bloods found in our twelve monthly surveys in five river villages, there were 251 "plus" infections (1 parasite or more to each thick-film microscope field) or 20.0 per cent. In Chilibre, the control town, in 570 positive examinations there were 109 "plus" infections, or 17.4 per cent. These rates are considerably higher in both groups than in the previous year, when they were 15.0 for the five villages and 11.3 for Chilibre. This increase in per cent of heavy infections is a reflection of the high parasite rates found during the epidemic period, and was doubtless due in part to lack of immunity in the treated population. The observed increase is yet another indication that radical cure of malaria infections in a hyperendemic area is inadvisable.

IMMUNITY

Still further evidence of a familial immunity, and its converse, was obtained during the past season. Two extreme examples, illustrating both ends of the scale, are presented in Table 3. The

TABLE 3

Comparison of monthly blood examinations of two native families over a period of two years

NAME	AGE	1933				1934												1935								NUMBER OF EXAMINATION	TIMES POSITIVE
		September	October	November	December	January	February	March	April	May	June	July	August	September	October	November	December	January	February	March	April	May	June	July	August		
Rafael M.	1	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	23	2
Nicolas M.	2	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–			–	21	0
Moises M.	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	23	0
Blasina M.	4	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–			–	–	–	20	0
Otilia M.	7	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		–	–	–	23	0
Demetria M.	8	–	–	–	–					–	–	–		–	–	–	–	+	–	–			–	–	+	17	2
Elpidia M.	9	–	–	–	–		–			–	–	–	–	–	–	–	–	–	–	–	+	–	–	–		20	1
Total																										147	5
Luisa V.	1													–	–		–	–	+	–	+	–	–	–		10	2
Eladia V.	5	–	–	–	+	+	–	–	+	–	+	–	–	–	–	–	–	+	–	+	–	+	–	–	+	24	8
Concepcion V.	6	–	–	–	+	–	–	+	–	–	–	–		+	–	–	–	+	–	–	+	–	+	–	–	23	6
Santos V.	10	+	+	–			+		–		–	–	–	+	–	+	–	–			+	–	–	–	–	18	6
Santana V.	12	–	–	–		–	+	+	–	–	+	–	+	–	–	–	–	+			+		+	–	–	20	7
Maria V.	14	–	–	+	+	+	–		–	–	–	–	–	–		–	+	–	–	–	–	–	+	–	–	22	5
Total																										117	34

first family, living in Gatuncillo, has for years helped to keep up parasite rates in this town, which has uniformly and consistently shown higher rates than any other of our treated towns. The second family, living in Guayabalito, has shown a very high resistance to infection over the entire five-year period of our observations. This is all the more remarkable, as the average age of the children in the immune family is lower than that in the highly susceptible family; hence it is to be expected that natural immunity would be less in the actually more immune family.

Thompson (9), working in Nyasaland in 1934, has made observations on African children which parallel ours in a remarkable degree. We have not had access to his original publication, but quote from a review of his work by Fletcher:

> An examination of 103 children made once a month for a whole year showed that some were much more susceptible than others to malaria. Four of the children remained consistently negative. This varied resistance in children under 10 years seems to indicate that certain individuals have an inherited tolerance; . . . tolerance is soon developed, and except in very young children, malaria causes little illness. The children seen in this survey showed few manifestations of malaria and all those who were old enough to walk could run about as if they were perfectly healthy, although they had parasites in their blood.

Capt. H. W. Mulligan (10) has noted the reverse of this situation in his studies in India, in that certain families examined in many successive surveys always have a higher parasite rate than do others living in the same conditions.

Such observations have an obvious bearing on drug control measures, particularly in areas of low endemicity; by attempting a radical cure of the individuals comprising the susceptible families, dangerous foci of the disease may be wiped out, with benefit to the families themselves and to the whole community.

RELAPSES

The matters of treatment, infection, immunity, etc., are all complicated by the question of relapses. No method is readily available by which to distinguish a relapse from a new infection,

so it is impossible to state definitely how many of our cases are due to one cause or the other. We see no reason to withdraw from our position taken in former publications, that a large percentage of our cases were true relapses. It is quite probable that the recent epidemic was touched off by carriers, who relapsed with the disease, and produced large numbers of gametocytes in the interval between surveys in December and January, 1934–1935, especially in our 4 treated villages. The number of crescent-carriers was low in December in these towns, being only 23.8 per cent of all subtertian cases found. It seems impossible that such a tremendous increase in number of cases (121.4 per cent) could have occurred in the short interval of a month (between December and January), given the few gametocyte carriers discovered in December (only 10 in 42 E. A. cases in all 4 villages), without believing that a large proportion of the infections were relapses. This supposition is borne out by the fact that the number of crescent carriers increased from 10 to 28 among a total increase from 42 to 93 E. A. cases (19.2 per cent to 30.0 per cent). It has been shown by other workers that gametocytes are more likely to be present early in relapses than in new infections, and this fact fits in with our supposition.

In our third report (3, p. 387) we state that there has been "an accumulation of evidence . . . that certain families among our villagers are more prone to show malaria parasites in their blood than are other families. . . . The members of these families, in spite of repeated treatment, relapse time after time, and are found among the list of those to be treated, month after month." Further evidence of the same sort accumulated during the past year, and was marked during the epidemic period. The second family noted in Table 3 was a good example of the tendency to repeated relapse in treated individuals. During the epidemic period, in three of the four atabrine-treated towns, we have records of 36 relapses (or recrudescences) which occurred at intervals of a month or less, after atabrine treatment. In March, 1935 there were 15 such relapses after treatment during the preceding January, forming 17.5 per cent of all positives found during that month in the three towns. In many cases the severity of symp-

toms was greater during the relapse than in the first attack; further, many relapses occurred at intervals too short for them to be considered as due to new infections.

