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A THIRD YEAR'S OBSERVATION IN PANAMA, WITH SPECIAL REFERENCE TO CONTROL WITH ATABRINE[1]

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I. OBSERVATIONS ON MALARIA CONTROL WITH ATABRINE

After the introduction of atabrine some few years ago, the first very favorable reports as to its efficacy in controlling the symptoms of malaria gave hope that it might be the long-hoped-for means of ridding the tropics of their greatest curse. We shall not review the already extensive literature on the drug, but will quote a typical example from an article by A. L. Hoops (1), who used it among estate laborers in Malacca. He states:

> The points in favor of the use of atabrine in place of quinine are: (1) The fever is usually reduced as quickly as with quinine. . . . . (2) No parasites of any description were found in the blood of any hospital case on the conclusion of the treatment. (3) The treatment is short, simple, and effective, one 1½ grain tablet 3 times a day for 5 days only, as against a prolonged course of quinine. (4) The drug is not unpleasant to take, and is not depressing. It is well tolerated, even by pregnant women and young children, and in blackwater fever. . . . . (5) Relapses are rare after atabrine, while with quinine the relapse rate is high. (6) Last, but not least, atabrine is a powerful preventive of malaria in the sense that most of those treated with it, being cured, are rid of the infection and completely non-infective to their fellows.

We agree with Hoops with regard to points 1, 3, and 4, but unfortunately our own work in Panama has rather definitely shown that his conclusions regarding relapse and cure are unfounded. The following data, upon which our conclusions are based, are submitted for judgment.

As a preliminary to field trials, during the spring of 1932 the sen-

[1] Read at the joint meeting of the American Society of Tropical Medicine and the National Malaria Committee at Richmond, Virginia, November 17th, 1933.

ior author observed a series of 20 cases of malaria treated in Gorgas Hospital with atabrine alone. The results were startlingly good, so far as clinical cure was concerned. However, in the great majority of estivo-autumnal cases, crescents were found in thick films taken on the day of discharge from the hospital. Knowing from this experience that atabrine would reduce the fever and free the blood of all but the sexual forms of the parasite, it was given a limited trial in the field. In August, 1932, a series of 32 cases among native Panamanians living along the Chagres River were treated with atabrine, being given the usual treatment of one 1½ grain tablet three times daily for five days. In every case the blood was freed of asexual parasites by this treatment. The majority of these cases could be followed during the succeeding eight months, their bloods being examined by the thick film method monthly. Of 24 individuals so followed, 19 relapsed, and only 5 showed no recurrence of parasites during the 8 months period.

One source of error which was not guarded against in this first trial was in the administration of the drug. Only the first dose was personally administered, the remainder being left to be taken according to instructions. However, as all cases were found negative for asexual parasites seven days after the treatment was supposed to have been completed, it is certain that a large percentage of it was taken. To guard against this source of error, which was thought to be one cause of the high relapse rate, it was determined to give the drug personally in any subsequent trial. In January, 1933, the regular monthly blood survey which has been made during the past three years was carried out in five towns along the banks of the Chagres River and its tributary the Gatuncillo. One week after this survey was made, all persons in four of the villages, known hereafter as the treated villages, who were found positive for malaria, were visited three times a day for five successive days, and were given 1½ grains of atabrine, personally administered, at each visit. At the end of the five-day period, a blood-smear was obtained from each person. One village, the largest of the five, was not visited except at the time of the monthly survey, but was used as a control. Here quinine sulphate, in capsules or tablets, was distributed by a native

woman of the place, to all those found positive during the previous survey.

This method of procedure was followed out during the succeeding seven months, in three of the four villages under atabrine treatment. It was found impossible to include the inhabitants of the smallest village, containing about 70 people, in the list of those receiving the drug at the hands of the senior author, because of the relative inaccessibility of the town, making it impracticable to visit it three times a day, and still cover the rest of the ground satisfactorily. During eight months, 400 cases of malaria were treated in the four villages. For various reasons it was impossible to follow up with blood examinations more

TABLE 1

DATE	THREE ATABRINE-TREATED TOWNS			CONTROL TOWN		
	Number examined	Number positive	Per cent positive	Number examined	Number positive	Per cent positive
January	255	55	21.6	136	39	28.6
February	262	74	28.2	133	43	32.3
March	301	69	22.9	157	30	19.1
April	302	76	25.2	165	55	33.3
May	284	56	19.7	188	43	22.8
June	274	51	18.6	178	51	28.6
July	278	51	18.3	179	43	24.0
August	279	52	18.6	198	63	31.8
	2,235	484	21.6	1,334	367	27.5

than 329 persons. Excluding also those 71 persons treated in the smallest village, who did not receive personal attention, there remain 281 persons, who were followed up during eight months, and who will form the basis for discussion of the results of treatment. Table 1 shows the number of "regular inhabitants" examined in the three treated towns, and in the control town, the number and per cent positive. If we omit from consideration the rates for January, which of course were obtained before the treatment with atabrine was begun, we find a difference of 5.8 per cent in favor of the three treated towns, during the seven months from February to August, 1933. This very small differential in favor of the treated towns is due, as will be shown, to the

high percentage of relapses in the treated cases. Table 2 shows the number of persons examined each month during the eight months period; the number positive; the per cent positive; the number treated, who were followed up during the succeeding months of the period; the number of times relapses followed treatment and were again treated during the period; and the number treated each month who remained negative thereafter.

