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MASS-ADMINISTRATION OF DIETHYLCARBAMAZINE CITRATE IN
PREVENTING TRANSMISSION OF APERIODIC HUMAN FILARIASIS

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The experiment described here was part of a programme of research undertaken in Fiji in 1957-59 on behalf of the Secretary of State for the Colonies and the Government of Fiji. A report giving unsummarized data has been prepared (BURNETT, 1960a) and is available to those requiring such information.

The purpose of the investigation was primarily entomological, but the complexity of the vector situation in Fiji, where there are four actual or potential vectors which collectively bite round the clock, indoors and away from villages, in bush and gardens (SYMES, 1955, 1960a, b), suggested that drug prophylaxis might be the most hopeful method of controlling transmission of *Wuchereria bancrofti* var. *pacifica*. It should also provide information on the effect of prophylaxis on infections in wild mosquitoes and the presence of non-human sources of infection which might confuse the epidemiological picture.

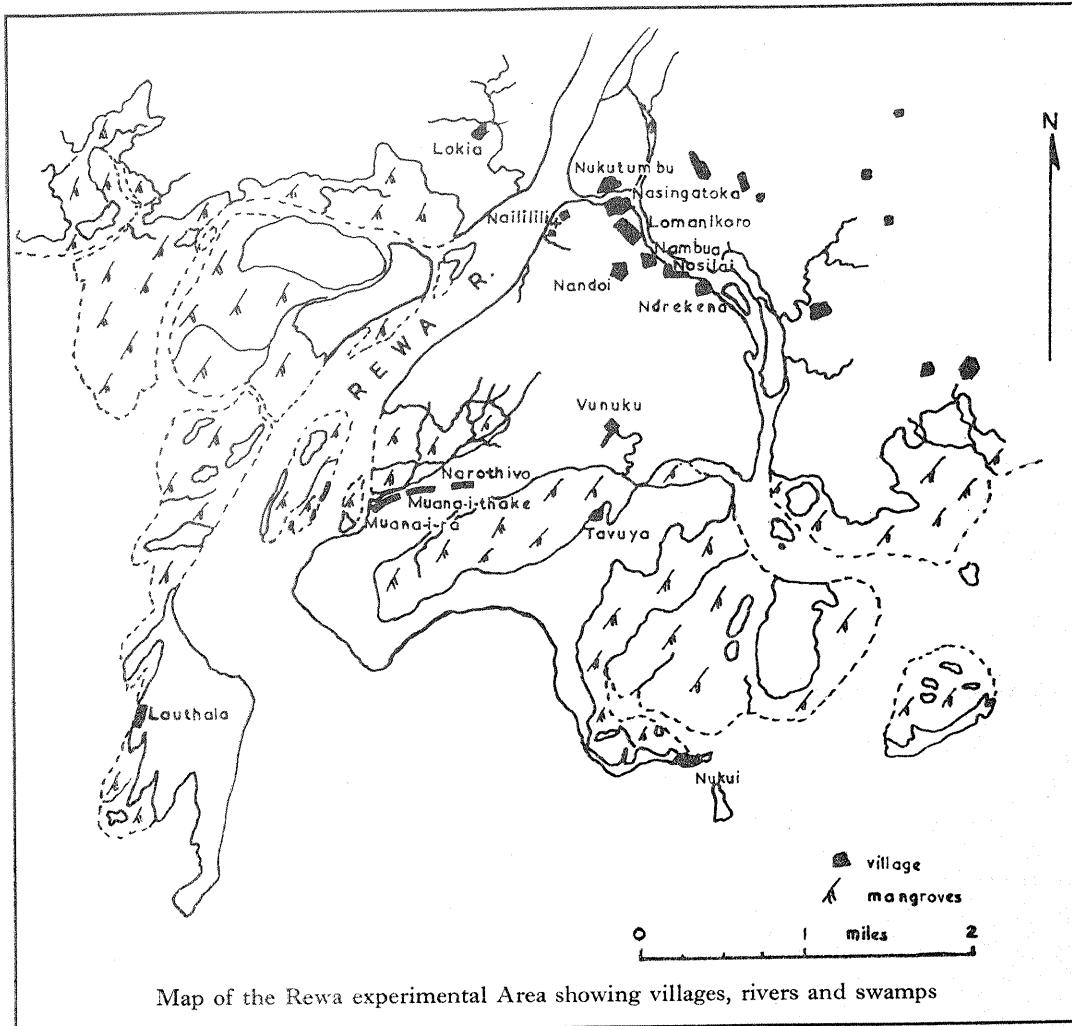
EXPERIMENTAL AREA

The area selected for the main experiment was chosen for a number of administrative reasons, guided by the results of the survey of filaraemia made throughout Fiji in 1946-50 by Amos and his assistants (NELSON and CRUIKSHANK, 1955). About 1,500 people was considered the greatest number that our small unit could adequately deal with and a suitable site was found at the tip of the delta of the Rewa River, a few miles east of Suva, the capital and only large town in Fiji (see Map). Of the 15 villages concerned, 12 lie on a piece of land isolated by the main Rewa affluent and its distributary, the Nasilai mouth, and the village of Lauthala is on its own island. It was hoped to stop transmission in these 13 villages, but in order to include in the experiment the whole of the local administrative division (Tikina), two other villages, Lokia and Nukutumbu, were treated as well. According to the unpublished figures filed in the Fiji Medical Department, on which NELSON and CRUIKSHANK (1955) based their report in 1944-49, 19.3 per cent. of people over 4 years old in this area showed microfilariae in their blood, a high figure for a population of this size in Fiji.

