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A SUMMARY OF TEN YEARS OF OBSERVATIONS ON MALARIA IN PANAMA WITH REFERENCE TO CONTROL WITH QUININE, ATABRINE, AND PLASMOCHIN, WITHOUT ANTI-MOSQUITO MEASURES

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IT is probably true that anti-mosquito measures are the most efficient methods of malaria control, but in many instances their cost has been prohibitive, particularly if it is necessary to apply them in rural areas in the tropics, where economic resources are low, and the cost per capita of the measures would be high. Considerable work in attempting to control malaria in rural native populations has been done by British workers in India, Malaya, and other parts of the East, and by the Italians in Italy, using anti-malarial drugs alone, or in combination with anti-mosquito measures. We have been interested in the possibilities of drug control of malaria, without the use of anti-mosquito measures for two reasons: it seems logical to assume that a great reduction in the number of infected mosquitoes might follow a reduction in the malarial parasite rate by means of drugs administered to a given population; and we wished to investigate the possibilities of the newer synthetic anti-malarial drugs, under conditions which made outlays for mosquito control measures impossible.

In 1929 the Republic of Panama granted us the privilege for an indefinite period of using some villages located near the middle of the Chagres River basin for an experiment in drug control of malaria. At the beginning of our investigations the towns selected had no means of communication with the outside world except by small dug-out canoes propelled by paddle and pole. The houses of the villagers were of the usual type common in the tropics, with thatched roof, side-walls of cane, and dirt floor. The villages were located along the river banks, just above flood level. There was no sanitation; water for drinking and cooking was obtained from the river, which was also used for bathing and laundering. There was no local medical attention and no drugs were available in any of the towns. The river with its small branches and many shallow lagoons, filled with aquatic vegetation, provided large breeding areas for the larvae of anopheline mosquitoes. These villages could be reached from our laboratory in Panama City in about one and one-half hours, by automobile and outboard motorboat.

At the beginning of our experiment, we knew that two large-scale construction projects would soon be under way near the villages, one of which was the Madden Dam across the Chagres River, some few miles above the villages, and the other of which was the Madden Highway from Panama City to Madden Dam, a distance of about 24 miles. The imminence of these projects and the probability that other changes would take place in the towns themselves, such as the installation of latrines, better schools, and the introduction of our own medical service, made them especially suitable for long-continued observation. We have limited our experiment to 10 successive years of observations. The towns se-

lected all lie between the Madden Dam and the eastern boundary of the Panama Canal Zone, and are situated on the banks or tributaries of the Chagres River. The towns of Santa Rosa, Guayabalito and Gatuncillo are on the right (north) bank of the river; Las Guacas lies opposite Santa Rosa on the left bank, at the junction of the Chagres and its Moja Pollo tributary. This latter town is almost surrounded by water full of aquatic vegetation, making ideal conditions for anopheles mosquito breeding. In February, 1937, the town of Agua Clara was added to the number of towns under observation. This town dates from 1936, when a group of people who formerly lived on Gatun Lake cleared the jungle from several hilltops just across the eastern boundary of the Canal Zone at boundary marker No. 50. The elevation of this town is about 100 feet, and the distance from Santa Rosa is about one and one-half miles.

During these investigations, we used chiefly the population located along the Madden Highway, in the towns of Chilibre, Aguas Buenas, and Buenos Aires as controls. These towns are located about 5 miles to the south of the left bank of the Chagres River, and about 150 feet higher than the river towns.

The populations of just such rural areas as these in which our observations were made are the sources from which large business organizations must draw their labor forces.

Survey Methods

Blood parasite surveys made monthly in all villages during the ten-year period have been used to measure our results. The thick-film technique of Barber and Komp (1929b) has been used throughout the period, and the staining and examination of the films has been done by experienced technicians, most of whom have been with us throughout the experiment. It was found that not all the inhabitants of the villages could be surveyed at any one survey during the month, but during the days for the period of treatment and during inspections, we were able to collect blood-films from all the permanent inhabitants. The migratory habits of some of our people have been a source of much inconvenience to us. It was impossible to examine or treat individuals adequately who did not reside permanently in the towns, and such persons might be undiscovered carriers of sexual malarial parasites, capable of infecting mosquitoes.

Treatment Methods

During the first year of our observations (Sept. 1930–Aug. 1931) we used quinine sulphate in all villages. A native Panamanian graduate nurse (assisted by school teachers and the corregidors (mayors) of the villages) was supplied with the list of names of those found positive in each monthly survey. Twenty grains (1.29 gm) of quinine sulphate to each positive per day for a period of 10 days constituted a course of treatment during the first year.