Table 2 shows that in this sort of work, it is impossible to treat all those found positive in the monthly surveys, because of their absence during the succeeding treatment period. Also, no positives showing crescents only were treated, as atabrine is

TABLE 2

DATE	NUMBER EXAMINED	NUMBER POSITIVE	PER CENT POSITIVE	NUMBER TREATED	NUMBER OF TIMES TREATED				NUMBER REMAINING NEGATIVE AFTER TREATMENT
					1	2	3	4	
January	255	55	21.6	27	27	0	0	0	4 for 7 months
February	262	74	28.2	39	39	0	0	0	7 for 6 months
March	301	69	22.9	33	30	3	0	0	6 for 5 months
April	302	76	25.2	42	29	13	0	0	10 for 4 months
May	284	56	19.7	32	18	10	4	0	18 for 3 months
June	274	51	18.6	37	14	19	4	0	
July	278	51	18.3	36	18	15	4	1	
August	279	52	18.6	35	15	12	6	2	
	2,235	484	21.6	281	188	72	18	3	

known not to affect crescents. There were 51 such untreated crescent positives. The remaining difference, 203, consisted in part of those treated, but not followed up, and in part of those who received no treatment for one reason or another. Of this latter group, there were 97 untreated positives. Fifty-eight were negative the following month, 18 were positive, and in 21 the blood was not examined during the following month. The number, 97, who received no treatment, may seem unduly large, but is explained by the fact that many positives were found during the five-day treatment period, rather than at the regular survey time, and hence too late to receive full treatment.

Relapses requiring a second course of treatment appeared two months after the first treatment. As time went on, the number of relapses increased, until in June, July, and August they outnumbered those who were treated during those months for the first time. This is graphically shown in figure 1. This chart

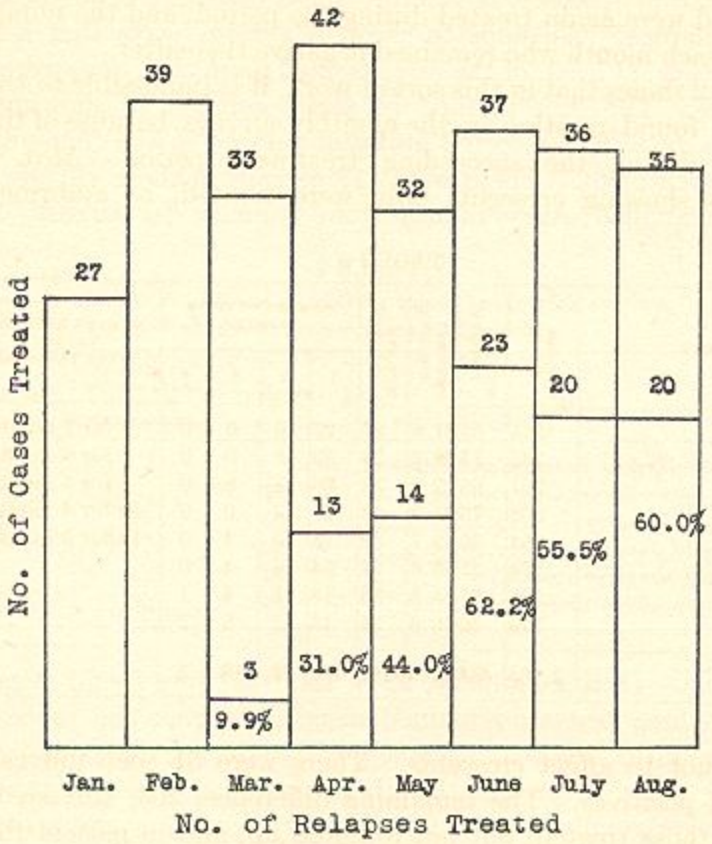

FIG. 1

shows quite definitely that a very large percentage of our treated cases relapsed within such short intervals after their original treatment that they made up in some instances more than half of the total number treated in any one month. The number remaining negative after treatment was very small, becoming smaller as the time-interval increased from the date of original

treatment to the date of the termination of the treatment period. This is shown in the last column of table 2.

RELAPSES

The first question that comes to mind in connection with this high rate of relapses, is whether these cases are reinfections or true relapses. We hope to show in various ways that a large percentage, at least, of the cases treated more than once were true relapses. The first method of proof consists in showing the malaria rates in a selected group of persons in the four villages under treatment. There were 117 persons in these villages who were examined every month from January to August, 1933,

TABLE 3

Number of positives in persons found positive or negative in January, who were examined for seven months thereafter

	NUMBER	NUMBER OF EXAMINATIONS POSITIVE THEREAFTER	AVERAGE
Total examined in January and followed up for seven succeeding months.....	117		
Positive in January.....	25	73	3.0
Negative in January.....	92		
Remaining negative thereafter.....	33	0	
Becoming positive thereafter.....	59	107	1.16

inclusive. During January, 92 of this 117 were found negative. Thirty-three persons remained negative during the succeeding seven months, while 59 became positive during the same period. During these seven months, there were 107 cases in these 92 persons originally negative in January, or an average of 1.16 attacks per person in this group.