The 15 villages had a total population at the 1956 census of 1,180, but we were told, when we made our first blood survey, that 1,773 claimed to have their homes there. Not more than 1,303 were actually discovered at any one survey, but the extensive movements of individuals shown by our files indicate that the higher figure is close to the truth. This population occupies an area about $3\frac{1}{2} \times 4\frac{1}{2}$ miles, an unusually high density for Fijian occupation. The whole area is but a few feet above sea-level, and subjected to flooding, and the villages, which are all readily reached by punt, and the gardens and plantations, occupy scattered patches of drier land among the swamps which are covered with grass or mangrove according to the salinity of the situation. The villages fall readily into two groups, those congregated in the north of the area and those scattered over the remainder. All four

* We wish to thank Dr. F. Hawking for his assistance in planning this experiment and Dr. P. W. Dill-Russel, Director of Medical Services, Fiji, for his interest and assistance in carrying it out. We are indebted to A.M.O. W. T. Malani for help at the start of the experiment and to many Fijian officials, especially Roko Tui Rewa, for their assistance at all times. For the mosquito dissections and blood examinations we are indebted to the staff of the Filariasis Research Unit, all of whom were concerned in this experiment.

potential vectors of filariasis (SYMES, 1955) are found in the area, but *Aedes fijiensis* Marks is scarce. In and around the first group of villages *Ae. pseudoscutellaris* (Theo.) is not common and *Ae. polynesiensis* Marks probably absent, but *Culex fatigans* Weid. is abundant throughout the year. In the other, more rural, villages this species is virtually absent but both *Ae. pseudoscutellaris* and *Ae. polynesiensis* are common to exceedingly abundant, according to locality.



Map of the Rewa experimental Area showing villages, rivers and swamps

EXPERIMENTAL PROCEDURE

The experiment was studied from two aspects, the effect of the drug on the parasite in man, and its effect on transmission of the disease as shown by the examination of the mosquito vector.

The main features of the experiment were those of the larger eradication scheme in Tahiti (KESSEL, 1957), modified to suit Fijian conditions. In Tahiti the procedure was (i) a complete blood survey, (ii) a course of drug for everyone, (iii) a complete blood survey, and (iv) continued treatment of all persons found positive, old and new, until they were

negative for two consecutive (annual) examinations. The complete first medication was intended to cure undetectable developing infections and those too light to be found by the methods of survey used. The second survey, apart from being a check on the progress of the campaign, should detect at least a proportion of such cases which have not responded to therapy, but it has to be complete. It makes possible a considerable saving of drug in the second and subsequent medications.