During the second year (Sept. 1931–Aug. 1932) quinine was used in the same manner, but in addition, plasmochin simplex in doses of 0.01 gm twice a week was given to all positives in all the villages under treatment except New San Juan.

During the third year (Sept. 1932–Aug. 1933), quinine sulphate was used in the same dosage throughout the year in New San Juan, but in the four other villages under treatment we used quinine sulphate during the first 4 months, and atabrine 0.1 gm three times a day for 5 days from January 1933 to August 1933.

During this latter period, one of us (W. H. W. K.) stayed a week during each month in the villages, and personally administered the atabrine to all those found positive in the preceding monthly surveys. It is only during this period that we are absolutely sure that the drug was administered according to schedule. It is well to mention that during this period blood-films were taken at the completion of treatment from all persons who received the drug; in every case but one these films were negative for asexual parasites at the end of the 5-day course of atabrine. Crescents, which are

little affected by atabrine, were of course present in many cases.

During the fourth year (Sept. 1933–Aug. 1934) tablets of quinine sulphate 15 grains (0.972 gm) a day for 5 days were given to positives in New San Juan, followed 2 days later by plasmochin simplex 0.01 gm twice a day over a succeeding period of 5 days. The populations of Santa Rosa, Guayabalito, Gatuncillo and Las Guacas were treated with atabrine 0.1 gm 3 times a day for 5 days, followed 2 days later by 5 days' course of plasmochin simplex 0.01 gm twice a day.

These treatment methods were continued in the towns named up to and including August 1940. The town of Agua Clara was added to the atabrine-plasmochin treated villages in February 1937.

During the fourth year (Sept. 1933–Aug. 1934) a definite policy of using non-medical personnel for the administration of the drugs was established. Six native girls who were residents of their respective villages were selected by the river supervisor (an intelligent native man), after consultation with the people of each village. These "nurses" were under the direction and inspection of a medical member of our staff, and thus soon succeeded in obtaining the necessary cooperation and administered the drugs in a fairly satisfactory manner. Weekly inspection trips to the villages by the medical staff made it possible to examine and treat cases of clinical malaria that developed between the monthly blood-film surveys.

Presentation of Data

For the period from Sept. 1930—Sept. 1940 the monthly and annual malarial parasite rates, the annual rainfall, incidence of malaria by age-groups, incidence of species of parasite, numbers of crescent-carriers and heavy infections, the incidence of malaria in infants, records of anopheline collections and dissections, and the relation of all these to the results of treatment can be more easily and briefly presented in tables.

Table I shows that the malarial parasite rate, as determined by the monthly blood-film examinations, bears no direct relation to the seasonal rainfall, because anopheles

TABLE I

Consolidated Report on Villages by Months. Adults and Children Combined

Months	1930—31		1931—32		1932—33		1933—34		1934—35		1935—36		1936—37		1937—38		1938—39		1939—40		Ten Years	
	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Malaria Parasite Rate	Rainfall in Inches	Average Malaria Parasite Rate by Months	Average Rainfall in Inches by the Months
September	36.2	12.65	25.1	17.52	21.2	10.35	22.8	15.20	6.2	20.35	8.9	15.94	14.0	15.62	7.4	13.87	5.5	7.45	20.5	11.84	14.8	12.16
October	15.6	10.25	21.6	8.85	25.4	17.49	20.2	7.04	8.1	18.51	9.6	14.64	10.9	14.65	6.6	15.31	5.9	15.57	15.5	16.92	13.7	15.44
November	20.0	3.08	25.1	29.25	No Record	25.41	18.3	14.09	20.9	20.55	15.4	22.22	10.3	9.99	6.9	17.63	9.8	12.73	11.2	18.47	15.6	18.19
December	27.0	0.85	15.7	4.65	16.5	4.99	11.0	7.77	13.2	5.98	14.4	6.07	13.1	0.65	4.8	18.31	7.8	14.35	27.9	7.55	14.1	7.13
January	21.5	0.24	25.2	1.06	21.2	1.01	19.1	1.43	25.6	0.84	16.0	0.05	12.8	3.52	6.9	9.20	10.8	0.02	14.2	2.16	17.0	0.88
February	20.6	0.35	12.2	0.22	15.5	0.0	11.[illegible]	0.37	21.9	0.46	9.7	0.07	14.7	0.25	8.1	0.06	12.1	0.01	16.7	0.55	15.8	0.19
March	15.6	2.35	16.5	0.36	15.9	2.47	19.1	0.12	28.0	0.12	10.7	0.09	9.3	0.25	6.1	0.65	6.7	0.06	8.7	0.05	12.7	0.64
April	21.1	2.29	14.2	5.74	13.6	0.25	10.4	4.47	22.4	1.63	9.6	1.02	8.5	0.90	5.9	3.87	5.7	0.31	11.2	0.15	12.9	2.62
May	26.5	11.08	16.7	17.55	16.8	12.31	8.9	16.57	14.6	14.35	10.8	12.00	7.5	13.96	6.5	12.25	7.5	3.39	9.9	5.59	12.1	11.89
June	26.6	15.72	13.8	11.45	16.4	10.75	6.4	11.66	16.5	13.30	13.6	6.88	11.1	10.29	8.0	15.92	6.3	11.56	7.3	6.99	12.5	11.22
July	20.2	12.81	15.9	6.79	16.5	10.54	7.6	9.68	10.2	22.52	12.6	13.00	7.1	5.48	6.7	7.97	6.9	7.05	9.1	7.75	11.5	10.72
August	27.8	9.06	12.4	11.55	11.1	12.68	8.9	11.21	11.5	14.56	11.5	8.82	11.8	14.45	8.4	9.50	11.2	11.93	8.0	12.24	12.3	11.62
	23.6 Average	79.32 For the Year	16.8 Average	114.21 For the Year	16.8 Average	104.64 For the Year	12.8 Average	98.51 For the Year	15.8 Average	122.35 For the Year	11.5 Average	110.15 For the Year	10.8 Average	88.33 For the Year	6.6 Average	112.15 For the Year	8.0 Average	85.58 For the Year	12.2 Average	88.12 For the Year	13.3 Average Monthly Parasite Rate	100.06 Average Annual Rainfall in Inches