During January, 25 of the same 117 persons examined 8 times were positive. Only 2 persons were negative for seven months thereafter, while 23 were positive during the same period. During this period of seven months, there were 73 cases in these 25 persons originally positive in January, an average of nearly three attacks per person in this group. To put it another way, of the 92 persons out of 117 who were negative in January, 59 were

positive at some time later during the seven following months, or 64.1 per cent. Of the 25 who were positive in January, 23, or 92.0 per cent were positive thereafter.

This material is presented in table 3. A second method of showing that these cases were actually relapses is to calculate, from the known figures, the probability that a person having malaria in January would have it again during the succeeding seven months.

A theorem in probability states that if the separate probabilities of each of several independent events are respectively $p1$, $p2$, $p3$, etc., the probability of their all occurring together is P equals $p1 \times p2 \times \times p3 \ldots$ From this theorem let us see what is the probability that those having malaria in January will have it again in the succeeding seven months. The total number examined 8 times, from January to August, is 117.

The number positive in January is 25.

The number negative in January is 92.

The number remaining negative thereafter is 33.

The number becoming positive thereafter, during the period February–August, is 59.

$$p1 \text{ is } \frac{25,}{117,} \text{ or } .214$$

$$p2 \text{ is } \frac{59,}{117,} \text{ or } .504$$

P is $.214 \times .504$, or .108.

$117 \times .108$ is 12.6 the probable number who, having malaria in January, will have it again later. Actually there were 23 such cases among the 25 who were first positive in January, nearly twice the expected probability.

In addition to this mutually supporting evidence, there is the accumulation of evidence over the last three years that certain families among our villagers are more prone to show malaria parasites in their blood than are other families. There are half-a-dozen such families in our treated villages in which, during the eight months of our study, we could always find one member with positive blood. 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. As will be seen from table 2, 18 persons were treated three times during eight months, and 3 were treated four times apiece. In each instance, the blood at the close of treatment was negative for malaria parasites.

TABLE 4

Individual records of persons treated three or more times in eight months

NAME	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST
J. C.....	Cr(1)	–	Cr(5)	T-f	–	EA-16	–	EA-f
D. C.....	EA-20	–	Ea +	–	EA-26	–	–	–
C. E.....	Q-6	–	EA +	–	EA +	–	EA-12	–
C. G.....	EA-f	–	–	EA-6	–	–	EA +	
G. I.....	EA-f	Cr(5)	–	EA-f	–	–	EA-f	EA-2
R. R.....	–	EA-7	–	EA-4	–	–	EA-f	–
C. C.....	–	T-17	EA-1	EA +	–	–	–	EA +
L. C.....	EA-f	–	EA-1	EA-f	–	–	EA-f	–
I. G.....	EA-7	–	EA-f	–	Cr(2)	EA-2	–	
P. M.....	EA +	–	EA-f	–	T-4			
J. V.....	–	–		EA-3	–	EA-4	–	EA-f
C. A.....	Cr(5)	EA +	–	–	–	T-10	–	T-f
F. T.....		EA +	–	EA-9	–	EA-5	–	EA +
G. T.....		EA +	–	–	–	EA-f	–	EA-f
M. V.....	Cr(6)	EA +	–	–	EA +	–	T-f	–
S. V.....			–	EA-43	Cr(4)	T-7	–	EA-26
I. M.....			EA +	–	–	T-f	–	EA-f

Explanation of symbols: EA, estivo-autumnal rings; Cr, crescents; T, tertian schizonts; –, negative. Numbers after symbols designate number of parasites found in entire thick film. "f" designates approximately 1 parasite in 10 fields; "+" designates 1 parasite per field or more; "++" designates 25 or more per field.

The presence of such family groups, in which malaria persists for long periods in spite of any form of treatment, seems to us to be the crux of the whole situation with regard to malaria control by drugs. This type of family and of individual is not amenable to drug treatment, and the persistence of infection in them, even after vigorous and long-continued treatment, is the stumbling-block in all attempts to control malaria by means of drug administration. As an illustration of this fact, table 4 is presented.

The records of some of the families showing high malaria incidence over the eight-months period are next shown, to illustrate the tendency of the disease to "run in families." This tendency may be the explanation of the so-called "malaria houses," in which the disease seems to show a predilection for certain dwellings. We have noted that this tendency is rather a matter of family, for we have observed several instances during the past three years of susceptible families moving from one town to another, taking their malaria with them. (See table 5.) Of the 209 times individuals in these groups were examined, they were positive 89 times, or 42.6 per cent. All these families were under atabrine treatment throughout the eight-months period.

TABLE 5

Malaria incidence in certain non-immune families

The first number indicates the number of individuals examined, the second, the number of individuals found positive in each month.

NAME	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	TOTAL
Galvan	3—1	6—3	6—2	6—1	6—1	5—2	5—3	5—2	42—15
Colpas	4—1	5—4	5—2	5—2	6—3	5—2	6—1	6—4	42—19
Gondola	4—3	4—2	4—3	4—2	3—1	3—2	2—0		24—13
Hernandex	2—2	3—2	3—2	3—1	3—2	2—1	3—3	3—1	20—12
Torres	3—2	5—2	5—2	4—1	5—0	5—3	4—0	5—3	36—13
Vasquez	4—4	5—3	6—0	6—3	6—3	6—1	6—2	6—1	45—17

On the other hand, there are families which show a high resistance to malaria, and whose members are very seldom ill, or show parasites in the blood. It is obvious that in these families there must be some factor producing a high individual immunity, for all these people live under practically identical conditions as to housing, absence of screening, and exposure to mosquito bites.