In any scheme to suppress the transmission of a disease by drugs, especially if the drug is unpleasant, or causes unpleasant effects, it is essential that its consumption is adequately supervised. This means that it must be administered personally by a medical officer or qualified auxiliary, who is then on hand to attend to any severe reactions and also to apply ameliorative treatment to clinical lesions, an important aspect of public relations in this sort of scheme. Because, except in some inland districts, virtually every village in Fiji contains people positive for microfilariae, the only saving made by the use of a second survey would be the cost of the drug which would otherwise be taken by uninfected people; the greater cost of actual administration remains the same. The cost per course was only about 9d. per person, and the saving possible would be considerably less than the cost of a blood survey. Further, it is likely that a post-treatment survey would miss more cases than it discovered after the intensity of nearly all infections had been reduced by treatment. We decided that in Fiji a suitable schedule would be (i) a complete blood survey, (ii) two courses of drug at an interval of some months or a year, for everyone, (iii) a blood survey of all people previously found positive, and a sample survey of part of an area to see if many new cases could be found, (iv) possibly continued medication to all known positives, or only those still showing microfilariae. This might be repeated until they were negative at two consecutive examinations, as in Tahiti. Since our experiment was a pilot scheme, complete blood surveys were made before each medication, and after the second. We hoped that only sporadic positives would remain, and a decision whether to continue treatment of these could be made in the light of the results of the last survey.

It was necessary to compress the experiment, apart from any follow-up observations, into 18 months, which precluded the possibility of an annual dosage cycle. It was decided to administer the two courses of drug about 6 months apart, with a third blood survey about 6 months after the second administration, leaving time for a third administration if needed. It was possible to start giving drugs before the blood survey samples had been examined.

Before the experiment started it was fully publicized locally through Fijian Affairs officials and radio, and a circular was prepared and circulated to all village headmen. The sequence of events is given below.

		1958	1959
March-June	1st mosquito survey.		Jan. 5-Feb. 28 2nd drug administration.
May 12-31	1st blood survey, samples taken.		April-June 3rd mosquito survey.
June 16-Aug. 16	1st drug administration.		June 1-17 3rd blood survey, samples taken.
Aug.-Dec.	2nd mosquito survey.		
Nov. 17-Dec. 18	2nd blood survey samples taken.		
Dec. 2nd	Hurricane and floods interrupted work.	1962	Proposed follow-up survey.

Blood surveys

It was desirable but not possible to examine 1 c.c. venous blood by the Knott technique as modified by Symes (SYMES, 1960b), since this detects more cases than the use of thick drops. Instead, three thick drops of 20 c.mm. from three different fingers were examined,

and microfilariae counted, after drying, dehaemoglobinization, fixing and staining in Giemsa (Gurr). At the same time that samples were taken a note was made of filaritic lesions and any history of filariasis.

Two indices of filarial infection were estimated from these surveys. The microfilarial infection rate (m.f.r.)—the percentage of people examined in whom microfilariae were detected, and the microfilarial density (m.f.d.)—the mean number of microfilariae counted in a single 20 c.mm. thick drop, although in fact three were examined. The m.f.d. can be calculated for positive subjects only, or for the population as a whole, the latter being more important from the epidemiological point of view. It is used when discussing the reduction in filarial load obtained in this experiment.

Entomological surveys

A series of standard catches was made for each survey in 11 of the villages in the area in which it was hoped to stop transmission, and as many as possible of the vectors caught were dissected. Pyrethrum aerosol was used for catches in houses and, in addition, night bait-catching was done in them. Daylight bush catches were made to a standard routine around villages and gardens, and along tracks leading from villages. All positive specimens were submitted to the senior author or to a very experienced Senior Mosquito Inspector for confirmation.