Rainfall records are from Madden Dam, Canal Zone.

mosquito production is not dependent upon rainfall in our village areas, as most of the larval breeding occurs in lagoons and backwaters of the Chagres River, which are always filled with aquatic vegetation, except during infrequent periods when this vegetation is washed out by flood-waters. Water impoundment behind Madden Dam, which was begun Sept. 1934, has exerted more influence on mosquito production than any other single factor. The gates of this dam are sometimes closed for months, and during such periods the only water released is that which passes through the hydro-electric plant at the dam. This impoundment causes a low water level, and sluggish current. Conditions of stagnation are most favorable for the growth and spread of aquatic vegetation, which at such times covers the river near all its small tributaries and in all its many shallow lagoons. The production of Anopheles mosquitoes is tremendously increased while such conditions exist.

TABLE II

AVERAGE MONTHLY PARASITE RATES. TREATED GROUPS COMPARED WITH UNTREATED CONTROL GROUPS

Year	Parasite rate	
	Treated groups	Control groups
1930–31	21.6	.....
1931–32	16.8	17.5 (12 months)
1932–33	16.8	27.5 (12 months)
1933–34	12.8	20.5 (8 months)
1934–35	15.8	22.5 (12 months)
1935–36	11.5	18.5 (12 months)
1936–37	10.8	16.2 (12 months)
1937–38	6.6	16.4 (1 survey)
1938–39	8.0	20.8 (1 survey)
1939–40	12.2	32.7 (4 surveys)

These control records are from various areas on the Madden Dam Highway where the migratory population made a very poor control group. Many of those who had malarial attacks went to Panama City for treatment and were not caught in the blood-film surveys.

The cumulative rate is obtained by dividing the total number of individuals positive during the year by the total number of persons examined.

TABLE III

MALARIAL PARASITE RATES. ADULT RATES COMPARED WITH CHILDREN'S (15 YEARS AND UNDER) RATES, THESE RATES ARE CUMULATIVE FOR THE YEAR. YEARS 1935–1940

	Adults	Children	Total
	%	%	%
Initial survey 1929. No treatment or control measures*	37.2	56.5	45.6
Cum. records Sept. 1935–Aug. 1936. All villages	29.1	41.5	35.3
Cum. records Sept. 1936–Aug. 1937. All villages	30.3	42.7	36.5
Cum. records Sept. 1937–Aug. 1938. All villages	21.2	28.8	25.0
Cum. records Sept. 1938–Aug. 1939. All villages	25.0	30.8	27.9
Cum. records Sept. 1939–Aug. 1940. All villages	37.9	42.0	39.9

* The rates found in the initial survey represent but one examination, while the cumulative rates include 12 monthly surveys, and all positives discovered. This shows very clearly that a single survey uncovers only a fraction of the annual malaria rate, even when drug control is in use. One favorable effect of treatment is shown in the decreasing children's rate relative to the adult rate, as treatment progressed. Usually children show a parasite rate almost double that of adults. After continued treatment, the two rates become more nearly equal. This is partially explained by the fact that children are more likely to be present at surveys, and can be more thoroughly examined and treated.