SELF-CURE AS AN ELEMENT IN EVALUATION OF EFFICACY OF ATABRINE

It is well known that malaria is a disease which shows a marked tendency to get well of itself. We found among the 594 positive bloods in our "regular" inhabitants of the four treated towns, 96 positives showing ring-forms in one survey, and not treated, who

were negative in the succeeding survey, a per cent of 16.2. In other words, one out of every six persons found positive in one survey would be negative, without treatment, in the succeeding survey. Of course, this means that atabrine got a good deal of credit for clearing up positive bloods to which it was not entitled, for about 1 in 6 of the atabrine-treated persons would have cleared up without such treatment.

TABLE 6

Treated and untreated towns compared as to individuals positive many times

TIMES EXAMINED	NUMBER EXAMINED	NUMBER POSITIVE	PER CENT POSITIVE	9 TIMES	8 TIMES	7 TIMES	6 TIMES	5 TIMES	4 TIMES	3 TIMES	2 TIMES	1 TIME	0 TIMES
TREATED TOWNS													
12	63	51	81.0				2	5	3	111	17	14	12
11	66	51	77.3		1		1	2	6	7	18	15	15
10	60	54	90.0			1	2	3	8	12	13	15	16
9	45	33	73.4					3	2	5	8	15	12
8	51	37	72.5					1	1	9	10	16	14
7	46	25	54.5					1	0	3	4	13	21
6	34	18	53.0							5	9	8	16
CONTROL TOWN													
12	13	10	77.0		2	2	1	0	2	0	0	3	3
11	14	13	93.0	1	2	0	2	1	3	2	2	0	1
10	19	17	89.5	1	2	1	3	3	3	2	1	2	2
9	18	17	94.5		0	0	0	3	0	4	6	4	1
8	35	25	71.5		1	1	2	2	1	4	8	6	10
7	41	27	66.0			1	1	1	1	2	7	14	14
6	36	20	55.6						4	2	4	10	16

THE CONTROL TOWN

In estimating the results of atabrine, the discussion has hitherto been confined solely to the results obtained by its use in the four towns under treatment. In our control town, quinine was distributed by a native woman to all found positive in the surveys. The malaria rate, with the exception of one month, was consistently higher than that in the atabrine-treated villages.

Unfortunately, because of our infrequent visits, we have little information as to the incidence of clinical malaria. However, the number of "plus" infections in the control town was higher than in the atabrine-treated towns, the percentages being 24.8 and 20.0 respectively. This is not much greater than the rate found in the treated towns, but it does not tell the whole story. In only 3 cases in which a full course of atabrine was taken was the blood positive during the month following the treatment. On the other hand, in the control town there were many individuals whose blood remained positive for many months in succession. Table 6 compares the treated towns with the control town in this respect.

The effect of treatment is noteworthy in reducing the number of persons positive over long periods. This can be shown if we take that portion of each table which contains those individuals examined 12, 11, and 10 times during twelve months, and the columns denoting 9 times, 8 times, 7 times and 6 times positive during the twelve months; we find that in the four treated towns there were only 7 persons who had malaria 6 or more times, out of 189 persons examined 10 to 12 times. In the control town, there were 17 persons who had malaria 6 or more times, out of 46 persons examined 10 to 12 times. The percentage of persons so positive was 3.7 and 36.9 respectively, showing that in the control town nearly 10 times as many persons had 6 or more attacks than did those in the treated towns.

This indicates that sufficient quinine was not taken by the inhabitants in the control town, which received no atabrine, to sterilize the blood, so that many individuals remained positive from month to month over relatively long periods. When it is remembered that in every case treated with atabrine save 3, the blood was negative during the succeeding month, some of the records from the control town show well the lack of good results from quinine distribution. There were 28 individuals in the control town who had positive bloods for three or more successive months. Table 7 shows the age-distribution in this group, and the number of times each individual was positive at successive monthly examinations.

Contrast this with the results of treatment with atabrine, in which only 3 persons treated were positive for two successive months. The table also shows that the lower age-groups, as is well known, show the highest incidence of malaria. No individual over the age of thirteen, in the 274 "regular" inhabitants of the town, showed parasites in the blood for more than two successive months. The element of chance enters into the formation of the table to a large extent, for in many instances the succession of months is broken by the omission of one examina-

TABLE 7

Showing number of times successively positive in control town

AGE	NUMBER OF INDIVIDUALS	NUMBER OF TIMES EACH WAS POSITIVE AT SUCCESSIVE EXAMINATIONS
1	2	3—6
2	1	3
3	3	3—6—6
4	3	5—5—8
5	3	3—4—5
7	3	3—4—4
8	2	3—5
9	4	3—3—4—4
10	3	4—4—5
12	2	4—4
13	2	3—3
	28	

117 positive examinations.
Average number of months successively positive is 4.2.

tion, the record of successive positives being taken up again when examinations were resumed. The great majority of the individuals showing a long succession of positive examinations were children, and illustrate the fact that quinine sulphate, unless administered in some disguising medium, is an unsuitable drug for the treatment of malaria in young children. As a matter of fact, so is atabrine, for its bitter taste makes it open to the same objection as quinine. In our own work this difficulty was overcome by suspending the atabrine in syrup of yerba santa (eriodictyon) and administering it with a medicine-dropper.