Drug administration

Some preliminary trials on different drug dosage schedules were made and are reported elsewhere (BURNETT, 1960a). The samples were small and conclusions could only be tentative but, generally speaking, extended schedules were more effective than an equal or somewhat greater amount of drug consumed in six doses a week apart. However, six weekly doses of 350 mg. gave very promising early results and because of the convenience and economy of a short course, especially when administered *en masse*, it was decided to try six doses each of 400 mg. diethylcarbamazine citrate at weekly intervals. The mean weights of adult Fijian men and women treated in the preliminary tests were 67 kg. and 60 kg. respectively and this dose is close to 6 mg./kg., which has frequently been used in diethylcarbamazine therapy (e.g., KESSEL, 1957).* Children under 2 years old were not treated, those between 2 and 4 years, if treated, were given one-quarter the adult dose, between 5 and 9 years, one-half, and between 10 and 14 years, three-quarters. Drug administration was personally supervised by one of us (J.U.M.) for the second administration but for the first, owing to his absence on leave, by an Asst. Medical Officer loaned by the Fiji Medical Department. To administer pills, the villages were toured once a week, but it was necessary to make eight rounds to complete the majority of courses. A few courses remained almost complete and the last dose was left with the subject, with instructions how to take it. Any person who had only started a course at this stage was not required to complete it.

Throughout the experiment the formulation used was "Carbilazine" brand of diethylcarbamazine citrate, B.P.C., manufactured by S.A. Union Chimique Belge N.V. Brussels. This came in 100 mg. tablets which were more suitable for the large doses than 50 mg. tablets. The cost, landed Suva, was about 31/- stg. per 1,000.

* We were later given the following weights based on much larger samples, by Dr. A. T. Hawley of the Central Medical School, Tamavua : 224 males over 20 years, mean wt. 70.4 kg. S.D. \pm 9.1 ; 233 females over 20 years, mean wt. 63.6 kg. S.D. \pm 10.

RESULTS

Clinical filariasis, and popular reaction to drug administration

Of the 1,200 people examined at the first blood survey, 146 were blood positive and 101 reported or showed clinical filariasis. Of these latter, 84 complained only of fever and of these only 30 were blood positive. Of 17 showing swollen glands or elephantiasis, five were blood positive, the others negative. All the six cases of elephantiasis were in the "rural" villages.

Response to the first course of drug was excellent and there were no refusals. Many people remarked that the drug made them drowsy and feel weak, and they preferred to take it in the evening and sleep it off. Its usual action on intestinal worms was noted with approval, even the voiding of *Ascaris, per os*. As usual, too, the tonic effect was remarked on and the cessation of attacks of filarial fever. Reactions were also reported after the start of the second course of treatment, but only 20 per cent. of these people had microfilariae apparent in the blood. There were three cases of what may have been a delayed reaction, abscesses developing about 10 weeks after the first dose of carbilazine. One was in a man with elephantiasis of the leg, the abscess forming in the same leg. All were cured rapidly by penicillin. Our data for reactions are incomplete and therefore not reported in detail. Children appeared little affected by drug reaction. Popular approval was sufficient for us to be asked to extend our experiment to the next Tikina.

The second course was treated with greater indifference because most people still felt quite well. There were no refusals, but subjects had to be sought out to a greater extent than before. It is possible that, with a longer interval between treatments, our reception would have been more enthusiastic.

Although 1,773 people were named as being resident in the areas, only 1,226 completed the first course, and 911 the second, out of 1,303 and 1,296 who started them. The balance was away working elsewhere, often with their families. (A few pregnant women missed one course or another and are not included in these figures).

