TRANSACTIONS OF THE ROYAL SOCIETY OF
TROPICAL MEDICINE AND HYGIENE.
Vol. 58. No. 6. November, 1964.

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

II. RESULTS OF A BLOOD SURVEY MADE FOUR YEARS AFTER DRUG ADMINISTRATION

BY

G. F. BURNETT

Tropical Pesticides Research Institute, Arusha, Tanganyika

AND

J. U. MATAIKA*

W.H.O. Malaria Eradication Pilot Project, Honiara, British Solomon Islands Protectorate

In 1961 we reported in this journal the results, up to 1959, of an experiment in the Rewa Tikina in Fiji in which we attempted to halt the transmission of *Wuchereria bancrofti* var. *pacifica* in a human population of about 1,700 people (BURNETT and MATAIKA, 1961). The experiment took place in 1958-59 and it was proposed to follow it up in 1962 with another blood survey, principally to estimate the degree of permanence of the cures apparently made in infected people. The survey was made in 1963 by two of our old team who had done the bulk of the work in the previous surveys and who are very experienced in this work. Information was obtained on the permanence or otherwise of cures, the likelihood of transmission being resumed, and the effect of the mobility of the people concerned on the results of such experiments. No mosquito surveys were made in 1963.

EXPERIMENTAL PROCEDURE

The area and its population, almost entirely native Fijian, were briefly described in our earlier paper. In June-August, 1958, and in January-February, 1959, two courses of diethylcarbamazine citrate were given to all residents over 2 years old, whether they showed symptoms of filariasis or not. Each course was of 6 doses of 400 mg. (for adults) at intervals of one week. Complete blood surveys were made before this treatment, between the courses, and 3 months after the second course. For each examination three drops of 20 c.mm. capillary blood were examined, the result being expressed as the mean of the count in the three drops. From these data the microfilarial rate (mf.r.—the percentage of subjects infected) and the mean microfilarial density in 20 c.mm. (mf.d. (20 c.mm.)) were calculated. It was intended to follow the same procedure in the 1963 survey, but in addition, as a result of our finding in 1959 that over 40 per cent. of apparently cured people were positive if 1 c.c. of venous blood was examined (BURNETT and MATAIKA, 1961, pp. 183-4), it was decided to take such a sample from all known positives and examine these for comparison with the standard three 20 c.mm. drops. Owing to a misunderstanding only the 1 c.c. samples from these positive subjects were examined and the results recorded. In order to make the results of the latest survey comparable with the earlier results it is necessary to employ correction factors for the 1 c.c. examinations in order to reduce the microfilarial infection and density rates to those that would have been obtained from three 20 c.mm. drops.

* This survey was carried out by Messrs. J. Kaisuva and J. Naserua, with the permission of Dr. C. H. Gurd, O.B.E., Director of Medical Services, Fiji, and under the supervision of Dr. D. W. Bookless, Deputy Director, and afterwards of Dr. A. J. Hibbell, Assistant Director. It is a great pleasure to acknowledge our debt to these gentlemen.

These correction factors have been calculated from comparative figures obtained in Fiji by SYMES (1956, tab. 40) and by BURNETT (1960a, tab. 9), from data for a total of 109 subjects. All carriers (83) showing over 50 microfilariae per 1 c.c. of venous blood were detected by the examination of three 20 c.mm. drops, but about 45 per cent. of those with fewer were missed (12 out of 26). The mf.r. is therefore recalculated accordingly. The mean mf.d. is obtained by dividing the mean mf.d. (1 c.c.) by 30. This factor applies for means of microfilarial counts up to 1300 (93 subjects), the highest count in our 4th survey being 1206. For 16 subjects with counts between 1,300 and 10,400 in 1 c.c. the factor was 50, the same as the volume ratio of the blood samples. For our purpose, which is to equate results obtained by a more sensitive and accurate method with others obtained by a less sensitive and accurate one, it is considered that these factors are adequate. Where corrected (i.e. reduced) figures for mf.r. or mf.d. are quoted, or percentages derived from them, they are printed in italics.

It is convenient to distinguish the four blood surveys made in the course of the experiment by numbers :

No. 1—Before treatment, May 1958.
2—Between 1st and 2nd course of drug, November-December 1958.
3—After treatment (i.e. three months after 2nd course of drug), June 1959.
4—Follow-up, four years after treatment, March-May 1963.