It is seen from the last line in Table IV that from 1 to 5 examinations of the same individual during the year give average annual parasite rates of 19.3 per cent, while 12 consecutive monthly examinations of the same individual increase these rates to 47.6 per cent. These data mean that approximately half the population of our area had malarial parasites in the blood at least once during the year.

The table also indicates one of the difficulties encountered in surveying and treating native population groups in the field, either in villages or in labor camps. Our river supervisor lives in one of the towns,

TABLE IV

PARASITE INDEX. THREE SURVEY GROUPS. ALL VILLAGES

Years*	1 to 5 surveys			6 to 11 surveys			12 surveys		
	No. examined	No. positive	Per cent positive	No. examined	No. positive	Per cent positive	No. examined	No. positive	Per cent positive
1935–36	789	152	19.2	379	197	52.0	230	134	58.2
1936–37	623	133	21.3	426	230	54.0	190	82	43.1
1937–38	689	100	14.5	410	156	38.0	171	63	36.8
1938–39	694	123	17.7	383	155	40.5	142	61	43.0
1939–40	583	155	26.6	407	226	55.5	71	43	60.6
Totals	3378	663	19.3	1805	964	53.4	804	383	47.6

* The intervals are from Sept. 1 to Aug. 31 of the following year.

has motor-boat transportation, and often visits all towns even outside of the regular treatment periods following blood-surveys. Our medical staff visits the towns on an average of 4 times a month. Yet with all these opportunities to collect blood-films from those not present on regular survey days, we found it impossible to secure blood-films from every individual for 12 successive months. Some of this difficulty may be explained by the habits of the population. Some of the inhabitants move from the towns, and others take their places; others have residences in the towns, but divide their time between these homes and their farms, which may be several miles from the villages; other persons examined are transient visitors over a period of weeks or months. The persons examined in 6 to 11 surveys and in 12 surveys per year, a total of 2,609 individuals, formed the permanent population of the area during the period of the survey. The remainder, 3,378 individuals, were transients who made satisfactory treatment of the persons examined very difficult because their presence in the villages increased the chances that mosquitoes would become infected, for many of them were untreated carriers of sexual forms of the malarial parasite.

For the past 3 years a steady diminution in the population of our towns has been taking place. However, enough inhabitants remain to show the benefits of drug control of malaria. In August, 1940, the atabrine-treated towns had a parasite rate of 11.5 per cent; the quinine-treated town a rate of 12.7 per cent; the Madden Highway untreated control group, mostly school children, a rate of 32.7 per cent; and Rio Pescado, another untreated group, a rate of 65.1 per cent. The number of heavy infections found was also much higher in the control areas than in our treated towns.

The age group from 5 to 10 years and from 10 to 20 years always have the highest rates, proving the importance of malaria in young adult labor force.

Both Tables V and VI show that inci-

TABLE V

CUMULATIVE INCIDENCE OF MALARIA BY AGE GROUPS FOR TEN YEARS IN THE TREATED VILLAGES. MIGRATORY AND PERMANENT INHABITANTS

Age in years	Atabrine-Plasmochin			Quinine-Plasmochin		
	Examined	Positive	Per cent positive	Examined	Positive	Per cent positive
0–5	665	162	24.3	635	190	29.9
5–10	397	177	44.6	388	173	44.6
10–20	712	293	41.1	618	274	44.3
20–40	855	237	27.7	811	215	26.5
40–60	452	146	32.3	336	60	17.8
Over 60	122	40	32.7	140	21	15.0
Totals	3203	1055	32.9	2928	933	31.8

TABLE VI

INDIVIDUALS SURVEYED 12 CONSECUTIVE MONTHS*

Ages	Chagres			New San Juan			Totals			Controls†		
	Examined	Positive	Positive	Examined	Positive	Positive	Examined	Positive	Positive	Examined	Positive	Positive
years	*No.*	*No.*	*%*	*No.*	*No.*	*%*	*No.*	*No.*	*%*	*No.*	*No.*	*%*
0–5	165	65	39.4	114	49	43.0	279	114	40.8	228	70	26.2
5–10	135	71	52.6	69	41	59.4	204	112	54.9	1020	385	37.7
10–20	69	45	65.2	38	28	73.7	107	73	68.2	1028	415	40.3
20–40	63	23	36.5	50	24	48.0	113	47	41.6	293	67	22.8
40–60	50	19	38.0	15	6	40.0	65	25	38.4	119	35	29.4
Over 60	15	5	33.3	17	5	29.4	32	10	31.2	25	4	16.0
Totals	497	228	45.9	303	153	50.5	800	381	47.6	2713	976	36.0

* Period covered September 1935 to and including August 1940.