In addition to the control town situated near the four treated villages, several towns and localities along the Madden Dam Highway, some 5 miles from our river towns, were surveyed monthly during the year. These towns were also under quinine treatment, it being dispensed to all positives, who were visited twice a month, sufficient quinine being left with each to cover the intervening period. These towns supply a goodly portion of the labor for the construction of the new Madden Dam. The popu-

TABLE 8

Malaria rates in Madden Dam Highway localities

DATE	NUMBER EXAMINED	NUMBER POSITIVE	PER CENT POSITIVE
September, 1932	633	50	7.9
October	765	41	5.4
November	713	46	6.5
December	759	65	8.5
January, 1933	711	78	11.0
February	732	99	13.5
March	752	138	18.4
April	740	112	15.1
May	747	127	17.0
June	745	128	17.2
July	772	133	17.2
August	748	237	31.8
Total	8,817	1,254	14.2
4 river towns	4,424	701	15.8
Last 8 months	5,947	1,052	17.7
Last 8 months	3,022	590	19.5

lation is of the same type as that in our river towns, many of whose people have moved to this locality in the past year, to be nearer their work. Table 8 shows the results of the monthly surveys made in this area, for the twelve months from September, 1932, to August, 1933. Unfortunately, no survey was made in this area after August, 1933, although in this latter month there was a sudden and sharp rise in malaria rate to twice its usual incidence. This rise was not shared by any of our river towns.

These figures are for the whole population examined, as no

separation was attempted between "regulars" and the total number examined. Therefore the figures given must be compared with those for the whole population in our four river towns, which are given in the row just below the totals for the Madden Dam Highway localities. It is seen that even without atabrine treatment these towns have a lower rate than the four river towns.

THE PRODUCTION OF CRESCENTS AFTER ATABRINE ADMINISTRATION

The crescents of estivo-autumnal malaria appear in the blood shortly after the beginning of the fever, and may persist for long periods of time, appearing in "showers" from time to time, and varying greatly in numbers from day to day. Quinine is known to have little or no effect upon the production of crescents, nor does it affect their power to infect mosquitoes. Atabrine is like

TABLE 9

NUMBER EXAMINED AFTER TREATMENT	NUMBER SHOWING CRESCENTS	PER CENT SHOWING CRESCENTS	NUMBER WITH CRESCENTS TWO WEEKS LATER	PER CENT WITH CRESCENTS
251	81	32.3	14	5.6

quinine in both respects. During the course of our work we had the opportunity to perform two infection experiments on two individuals who had had five days of atabrine treatment, and whose blood contained crescents only. In each case abundant infection of *Anopheles albimanus* resulted. Several workers have reported that crescents are produced in greater numbers after atabrine treatment than after quinine, but we feel that their observations are too few upon which to base such a broad generalization. In our work, blood-specimens were taken at the end of the last day of treatment, to determine the effectiveness of the drug. Table 9 presents our findings.

Of the total showing crescents after treatment was completed, only 3 showed at least 1 per microscope field (6× ocular and 100× objective), and hence might have proved good vectors of the disease. None of the 14 with crescents two weeks after treatment showed enough to be considered good infectors of anopheles.

As we have no observations on the course of the crescent curve during the period between the completion of treatment and the next monthly examination, it is impossible to say how many of those showing light crescent infections became possible infectors during the period. In addition to the 81 estivo-autumnal cases showing crescents after treatment, there were 3 cases showing tertian schizonts before treatment, who showed crescents only, at the completion of treatment, proving that they had mixed infections. All 3 of the heavy crescent-carriers were young children, who had "plus" estivo-autumnal ring infections at the time treatment was started.

Undoubtedly a course of plasmochin administered either with the atabrine or after this treatment was completed would have reduced the number of crescent-carriers, and hence the number of human vectors. It was deemed unwise, however, to complicate the study of one drug by the use of another, with different properties and effects. In a few cases, not reported in detail, we used plasmochin, and in every case in which crescents were found before this treatment, the blood was freed from them in five days, using a dosage of 4 centigrams a day. However, we observed two cases of severe abdominal cramps in two adult women after the use of this dosage for a period of only two days.

THE RELATIVE COST OF ATABRINE AND QUININE

Using an arbitrary figure of 180 grains of quinine sulphate, given over a period of five days, as a dosage equivalent in effect to 1 gram of atabrine given over the same period of time, we can estimate the relative cost of the two drugs. The Panama Canal obtains quinine sulphate powder at $6.32 per avoirdupois pound. Atabrine, for 1 gram, the five-day treatment, costs about 39 cents, duty-free in Panama. The cost of 180 grains of quinine sulphate is about 15 cents. So that atabrine is a little more than two and one-half times as costly as quinine.

SUMMARY AND CONCLUSIONS

Atabrine was used over a period of eight months in the treatment of 400 persons living in native villages in Panama, and who

showed malaria parasites in the blood. The predominant type of malaria was estivo-autumnal (malignant tertian). Two hundred and eighty-one out of the 400 persons treated were subsequently followed up during the eight months. Among the "regular" inhabitants of the treated towns, the parasite rate during the eight months, as determined by the thick-film method, was 21.6 per cent, as against a parasite rate of 27.5 per cent among the "regular" inhabitants in a control town. In August, after eight months of atabrine treatment, the rates were 18.6 and 31.8 per cent, respectively. The small difference in rate, even after intensive treatment, is accounted for by the high relapse rate occurring in treated individuals. Atabrine has no effect on the viability of crescents, nor does it prevent their appearance in the blood. The cost of the drug is about two and a half times that of an equivalent course of quinine sulphate. In view of the small differential in parasite rate brought about by its administration, the use of atabrine does not seem to be a practicable method of malaria control under the conditions existing in certain native villages in Panama.