CYCLICAL VARIATIONS IN MALARIA INCIDENCE IN PANAMA

As we have indicated in previous publications, malaria infection in our River Villages is not static but rises and falls in waves of varying amplitude from year to year (see chart 1). These waves show peaks varying in height and depth, but in general, during the past few years at least, the greatest incidence of malaria occurs in the winter months, at the cessation of the rainy season, while the lowest incidence usually occurs in late fall, before the heaviest rains. At present, we are unable to correlate the increases in infection with climatic factors. During the past few years, normal seasonal mosquito-breeding conditions in the Chagres River have been interfered with by the operations connected with the construction of Madden Dam. It is possible that they may be further modified, intentionally or not, by the spilling of water through the gates of the newly completed dam. Changed conditions may result which will be unfavorable to mosquito breeding, and thus decrease transmission of malaria. However, we believe that there is no strict correlation between seasonal abundance of anopheles mosquitoes and peaks of malaria incidence. Anopheles are present throughout the year, in sufficient numbers to transmit the disease. We believe, rather, that the peaks of incidence are due to variations in immunity in the population. Epidemics are followed by periods of relative freedom from malaria, but the immunity is soon lost, and another epidemic occurs. Such cyclical variations occur also in temperate climates, but there the intervals are usually much longer. The great general rise of malaria in the United States in 1934 is an example of the long-time variation.

SOME CRITERIA FOR FUTURE EXPERIMENTAL WORK, ESTABLISHED BY OUR OBSERVATIONS ON MALARIA INCIDENCE

As so often happens in experiments planned for a specific purpose, the by-products of our work have proved to be as profit-

able as the main object, the evaluation of certain new drugs in malaria control. We are now able to indicate some essential precautions which must be observed in future observations of this sort. Chief of these precautions is the absolute necessity of determining in advance of any proposed experimentation, the natural trend of the malaria rate. We now know that a knowledge of the amount of malaria present in any community at any one time is an insufficient datum or baseline from which to draw conclusions as to the success of control measures. The literature is full of reports of such successes, which were judged successes because malaria rates dropped *after* control measures were instituted. The usual history of such reports is that control measures were begun because malaria had suddenly become an acute problem, which cried for immediate solution or alleviation. Control measures begun in response to such a call were successful, and the success has been attributed to the measures used. In view of our present knowledge, we believe that such control measures were begun after the peak of an epidemic had been reached, and that malaria rates soon would have reached normal limits, without intervention.

Therefore, in order to reach satisfactory conclusions in regard to the value of anti-malaria measures, the natural trend of the disease must be observed over a period sufficiently long to pass through several cycles of increase and decrease. Otherwise, what may appear to be a success may be only a swimming with the tide. In order to correctly evaluate a drug, it should be administered over a period long enough to include one of the cyclical upswings of the malaria rate. Only if it is successful under these conditions can it be considered of any value in community malaria control or prevention. Unfortunately, judged by this standard, atabrine, or atabrine and plasmochin in combination, in our experience, offer little hope of preventing or controlling malaria under existing conditions in Panama. We do not wish to give the impression that atabrine or plasmochin are valueless in the treatment of clinical malaria, for we believe that in certain respects atabrine is superior to quinine, especially in its ease of administration, and in lack of by-effects. The specific

action of plasmochin on subtertian gametes is too well proved to merit further mention.

It is highly important, in experimental work undertaken to determine the efficacy of drugs in malaria control, to keep individual records of blood-findings, treatment, and any other pertinent data. It is quite possible, that results may be considerably modified if successive surveys are made which include a proportion of transients, present at the time of survey but untreated, and turning up later in subsequent surveys. The presence of such transients may considerably modify the monthly survey rates. We have obviated this possibility in our work as far as possible by excluding from consideration all such transients. The simplest method of keeping records which may be checked is the individual card index; at the end of the year the monthly records are transferred to sheets, which show the yearly record of examinations and treatment for each individual. This seems to us the most practical way of obtaining a general picture of the annual parasite rates, the efficacy of treatment, the incidence of crescents, or heavy infections, and any other required data. By using such yearly summaries of individual records, we discovered the existence of immune and susceptible families, and such records make it easier to follow up individuals or groups in which one may be particularly interested.

SUMMARY AND CONCLUSIONS

The present paper records observations made during the fifth consecutive year of studies on malaria in Panama. For reasons given, the same methods of treatment were used as in the preceding year. None of these methods were able to prevent or to check the course of an epidemic, caused by subtertian parasites, which occurred during the first four months of 1935. This epidemic was a manifestation of the cyclical variations in malaria parasite rate which are characteristic of malaria in Panama. Our increased knowledge of the local conditions has caused us to abandon the method used in the past, the attempt to reduce malaria incidence by treatment directed against the reservoir of malaria in young children and adolescents. We fear that more

harm than good has been done by this method, and believe that our objective, to increase labor efficiency, may be more easily obtained by treatment of clinical cases as they occur, using atabrine as the drug of choice.

Part II of the paper gives a summary of the malaria parasite rates found during the year, and compares them with former years. Further evidence that a familial immunity to malaria may exist is presented, and finally, some essential criteria which must be used in future experimental work are outlined.

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