† Controls: Madden Highway schools, 4 surveys; Chilibre (town on Madden Highway), 1 survey; Rio Pescado, Gatun Lake shore, 1 survey.

dence is highest in ages 5 to 20 and that those above 60 years of age, who have spent their lives in these highly endemic centers, are not immune to malaria.

In addition to the figures given above, the Buenos Aires schools (on the Madden Highway) were examined 4 times (Oct. 1939, Jan., May and Aug. 1940). The number of positives found was 203. No treatment was given in this area, except quinine sulphate, which was provided for the positives, to be used if they so desired. There was no supervision of treatment. The results of the survey show that of the 203 positives, 115 were positive once; 55 twice; 23 three times; and 10 four times. Thus 88, or 43.3 per cent, were positive from 2 to 4 times.

TABLE VII

INDIVIDUALS (405) POSITIVE FOR MALARIA WHO WERE SURVEYED REGULARLY FOR 12 CONSECUTIVE MONTHS. PERIOD OF SEPT. 1, 1935–AUG. 31, 1940

Times positive	Chagres	New San Juan	Chilibre	Total
1	124	75	2	201
2	54	35	5	94
3	27	18	5	50
4	12	13	2	27
5	8	7	2	17
6	1	4	4	9
7	2	3	0	5
8	0	0	1	1
9	0	0	1	1
Totals	228	155	22	405

We believe that the larger proportion of positive findings is due to relapse, not to new infections. This is well shown in those who were repeatedly positive over long periods. These repeaters were certainly less tolerant to malaria than others living in the same area, for they kept a high parasite rate even though they were subjected to treatment at frequent intervals. Certain families, regardless of the location of their homes, show very low tolerance to the disease, and these people defeat our efforts to attain a further reduction in malarial parasite rates.

Mixed infections are no doubt more common than is indicated in Table VIII, as it is often necessary to examine blood-films made on successive days to discover such infections. Table VIII shows that *P. falciparum* infections constitute the majority of our positives and that *P. vivax* and *P. malariae* infections are more common in the Madden Highway groups than in the Chagres River villages.

The crescent rates among *P. falciparum* infections seem very high, yet during 9 years of our observations only about 43 heavy crescent-carriers were found in the

TABLE VIII

SPECIES OF MALARIA PARASITES FOUND IN 2,939 POSITIVES

Species of parasites	Chagres	New San Juan	Madden Highway*	Rio Pescado†	Totals
P. falciparum	782	744	528	54	2,108
P. vivax	163	86	135	21	405
P. malariae	21	10	52	4	87
P. falciparum & P. vivax	90	80	99	4	273
P. falciparum & P. malariae	15	10	16	1	42
P. vivax and P. malariae	2	1	11	0	14
P. falciparum, vivax & malariae	3	2	5	0	10
Totals	1,076	933	846	84	2,939

* Five years records of Chilibre and Madden Highway schools. Infrequent surveys.

† One survey, August 1940, in a town on Gatun Lake. A period of ten years for New San Juan and the Chagres villages. Monthly surveys.

5 Chagres River villages. Of course this figure was obtained from the results of single examinations; if a series of examinations had been made in the same individuals, probably more would have been found. However, it is not an easy task to find in any one survey a suitable crescent-carrier for mosquito infection experiments. This is true of the untreated control areas, as well as of the treated groups. The crescent rate is apparently higher in these treated groups, but this may be only the result of more frequent examinations. The gametocyte carrier is still a great problem in areas where drug control is attempted.

Table X shows the interesting and important fact that a greater percentage of all malarial infections were "heavy" among the cases found in the treated Chagres River groups than in the untreated control groups. Heavy infections were more numerous in the treated groups after 10 years of treatment than they were in the early years of our work. Yet the average annual malarial parasite rate in the treated groups in 1939–40 was only 12.1 per cent, while in the initial survey made in 1929 the rate was 46.5 per cent.

We believe that a partial explanation of this otherwise discouraging fact lies in the possibility that treatment of all parasite-positive cases rids so many of them of parasites that immunity is lost. When such individuals with lowered immunity become newly infected, they are more likely to be clinically ill, with many parasites in the blood, than are others who retain a few parasites at all times but rarely become actively ill.