Blood surveys

The initial blood survey gave the surprisingly low microfilarial infection rate of 12.2 per cent., compared with 19.3 per cent. in 1944-9, or, excluding Lokia and Nukutumbu, 13.4 per cent. compared with 19.8 per cent. Part of the discrepancy is due to our inclusion of children under 5 years, who were not infected, and part to the use of 1 c.c. samples in the previous survey. The rest can be attributed to sampling error, which is fully discussed elsewhere (BURNETT, 1960a), inflated by movement of people. Our initial survey was as complete as one can hope for in practice, but there was a considerable influx of people before the second was made and it was the arrival of untreated carriers which increased the crude count of microfilariae from 2.2 per cent. to 9.95 per cent. of the original level (Table 1). In the same way untreated carriers inflated the microfilarial count in the third survey from 0.79 per cent. to 8.9 per cent. of the original level. The 15 immigrant carriers equal the number of positives persisting after treatment; therefore the examination of the crude blood survey figures alone does not give a true indication of the effect of medication. For this reason the effect on microfilarial rate and microfilarial density when immigrant carriers are excluded has been included in Table I. Carriers who moved away before the second and third surveys have not been excluded; if they had stayed and been treated they would have had a much smaller influence on the microfilarial count than untreated carriers. The movements of

TABLE I. Summary of results of three blood surveys in the Rewa experimental area.

	Survey		
	1	2	3
Total examined	1200	1089	1123
Total positive for m.f.	146	73	30
m.f.r. %	12.2	6.7	2.7
Total m.f. found *	4857	438	400
m.f.d. positives only	33.3	6.0	13.3
m.f.d. total examined	4.048	0.402	0.360
Persisting m.f.r. % of original		55	22
Persisting m.f.d. % of original		9.95	8.90
No. of positives not examined at previous survey, nor treated		14	15
Total m.f. in these *		342	364
Omitting these subjects			
m.f.d. positives		1.63	2.40
m.f.d. total		.089	.032
Persisting m.f.r. % of original		44	11
Persisting m.f.d. % of original		2.2	0.79

* $\frac{1}{3}$ total counted in three 20 c.mm. drops from each subject.

uninfected people have been ignored. In Table III are given the results when only known positive cases are considered.

Infections were not intense, the highest m.f.r. found was 507. Out of 153 positive subjects, 22 per cent. had counts of 3.3 or less; 42 per cent. less than 10.3; 83 per cent. less than 50.3; 93 per cent. less than 100.3; 98 per cent. less than 200.3 in 20 c.mm. After the first medication among treated subjects the highest m.f.r. was less than 30, and 90 per cent. of those still positive had counts of 3.3 or lower. After the second medication the highest count was 13, and 87 per cent. had counts not exceeding 3.3.

An important result was obtained when 1 c.c. of venous blood was examined by the modified Knott technique from all the people of three villages who had been found positive

TABLE II. Distribution of mf. incidence by age-groups, before and after treatment (omitting all those receiving less than one full course).

Age	1st survey		3rd survey	
	No. examined	No. positive	No. examined	No. positive
0-4	127	0	75	0
5-9	221	5	216	0
10-14	198	7	180	0
15-19	94	9	47	1
20-24	73	9	45	1
25-29	71	9	53	1
30-34	65	16	52	2
35-39	68	6	55	3
40-44	70	21	69	3
45-54	54	17	45	1
50 and over	159	47	125	3
Total	1,200	146	962	15

TABLE III. Drug administration—positive cases only.

	1st survey			2nd survey			3rd survey				
	No. pos.	Total m.f. counted (mean of 3 drops)	% pos.	No. pos.	Total m.f.	% of 1st m.f.d.	No. pos.	% pos.	Total m.f.	% of 1st m.f.d.	
A. Treated twice, sampled 3 times	82	2960.3	36.2	32	39	0.47	1.3	5	6	5.9	0.7
B. Treated twice, sampled 1st and 3rd survey	7	751.2	107.5					2		3.0	0.43
C. A + B	89	3711.5	41.7								
D. Treated once, sampled before and 6 mths. later	122	3842.3	31.7	43	35	144.6	1.19	3.76			
E. Treated once, sampled before and 1 yr. later	5	58.6	11.7	1			2.0	0.4			
F. D + E	127	3900.9	30.7	44	34.6	146.6	1.15	3.76			