RESULTS

In Table I are given the results of the fourth survey, combined with those of the first three surveys already published in our earlier paper ; the latest survey included considerably more people than the others. The crude infection rate was already nearly half its original value, but the intensity of infection was still low, only *12.3* per cent. of the pre-treatment value. Between June 1959, and March-May 1963, a large number of new residents had appeared (this is discussed below), including 14 positives not present at any previous survey, and not treated, and these have inflated the mf.r. and mf.d. by about one third. Only 507 people were present at all four surveys and the results for these alone are given in the lower part of Table I ; their treatment experience is included in Table V. Their initial mean infection rate was rather higher than that of the general population and they showed a considerably greater fall during treatment, but with a correspondingly greater rise since. The experience of this sample is what might be expected in the population as a whole if drug administration had been part of a comprehensive scheme, so that no immigration of untreated persons was possible.

Only one report of symptoms of filarial disease in the last 4 years was obtained during this survey. This was a case of fever.

RESUMPTION OF TRANSMISSION

There is little direct evidence of resumption of transmission. Although at the fourth survey 22 positive subjects were found who had been examined previously and found negative, 12 may have had prepatent or suppressed infections at the earlier examination, which took place only after some treatment had been given. The remaining 10, who are known to have been negative before treatment, are included in a total of 886 people who had been present at earlier surveys, the other 876 being negative at the fourth, and either never positive or positive and cured. Thus even if all ten were infected after treatment ceased, they represent a rate of only 1.1 per cent. over 4 years. The current mf.r. and mf.d. can also be compared with Kessel's conclusions from his campaign in Tahiti (KESSEL, 1957), that if the

TABLE I. Summarized results of four blood surveys carried out in the Rewa experimental area

Survey	1	2	3	4*
Dates	May '58	Nov.-Dec. '58	June '59	Mar-May '63
Total examined	1200	1089	1123	1430
Mf. r. per cent	12.2	6.7	2.7	*5.5*
Mf.d. (total sample)	4.05	0.40	0.36	*0.50*
Mf.r. as percentage of original		55	22	*45*
Mf.d. as percentage of original		9.9	8.9	*12.3*
For 507 *subjects present at all* 4 *surveys*				
Mf.r. percentage	16.0	5.9	1.2	*6.9*
Mf.d. (total sample)	7.08	0.080	0.012	*0.51*
Mf.r. as percentage of original		37	7.4	*43*
Mf.d. as percentage of original		1.14	0.17	*7.2*

* The figures in italics in this column have been corrected as described in the text to make them comparable with those from the 3 earlier surveys.

mf.r. could be reduced to 5 per cent. and the mean mf.d. (20 c.mm.) to 1, transmission would not persist. In Rewa in 1963 the mf.r. was 5.5 per cent. and the mean mf.d. 0.5, and by Kessel's criteria renewed transmission is unlikely.

POST-TREATMENT HISTORY OF INFECTED CASES

Summarized information on all treated positive subjects present at the fourth survey is given in Table II. Fifty-two were found still positive. A post-treatment reinfection rate of 1.1 per cent. (see above) would have produced a case rate of 0.58 and this possibility has been disregarded in the discussion that follows. An apparent cure was obtained even with a single dose, but the principal interest lies in the first line of the Table, which refers to the only fairly large sample. It includes 15 people who missed one dose in either or both courses of drug but who are considered to have completed their treatment ; there was no close correlation between number of doses and cure, 8 of these 15 were cured and 7 were not, and in any large scheme to suppress filariasis by treatment there would be many such cases. Some people were found negative at Survey 1 and positive at Survey 2. The interval between the first course of drugs and Survey 2 was too short for new infections to develop and these people must have already been infected, but at too low an intensity to be detected by the method in use ; for this reason the infection rates in the third column of Table II are sometimes less than 100 per cent. Some subjects missed Survey 3, but filarial indices are calculated only for those actually examined. The last two columns of Table II give the observed results of the fourth survey, and the previous two columns give these results reduced, as described above, to what would be expected from an examination of three 20 c.mm. drops ; this makes possible a direct comparison with Surveys 1-3.

TABLE II. The results of medication of blood-positive subjects (excluding those found positive only at Survey 4)

Survey No :	1			3			4 corrected *			4	
No. of doses of drug	No.	% pos.	Mf.d. (20 c.mm.)	No.	% pos.	Mf. d. (20 c.mm.)	No.	% pos.	Mf.d. (20 c.mm.)	% pos.	Mf.d. (1 c.c.)
10 – 12	85	96	36.8	83	7	0.09	85	*35*	*3.1*	46	94.3
7 – 9	9	100	32.9	7	14	0.11	9	*45*	*2.8*	56	85.1
5 . 6	14	86	5.2	12	25	0.58	14	*36*	*0.8*	43	23.4
1 . 3	7	100	9.6	3	—	—	7	*29*	*4.8*	43	143

* see text.