Of the 20 infants found positive in the control areas, the first infection of at least one was found in each month of age from

TABLE IX

INCIDENCE OF P. FALCIPARUM CRESCENTS IN FIVE CHAGRES RIVER VILLAGES AND IN MADDEN HIGHWAY CONTROL GROUPS

Years	Chagres Villages	Madden Highway	Rio Pescado
1931–32	13.2	28.7	
1932–33	29.2	34.6	
1933–34	22.8	17.9	
1934–35	28.2	25.3	
1935–36	26.5	18.3	
1936–37	39.8	31.7	
1937–38	44.0	27.2	
1938–39	37.9	25.6	
1939–40	45.1	54.8	38.9

TABLE X

ANNUAL PERCENTAGE OF HEAVY MALARIAL INFECTIONS DURING THE PAST TEN YEARS

Years	Five Chagres River villages (treated)	Madden Highway and Dam (controls)
1930–31	16.7	6.5
1931–32	11.6	8.8
1932–33	21.8	19.6
1933–34	15.0	12.2
1934–35	20.0	17.4
1935–36	15.0	11.3
1936–37	19.3	10.5
1937–38	17.3	10.0
1938–39	20.4	12.9
1939–40	23.1	10.3

TABLE XI

SURVEYS OF INFANTS 12 MONTHS OR LESS OF AGE. SEPT. 1935–AUG. 1940

Period covered	Chagres River towns		Control areas		Positive during first six months	Positive during last six months
	Number examined	Number positive	Number examined	Number positive		
1935–36	53	5	13	1	0	6
1936–37	59	8			4	4
1937–38	53	1			1	0
1938–39	65	1			0	1
1939–40	42	1	7	3	1	3
Totals	272	16	20	4	6	14
Per cent		5.9		20.0	30.0	70.0

the second to the twelfth. The highest incidence was 4 in the seventh month, but too few infections were recorded to give the result significance. Of the 20 infants found positive, five had *P. vivax* infections and 15 had *P. falciparum* infections, a ratio which is quite comparable to that existing for these types in the general population.

The infant rate of infection is a yardstick with which to measure transmission. Table XI shows an infant rate of 5.9 per cent among the babies in the treated villages, surveyed 12 times a year, as compared with a rate of 20 per cent among infants living in the control areas, which are surveyed only at infrequent intervals.

CYCLICAL VARIATIONS IN MALARIA INCIDENCE IN POPULATIONS UNDER OBSERVATION

During the 10 years of our observations, great fluctuations in the malarial parasite rate have been noted, in both our treated towns and in the control groups. The chart which will be found on page 112 of our fifth annual report (1936) indicates these fluctuations for the first five-year period, and Table I of the present paper shows the variations in the rates observed in the treated population since 1935. The existence of such fluctuations is undeniable, as shown in the chart and the table, but the authors are not in agreement as to their causes. The first author (H. C. C.) believes that they are caused by unusual increases in the numbers of anopheles mosquitoes in the villages, owing to favorable conditions for larval production caused by periodic lowering and stagnation of the waters of the Chagres River. Such favorable conditions recur annually at the beginning of the dry season (January), and have been particularly marked since the beginning of impoundment of water behind Madden Dam (Sept. 1934). Unfortunately no data as to mosquito prevalence at various seasons of the year are available, except for the last two years of our study (Sept. 1938–Sept. 1940). The figures for these years show that mosquito production is heaviest during the dry season (January-May), when low water, sluggish current and bright sunlight combine to make larval breeding conditions very favorable. In support of the idea that increased mosquito production is responsible for high malarial rates, it is pointed out that two notable peaks of incidence occurred in the villages along the Chagres River, in the midst of the breeding areas, at the beginning of the dry season in 1933, and again in 1935. Since 1935, only one such peak has occurred, and this increase began in August, 1939, and continued for several months thereafter. In 1936 and 1937, malarial rates were higher in the first 5 months of the year, corresponding with the dry season, but in 1938 and 1939, higher rates were obtained in the second half of the year, particularly in 1939, when a parasite rate of 17.5 per cent was found in August in the 4 Chagres River villages. This was higher than any rate noted in these villages since the great epidemic of the first 4 months of 1935, when parasite rates as high as 28.8 per cent were obtained in the 4 Chagres River villages. This relatively high rate of 17.5 per cent occurred in the early part of the rainy season, and was more than three times as high as the rates found during the dry season months of March, April and May of the same year, when they averaged about 5.4 per cent.