TABLE IV. Dissection of vector mosquitoes taken in the Rewa Drug Experimental Area. Microfilariae and developing larvae (1st, 2nd, early 3rd and mature).

at the first survey. The great majority (31) were negative to examination of three thick drops, but when the larger samples were examined no less than 13, or 42 per cent., were found to be positive and of these, five (39 per cent.), had been negative to the second survey. Of the total of 31, 19 (61 per cent.) were found negative at two consecutive surveys and, no doubt, there were others in whom a still larger sample would have detected microfilariae. The counts, in 1 c.c., of these 13 people ranged from 1 to 19. Before the first treatment they had ranged from 30 to 382 in 20 c.mm. The 18 negative for 1 c.c. had pre-treatment counts of 1 to 296 per 20 c.mm.

The true value of medication lies in the permanence of its effects and this can be assessed only by another blood survey in a few years' time. It is hoped that some of these low intensity infections will die out.

Mosquito surveys (Table IV)

The intention of the mosquito surveys was to demonstrate any reduction in transmission due to drug administration. In Table IV the two bush vectors are grouped together because the females can only be doubtfully distinguished. Before treatment began only eight *Aedes* showed mature infections; 0.66 per cent. in 1,208 mosquitoes. The total infection rate was 4.6 per cent. *Ae. fijiensis* was too scarce to be of importance, and the status of *C. fatigans* has been discussed elsewhere (BURNETT, 1960b), where largely as a result of the surveys made in Rewa, it is concluded that its importance as a vector is low. The percentage infected, even with microfilariae, is extremely low, no doubt because so few of the people in these villages are infected. After the first drug administration *C. fatigans* was not found infected but eight bush vectors out of 841 were, one with infective larvae. These findings represent reductions in total and mature infection rates of 79 per cent. and 82 per cent. when feeding on a population showing a reduction in m.f.r. of 50 per cent. and in m.f.d. of 90 per cent. After the second course of drug only one positive case, not mature, was found in 832 mosquitoes, reductions over the second survey of 87 per cent. and 100 per cent. The reduction in m.f.d. in the population as a whole was negligible, but positive cases were reduced by more than one-half.

After medication *Dirofilaria immitis* continued to be found in mosquitoes and were readily identified, but the only other filarial larvae found were the few *W. bancrofti* reported. The great reduction in these caused by the drug administration confirms that there was no other source of larvae (i.e., an animal reservoir) to obscure the epidemiological picture.

DISCUSSION

There seems little doubt that transmission has been reduced and perhaps ceased, at least for the time being, in the experimental area. Mature infection rates in mosquitoes in Fiji are low in any case, but the complete disappearance of infective larvae is presumably of some significance. It is unfortunate that this cannot be tested rigorously, but it can be shown that the decrease in total infections was very highly significant even after the first treatment ($P = 0.001$), and the reduction in infective larvae was in the same proportion, and therefore presumably equally significant.* The second drug administration further reduced both m.f.d. and m.f.r.*; and although the reduction in the latter was almost outweighed by

* No test can be applied to these figures because the expected frequencies are too small to make a valid χ^2 test.

infected immigrants one may assume that in a well-planned scheme to control filariasis, in which all areas are treated, this factor would be of minor importance.

The reduction in total infections in mosquitoes given by the two drug administrations was 97.4 per cent., compared with reduction in circulating microfilariae in the human population of 91.1 per cent. Obviously, with infections so scarce, the exact percentage discovered by collection is largely a matter of chance. It has been stressed elsewhere (e.g., OTTO et al., 1953) that heavily infected carriers with m.f.d. over 200 per 20 c.mm. kill a high proportion of the mosquitoes feeding on them, and that therefore a reduction in their m.f.d. may make them a more serious source of infection and not a less important one, because the proportion of mosquitoes feeding on them which lives to become infective, increases. In the present case only three (2 per cent.) of our original carriers were in this class and the maximum m.f.d. in these people at the end of the experiment was 13.0, and it seems unlikely that, in our experiment at least, this factor is of importance.