II. Observations on Malaria Rates and Associated Phenomena in Certain Native Villages in the Republic of Panama

The observations reported in this second part of our paper are a continuation of the record of work done in 1930, 1931 (2) and 1932 (3), and bring it up to the end of August, 1933. As the experimental treatment work done during the last eight months of the period has already been described, it will not be discussed further, except to caution the reader that the parasite rates obtained were those found in a population part of whom at least were undergoing treatment for malaria.

The usual monthly surveys were made throughout the year, in five villages situated along the banks of the Chagres River, having a population estimated at 800. As already related, during the first eight months of 1933 atabrine was used in four of the villages, Santa Rosa, Guayabalito, Gatuncillo and Las Guacas, and quinine was distributed under rather inadequate supervision

in another, New San Juan. Table 10 gives the combined rates for all inhabitants of the five towns, for the period from September, 1931, to August, 1933. The lowest incidence found in any of our 36 monthly surveys, which occurred in the fall and early winter months of 1932, is followed by a strikingly abrupt rise to a relatively high rate in January, 1933, which persisted in spite of all efforts at control by intensive treatment in four of the five villages. This tendency of the malaria curve to show large cyclical variations, apparently unrelated to any demonstrable external factor, is strikingly illustrated by this sudden rise

TABLE 10

Combined malaria rates in five Chagres River villages

	EXAMINED	POSITIVE	PER CENT		EXAMINED	POSITIVE	PER CENT
September, 1931	376	80	21.2	September, 1932	485	50	10.3
October	398	101	25.4	October	553	67	12.1
November	No survey			November	506	45	8.9
December	416	68	16.3	December	519	58	11.4
January, 1932	397	84	21.2	January, 1933	486	105	21.6
February	429	58	13.5	February	501	133	26.6
March	495	79	15.9	March	585	125	21.3
April	491	67	13.6	April	619	157	25.4
May	616	91	14.8	May	576	122	21.2
June	440	72	16.4	June	614	124	20.2
July	535	87	16.3	July	666	121	18.2
August	540	60	11.1	August	709	152	21.4

after a period of quiescence. These variations must be carefully allowed for in any evaluation of control measures, as otherwise undue credit may be given for reductions in incidence which are not caused by the measures used. Adequate controls are a prime requisite in this type of work. During our work with atabrine, happily for the experimental conditions, the malaria rate in our control areas remained at a fairly constant high level throughout the period of our observations.

In addition to the rates obtained in the five Chagres River villages, some localities along the Madden Dam Highway have

been surveyed monthly over a period of thirty months. These rates are compared for the years 1931, 1932 and 1933 in table 11. They also show, even more strikingly than our river villages, the great drop in rate which occurred in the latter part of the year 1932, and the sudden rise which began in January, 1933.

OBSERVATIONS ON TYPE OF MALARIA PARASITE, CRESCENT INCIDENCE, INCIDENCE IN INFANTS, CLINICAL INCIDENCE, INTENSITY, AND IMMUNITY

Table 12 shows the relative incidence of the various species of malaria parasites found during the period from September, 1931,

TABLE 11

Combined malaria rates in Madden Dam Highway localities

	EXAMINED	POSITIVE	PER CENT		EXAMINED	POSITIVE	PER CENT
September, 1931	432	140	32.5	September, 1932	633	50	7.9
October	443	108	22.7	October	765	41	5.4
November	No survey			November	713	46	6.5
December	470	101	21.5	December	759	65	8.5
January, 1932	442	98	22.2	January, 1933	711	78	11.0
February	459	82	17.9	February	732	99	13.5
March	481	71	14.7	March	752	138	18.4
April	430	64	14.9	April	740	112	15.1
May	504	47	9.4	May	747	127	17.0
June	507	70	14.0	June	745	128	17.2
July	515	74	14.3	July	772	133	17.2
August	634	95	14.9	August	748	237	31.8

to August, 1933. There is apparently no significant difference from year to year in the proportions of the various species of parasite.

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. As already noted, the 3 most potent crescent-carriers found in our four treated towns during 1933 were young children, who were recovering from

"plus" infections. The appearance of crescents in the blood without any apparent antecedent infection was a curious phenomenon noted. In 56 instances among the positives in our "regular" inhabitants in the five towns, crescents alone, unaccompanied by ring-forms, were found in the blood at the monthly survey; in every case the preceding monthly survey showed the blood negative. This doubtless means that an infection, either newly acquired or latent, ran its course during the preceding

TABLE 12

Relative incidence of types of malaria in five river towns

	P. FALCIPARUM	P. VIVAX	P. MALARIAE		P. FALCIPARUM	P. VIVX	P. MALARIAE
September, 1931	81	16	8	September, 1932	38	12	0
October	57	9	2	October	54	12	1
November	52	6	9	November	40	5	0
December	45	10	4	December	48	9	1
January, 1932	64	17	2	January, 1933	95	6	4
February	45	8	0	February	123	10	0
March	66	17	0	March	113	12	0
April	71	11	1	April	146	10	1
May	69	21	0	May	114	7	1
June	76	10	0	June	102	22	0
July	97	8	0	July	110	11	0
August	70	3	1	August	141	11	0
Totals	793	136	27		1,124	127	8
Per cent	82.9	14.2	2.8		89.2	10.1	0.7

month, leaving the crescents behind as the only evidence of its existence. Table 13 gives the incidence of crescents by months, in the five river towns, and in the localities along the Madden Dam Highway, for the period from September, 1931, to August, 1933, inclusive.