The evidence that cyclical variations in malarial parasite incidence is due to some other factor than mosquito abundance is contained in the tables showing parasite rates obtained during the past 10 years. In Table III the high parasite rate of 45.6 per cent for the initial surveys (including New San Juan) is mentioned. These surveys were made in September and December, 1929, during the heavy rainy season, 5 years before Madden Dam was completed. The next surveys were made a year later (Sept. 1930), revealing a parasite rate in the same population of only 16.2 per cent. Meanwhile no treatment had been given. This diminution in parasite rate, which was not in any way influenced by treatment, was apparently the normal decline from a peak of high incidence, in which we had unwittingly made our initial surveys. Increases in parasite rate were noted during the first year of our treatment, until in August 1931 they reached another peak with a rate of 27.8 per cent, in spite of treatment. They declined thereafter almost steadily, even through the dry season, until 1933, when high rates were again found, which continued throughout the year in spite of intensive treatment of 4 towns with atabrine, personally administered by one of us (W. H. W. K.). In 1934, rates dropped precipitately, even through the dry season, and remained at low figures throughout the year. Then in the first 4 months of 1935 we experienced an epidemic, when rates rose to high levels (28.8 per cent in the treated towns) during the dry season (January through March), and declined rapidly thereafter (see chart on p. 112 of our fifth year's observation). No significant increases were noted in 1936, 1937, or 1938, and none occurred in 1939 until August, when the rate increased to 17.5 per cent from 6.9 per cent in the preceding month. Thus 4 dry seasons passed without any significant rises in parasite rates; the first such increase occurred in August, 3 months after the rains had begun. Apparently, judging from this experience, an epidemic may occur at any season of the year.

If river conditions favoring increased production of anopheles mosquitoes are the cause of increased parasite rates, such increased rates should reoccur each dry season, after the completion of the Madden Dam (September 1934), which impounded water during the dry season. However, with the exception of the epidemic in the early months of 1935, the next 5 years passed with no significant rise in parasite rates in any dry season. The first notable increase came in the month of August 1939, several months after the rains had begun.

If mosquito density were the answer to the problem of cyclical increases, towns along the river bank should have the highest parasite rates, as they are nearest the source of mosquitoes. The town of Las Guacas, which is nearly surrounded by water and in which the highest density of mosquitoes was found in 1932, has had consistently the lowest rate of any of our villages. On the other hand, New San Juan, which lies some 2 or 3 miles to the north of the Chagres River, has had consistently the lowest density of mosquitoes of any of our towns. Yet at times the parasite rate in New San Juan has been higher than in any of the other villages.

Malarial parasite rates in our area exhibit large variations over periods of varying lengths. One of us (W. H. W. K.) believes that these variations are caused by great increases in new infections, following a loss of tolerance, which may be due to natural causes or to treatment. Relapses certainly play a part in the increases noted, but they are believed to be significant as compared to the numbers of new infections found during epidemic periods.

The same author believes that the increased numbers of "heavy infections" noted as occurring since our drug treatment was begun is also due to a decrease in tolerance brought about by ridding the population of its parasites. When malaria attacks such a non-immune population, the number of clinical cases is higher than in a control group, which has had little or no treatment. This point is brought out strongly in our fifth annual report (2), and

is confirmed by the figures in Table X, which show a steady increase of "heavy infections" among our treated population.

Whatever may be the cause of the cyclical variations which occur in the malarial parasite rate, their existence must be considered in evaluating the results of control measures. By an unfortunate chance, our initial surveys made in 1929 showed high rates, and much of the success of our efforts has been referred back to these high rates as a base-line. If, however, we had made our initial surveys in September 1930, we would have been much less encouraged by our results, as the 1930 figures, 16.2 per cent, were low. In fact, they were a fraction lower than the average monthly rate for the 12 months ending August 1932, after two years of treatment with quinine and plasmochin (Table 1 of our second year's observations, 1932).

"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 the disease. 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." The value of our observations is enhanced because they have been made over a period of time long enough to encounter a number of normal cyclical variations. There has been a steady diminution in average annual parasite rate, as determined by monthly surveys in the treated groups. As shown in Table I the average annual rate for these groups was 21.6 per cent, in the first year of treatment. Nine years later, in 1939–1940 this rate was reduced to 12.1 per cent. A comparable decrease was not noted in the control groups, so far as figures for these groups are available. We believe that the reduction in the annual parasite rate in our treated groups is a fair measure of the success of our work.

Summary

1. This report deals with an experiment in the control of malaria with drugs alone, conducted in a rural region of high endemicity in Panama, where no anti-mosquito measures were used. The experiment has extended over a period of 10 years. The population concerned were native Panamanians, with a large negroid strain, living in six villages located on the banks of the Chagres River between Madden Dam and the eastern boundary of the Canal Zone; and a control group living about five miles away on Madden Highway. Breeding of *A. albimanus*, the principal malaria vector, was abundant in the aquatic vegetation along the river-banks and in the many lagoons and backwaters near the towns. Such breeding became extremely abundant at periods of low water, caused by the impounding of water behind Madden Dam, which resulted in slow current and semi-stagnant conditions in the river.