The confusing effect of immigrants with high m.f.d. has been referred to already and in Table III information on all positive cases has been extracted. Only 89 people received two full courses of drug (those who missed one dose, or one dose in each course, are included here), and they were also examined before the first and after the last course. Ninety-two per cent. were apparently cured, and the mean m.f.d. was reduced by 99.76 per cent. This is slightly better than the crude survey results, after immigrants have been eliminated. More people completed a single course and were examined before and after it—127, 82 of the previous sample. Only 65 per cent. were apparently cured and 96.24 per cent. of their circulating microfilariae removed. The second course of drug therefore had a considerable effect in reducing both the number of carriers and the mean m.f.d. by about 75 per cent., but its prime importance should be to increase the number of permanent cures. The check made with 1 c.c. samples of venous blood is important. If over 40 per cent. of our apparently cured subjects were still really positive, the true percentage of persisting positives (Table I) rises to 69 per cent. after one course, and 46 per cent. after two courses of drug. There must be others, for SYMES (1960b) was able to infect mosquitoes by feeding them on people negative to the usual methods of detection. It should be borne in mind that such people have a negligible effect on the recorded m.f.d., and on the proportion of mosquitoes infected, and it is to be hoped that their infections will die out. It would, however, be futile to give a third course of drug to the 10 per cent. of the original patients still overtly positive to thick drop examination when a further 46 per cent. are also infected but not overtly. If we followed the rule used in Tahiti and did not continue medication to positives that become negative to two consecutive examinations, we would continue to dose about 36 per cent. of our initial positives (10 per cent. overt plus 26 per cent. negative for one examination) while omitting 16 per cent. negative to two ordinary examinations, but known to be positive by examination of 1 c.c. venous blood, plus others not detected. It was therefore decided not to give these people a third course, but to make a new examination in about two years' time. This should give time for persisting cases to relapse or die out, but not time for enough new infections to become overt to spoil our conclusions. The large number of positive immigrants, likely to be reinforced, makes it rather futile to try and determine how long transmission will remain negligible.

The only comparable published results from the Pacific which we have seen are those of Kessel in Tahiti (KESSEL, 1957). In our two courses we administered the same total amount of drug as was received by the people included in lines 2 and 4 of his Table VIII. The reductions in carriers and in microfilariae are comparable. The m.f.d. in our positives at

the start was well below that in Tahiti, and no doubt lower than in some other parts of Fiji, but, even including immigrants, both the m.f.d. and m.f.r. in Rewa are now about half the levels of 1 per cent. and 5 per cent., respectively, which Kessel thinks too low to maintain transmission. Bearing in mind that we detect more positives with three thick drops than with one—as in Tahiti—(BURNETT, 1960b), and that therefore our percentage of positives detected is higher, it appears likely that the method used in Rewa would be successful in areas with at least twice the filarial incidence we experienced, i.e., any area in Fiji.

SUMMARY

A mass-administration of diethylcarbamazine citrate was made in Fiji in an attempt to interrupt transmission of aperiodic human filariasis. Two courses of drug were given to everyone, of approximately 6 mg. per kg. per dose, six doses being given at weekly intervals; 1,226 people completed the first course, 911 the second. The mean microfilarial infection rate was reduced from 12.2 per cent. to 2.7 per cent., five months after the end of the second course, and the mean microfilarial density from 4.048 to 0.360, reductions of 79 per cent. and 91.1 per cent. There was a considerable movement of people in and out of the area, which reduced the apparent effect of the drug. Reductions in m.f.r. and m.f.d. for people found positive were 65 per cent. and 96.24 per cent. for one course (127 subjects) and 92 per cent. and 99.76 per cent. for two (89 subjects). Transmission of filariasis may have ceased, no mature infections being found in the vector species after medication of the people.

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