Of particular interest, as partially answering the argument of those who hold that atabrine treatment causes the appearance of more crescents than does quinine, is the comparison of the crescent rates in the four river towns for the seven months of the

TABLE 13

Incidence of P. falciparum crescents

	NUMBER OF ESTIVO-AUTUMNAL CASES	NUMBER OF CRESCENT CARRIERS	PER CENT		NUMBER OF ESTIVO-AUTUMNAL CASES	NUMBER OF CRESCENT CARRIERS	PER CENT
Five river towns							
September, 1931	92	22	23.8	September, 1932	38	5	13.1
October	67	14	20.9	October	54	14	25.9
November	75	15	20.0	November	40	10	25.0
December	53	10	18.8	December	48	16	33.3
January, 1932	64	19	29.7	January, 1933	96	33	34.4
February	68	2	2.9	February	123	32	26.0
March	62	2	3.2	March	89	41	46.1
April	58	1	1.7	April	146	48	32.9
May	69	8	11.6	May	114	35	30.7
June	62	6	9.7	June	102	27	26.5
July	80	1	1.3	July	110	21	19.1
August	71	8	11.1	August	141	39	27.6
	821	108	13.2		1,101	321	29.2
Madden Dam Highway localities							
September, 1931	98	33	33.7	September, 1932	30	9	30.0
October	74	27	36.5	October	24	7	29.2
November				November	32	9	28.1
December	70	18	25.8	December	43	18	42.0
January, 1932	64	18	28.2	January, 1933	47	15	32.0
February	52	21	40.5	February	65	43	66.2
March	51	11	21.6	March	108	27	25.0
April	43	6	14.0	April	95	33	34.8
May	24	5	20.8	May	99	35	35.5
June	36	2	5.6	June	103	35	34.0
July	63	4	6.4	July	110	27	24.6
August	62	10	16.1	August	195	71	36.4
	637	173	28.7		951	329	34.6

treatment period, with the rates in the road towns, which received quinine only, for the same period. The crescent rate in the road towns was 35.5 per cent, and 32.8 per cent in the atabrine-treated towns.

Of special interest, as showing the probability of contracting a new infection during the year, is table 14 showing the incidence among infants one year old and under, in our four river towns, and in our control town, New San Juan. Altogether, 55 infants were examined during the year, 26 in New San Juan, and 29 in our four river towns. The youngest age at which infection was discovered was one month and nine days. In this case, while mosquito-borne infection is not inherently improbable, the possibility of a congenital infection cannot be ruled out, as the mother

TABLE 14

Incidence of malaria in infants—four river towns

AGE WHEN PARASITES WERE FOUND	NUMBER OF EXAMINATIONS OF INFANTS OF STATED AGE	NUMBER OF POSITIVE EXAMINATIONS
months		
0–1	1	
1–2	19	1
2–3	18	
3–4	18	1
4–5	13	2
5–6	16	3
6–7	13	1
7–8	12	1
8–9	6	
9–10	6	
10–11	3	
11–12	3	
	128	9

also had the same type of malaria at the time of the survey. In 3 cases, 2 infants had positive blood twice, and 1 had positive blood for three months, so that in all there were only 6 new infections discovered among 29 infants ranging in age from less than one month to twelve months. This gives a rate of 20.7 per cent among these children, which is probably somewhat lower than the expected rate, for the number of children in the higher age-groups is small compared to the number in the lower age-groups.

The examinations of infants living in New San Juan were few

and scattered. The earliest recorded infection occurred at the age of four months, and another was found at six months.

INCIDENCE OF CLINICAL MALARIA

In a highly tolerant population, such as we are dealing with in Panama, it is often puzzling to determine the amount of actual illness caused by malaria. In all of our many visits and stays in the villages, we have found very few instances of acute illness caused by malaria. Undoubtedly the disease does cause a certain amount of discomfort and lowering of efficiency, but acute clinical malaria is rare, so far as our limited observations go, when compared with the relatively high rate of infection, as shown by blood examination. Our visits were too few to enable us to obtain accurate data regarding the incidence of clinical malaria, sufficiently complete for analysis. During the past three years, we have not learned of a single death from malaria in any of our five river towns. This of itself bespeaks a high tolerance for the disease.

INTENSITY OF INFECTION

During the year from September, 1932, to August, 1933, in our four treated towns we have found 116 infections which we characterize as "plus," meaning those in which the blood showed more than one parasite in each microscopic field, in thick films, out of a total of 594 positive bloods, or about 20.0 per cent. In the control town, there were 113 "plus" infections out of 456 positive bloods, or 24.8 per cent.