2. During the entire period of our studies, no correlation between the monthly malarial parasite rate and monthly rainfall was noted. The annual rainfall varied from 73.32 inches to 123.15 inches, with an annual average of about 100 inches.

3. The population involved in our studies was divided into three groups, two of which were treated, and the other used as a control. In all our work, only those individuals who were found parasite-positive, as indicated by examination of blood-films, were treated. Mass treatment of the population was not attempted at any time. The control group was provided with quinine sulphate, which was taken voluntarily, with no attempt at supervision of treatment. This method was used in the control groups throughout the course of the experiment.

From September 1930 to September 1932, the two treated groups were given quinine sulphate alone, or with plasmochin. In September 1932, one group was treated with atabrine 0.1 gram 3 times a day for 5 days, followed 2 days later by plasmochin simplex 0.01 gram twice a day for 5 days. The other group was treated with quinine sulphate (tablets) 0.972 grams a day for 5

days, followed 2 days later by plasmochin simplex 0.01 gram twice a day for 5 days. These methods of treatment were continued from September 1932 to September 1940.

During the course of these experiments, one case of quinine idiosynerasy was noted. Plasmochin simplex, given either following quinine or atabrine, gave trouble in many instances when administered twice a day for 5 days. We found one family the members of which cannot take plasmochin in any quantity without experiencing abdominal distress.

4. Blood-film surveys for malarial parasites were made monthly throughout the entire ten-year period, to measure our results. The thick-film technique of Barber and Komp (1) has been used, and the staining and examination of the films have been done by experienced technicians.

5. Administration of treatment during the first years was in the hands of a native graduate nurse, assisted by the local school teachers and civil authorities. One of the staff also had charge of the administration of the drugs in the Chagres River towns.

A definite policy was later established of employing native girls to give the treatments under the supervision of the river supervisor. Thus the administration of the drugs was by non-medical personnel; visits of inspection were made by a member of our staff 4 days a month.

6. During the later years, large shifts of population in our towns interfered seriously with the continuity of our work. The population has declined in number steadily since about 1938. Many families have moved to Madden Highway, where better transportation and school facilities are available. Greatly increased labor demands in the Panama Canal Zone have drawn many of our villagers from the river towns. A large number of these people had been permanent inhabitants of the towns from the early years of our work.

7. The part played by new infections, as compared with relapses from previous infections, is believed to be relatively small. In the quinine-plasmochin treated group, 51.6 per cent of all positive for malarial parasites were positive from 2 to 7 times during a year's observations. In the atabrine-plasmochin treated group, this percentage was 45.6 per cent. A certain portion of the percentage of repeated positives is doubtless due to insufficient or incomplete treatment, but in the main it is the result of low tolerance to the disease. Persons repeatedly positive keep up the parasite rate, even though given frequent complete courses of treatment. These individuals defeat our efforts to effect a further reduction in the parasite rate. We believe that they represent cases of relapse, in most instances, rather than new infections. Some confirmation of this view is found in the low monthly parasite rates, and the low percentages of infections in infants, which point to low transmission rates.

8. During the past 10 years, the incidence of the several species of malaria parasites among all positives has been as follows: *P. falciparum,* 77.8 per cent; *P. vivax,* 19.3 per cent; *P. malariae,* 2.9 per cent.

The percentage of crescent-carriers in *P. falciparum* infections has increased rather than diminished from year to year; however, exceedingly few carriers are found in any year which are good subjects for mosquito infection experiments. The percentage of heavy infections found among positive individuals has not decreased in the treated groups; however, the majority of positives in these groups show very few parasites in the films, while positives in control areas show many parasites, requiring less time to discover them.

9. Surveys of infants under one year, from 1935 to 1940, show positive rates of 5.9 per cent in the 272 examined in the treated areas, as against 20 per cent of 20 examined in the control areas.

10. The highest parasite rates were found in the age-groups from 5 to 10 years, and from 10 to 20 years. The latter group contains the young adults who form a large

percentage of any tropical labor force. Adequate treatment of this latter group is necessary, therefore, to maintain its efficiency under conditions of hard labor and exposure. Such treatment can be administered in the field with small personnel and little expense.

11. Non-medical personnel selected from camp or village residents can be instructed to administer anti-malarial drugs in a reasonably satisfactory manner. However, a physician qualified and interested in tropical and industrial medicine should supervise such non-medical personnel, making visits at least once a week to the areas under treatment.

12. We consider quinine sulphate and atabrine to be of equal therapeutic value in the treatment of malaria. In our work, atabrine has the advantage that it is preferred to quinine by the native population. It is, of course, considerably more expensive than an equivalent course of quinine treatment. We do not believe that plasmochin has played a very important role in our work.