The element of chance enters here, for our examinations, made only once each month may encounter the infection at a time when the parasites may have left the peripheral circulation. In many instances the senior author has examined the blood of persons complaining of "fever," who had been reported negative in the monthly survey made from three to eleven days previously, and found it with a "plus" infection. This illustrates the rapidity with which an estivo-autumnal infection may increase in the blood. The record, in all such instances found, was the case of a ten-year-old girl, who three days after being reported nega-

tive, was found with a "plus" infection. Altogether, we observed 10 cases of this sort, and in only 2 of them had the blood been positive during the preceding month. Table 15 presents these cases in tabular form.

In a number of instances, being led astray by the fewness of parasites found in certain persons at the monthly survey, no treatment was given them during the usual treatment period the week following. At the time of the next monthly survey, these individuals were found with clinical malaria, and required im-

TABLE 15

Illustrations of rapid rise of estivo-autumnal infections

NAME	DAYS FROM LAST NEGATIVE EXAMINATION	INTENSITY OF INFECTION	NUMBER OF MONTHS PREVIOUSLY NEGATIVE
A. L.	3	Plus	2 months
S. M.	4	Double plus	3 months
L. D.	6	Plus	5 months
M. G.	6	Plus	1 month
A. V.	6	Few	Positive preceding month
C. R.	7	Plus	9 months
O. Q.	7	Double plus	10 months
L. R.	7	Plus	2 months
J. S.	8	Double plus	Positive preceding month
A. V.	8	Plus	1 month
C. P.	11	Double plus	1 month
A. V.	11	Few	1 month

mediate treatment. There were also many instances in which the infestation, very light at the time of the survey, had developed to clinical proportions in the six intervening days between examination and treatment period.

IMMUNITY

The problem of the existence of individuals and families with a low tolerance to malaria is discussed in the first part of this paper. Mention was made of individuals and families who, on the contrary, are extremely resistant to infection. It is hoped to follow up both sets of people, to determine if possible whether this difference may be dependent on some inheritable factor.

The existence of individual immunity is a demonstrable fact, but the reasons therefor are obscure. As an example, we present the case of one J. A., a girl, the eldest of seven children, ranging in age from one and one-half years to twelve years, all living in the same dwelling with the mother, aged thirty-four. The mother had malaria parasites in her blood at one examination out of twelve monthly examinations during the year. The 6 younger children were positive over the greater part of the time. Apparently immunity increases with age, as the 3 youngest children were positive half to three-quarters of the time. In extreme contrast to their cases, the eldest child, examined in every month of the year, proved uniformly negative.

Incidentally, the findings in this family illustrate the futility of trying to control malaria by merely distributing quinine, without adequate supervision. The mother of these children was the person entrusted with the distribution of quinine to all those found positive in our monthly surveys in the control town.

What appears to be immunity may be in large degree a matter of chance, for in 3 instances we have records going back over a period of years, during which the individuals were uniformly negative. Two were in adult women aged forty-nine and forty-seven respectively, and one was in a girl aged twelve. The forty-nine-year-old woman had been previously negative for seventeen months, but was found in bed with fever, and showed large numbers of malaria parasites, in May, 1933. The forty-seven-year old woman had been negative for fourteen months, but in April, 1933, suffered a severe attack of estivo-autumnal malaria. The girl had been negative for twelve months past, but eventually became infected, showing high temperature and great prostration.

It seems that the severity of clinical symptoms is greater in these "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, and thought given as to the best methods of preventing such a calamity.

THE ANNUAL PARASITE RATE

In former reports we have shown that the annual parasite rate determined by examinations made at monthly intervals, is very high, so that as the number of monthly examinations increases, the number of individuals found positive increases. This means that nearly every inhabitant of our five villages, if he could be examined at monthly intervals throughout the year,

TABLE 16

	NUMBER OF TIMES EXAMINED									
	3	4	5	6	7	8	9	10	11	12
Number of persons	51	44	67	72	84	77	67	89	80	76
Number positive	14	17	36	38	53	60	52	71	65	61
Per cent positive	27.5	38.6	53.7	52.8	63.1	78.0	77.7	79.8	81.3	80.3

would doubtless show parasites in his blood one or more times. Under such conditions, any control method, no matter how efficient, would be slow in showing any immediate effect, considering the great reservoir of parasites which exists in such a population. Table 16 gives the parasite rates found as the number of times the inhabitants were examined, increased. The most interesting phenomenon brought out by this table is the existence of a group of 15 highly immune persons, all of whom had been examined 12 times during the year, and none of whom showed parasites in the blood.

SUMMARY

The observations made during the year from September, 1932, to August, 1933, on the malaria rates among the inhabitants of

five villages in the mid-basin of the Chagres River in Panama are summarized. With regard to the parasite rate, a notable decrease occurred during the late fall and early winter months of 1932, followed by a sudden rise in January, 1933, to a relatively high rate, which persisted to the end of the period. The proportions of the three types of parasite during the preceding year and in the year under consideration are given, showing that estivo-autumnal malaria, the most common, increased slightly during the last year, forming 89.2 per cent of all malaria found. Crescent incidence showed a very small variation from month to month, averaging 29.2 per cent for the period. A rate of 20.7 per cent was found in a small number of infants examined. The incidence of clinical malaria, intensity of infection, immunity, and associated phenomena are discussed. The high annual parasite rate of 803 per thousand was found in persons examined 12 times at monthly intervals throughout the period.

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