On comparing the corrected results of Survey 4 with those of Survey 3, for those subjects receiving at least 10 doses, there appear to have been a considerable number of relapses, accompanied by a 35-fold increase in mean mf.d. In fact the increase in mf.r. is more apparent than real. When in 1959 we examined 1 c.c. of venous blood from each of 31 people who had been apparently cured (i.e. no microfilariae found in three 20 c.mm. drops), 42 per cent. of them were found to be still positive (BURNETT and MATAIKA, 1961, p. 185). If a similar percentage of all the subjects reported as cured were in fact still blood-positive at Survey 3, then the proportions still positive would be not 7, 14 and 25 per cent. but 46, 57 and 58 per cent. respectively, of the same order as those found in Survey 4. It is not, however, simply a matter of light residual infections becoming more intense. 22 of our 31 subjects from whom 1 c.c. of blood was examined in Survey 3 were still present in 1963. Their histories are given in Table III, where both relapses and spontaneous remissions are recorded.

TABLE III. The results from examination of 1 c.c. of venous blood from each of 22 people negative to examination of 3 × 20 c.mm. drops in the 3rd survey

No. of subjects	Mean Mf.d.—3rd survey	Mean Mf.d.—4th survey
9	0	0
4	0	22.5
6	8.5	50.7
3	2.3	0

The corrected mean microfilarial densities of all samples in Table II are still considerably below the premedication levels. These means include cured cases, but even for uncured subjects the mean mf.d. have been reduced by *87* per cent., *86* per cent., *46* per cent. and *23* per cent. for descending order of dosage level. This gradation suggests that the second course of drug had an important effect in preventing recovery of the infection to its former level, although the proportion cured was not significantly greater at the higher dosages.

This is surprising but is probably due to the fortuitous correlation between mean mf.d. and amount of drug taken, only the easier cases receiving the low dosage rates. Strong confirmatory evidence is the very highly significant difference in initial mean mf.d. between those cured and those uncured (Table IV). There is no doubt that low pretreatment mf.d. is the factor which determines that patients will be cured. Thus, less intense infections respond most readily to a given dosage level and more drug is as effective against more intense infections as a lower dose against less intense infections, as found for example by JORDAN (1959).

TABLE IV. Relation between cure and initial mean microfilarial density (in 20 c.mm). Number of subjects in brackets

No. of doses of drug	Pre-treatment mf.d. (20 c.mm) in subjects:		Significance of difference*
	Cured	Not cured	
10 – 12	18.7 (46)	56.0 (39)	$P < .001$
7 – 9	11.3 (4)	54.1 (5)	$P < .001$ } $P < .001$
5 – 6	4.2 (8)	5.7 (6)	$P > .2$ }
1 – 3	2.6 (4)	23.5 (3)	

* data transformed to log (x + 1)

MOVEMENT OF PEOPLE

It was noted above that the experiment was greatly affected by movement of people into and out of the area, with consequent confusion of the epidemiological picture. Some idea of the consequent loss of experimental material and waste of effort and resources is given by Table V, where all subjects have been cross-classified according to the amount of drug taken and their presence at blood surveys. The only subjects who have undergone the complete experimental procedure are the 401 in the top left-hand corner of the Table ; 79 of them were positive. For the purpose of calculating the final cure rate, but with loss of information on their history, we can add the 149 (10 positive) present at 1st and 4th surveys in the next column, giving a total of 550 people examined well enough to give useful information on the effect of two courses of drug (some of these were not found positive until Survey 4). These survive from the 1200 examined in our first survey (Table I). The total number of people alleged to be living in the area at the start of the work was 1,772, of whom 120 were never contacted. 439 (14 positive)—some of them children born after our 3rd survey—arrived between the 3rd and 4th surveys, making a total population taking part of 2211 (229 positive), of whom 2091 were actually examined, and in most cases received some treatment. Thus the total wastage, in the sense of people taking some part, but a fruitless one, in the experiment, was 74 per cent. and the reduction in microfilarial load and in disease transmission attained in these circumstances is encouraging. Of course, the majority of these people eventually returned to their homes and although they were of no use in calculating cure rates, the removal of their microfilariae from circulation reduced the amount of disease transmission taking place.

The section of the population of particular interest comprised the 229 carriers detected at some stage of the investigation. Only 146 were found at the first survey and 85 of these

have been used in our final assessment of the effects of the full two courses of drug. Although 179 infected people completed at least one course of drug, 17 were not found positive until the last survey, 11 died and 43 moved away, leaving the 108 included in Table II.

Discussion

The increase in mf.r. at the 4th survey comes as no surprise, but the fairly low mf.d. and therefore lack of renewed transmission, is less expected. After 4 years it may be assumed that the effects of treatment will be stabilized, any recovery of parasites from the treatment having taken place. The influx of untreated carriers and the data presented on movement and consequent experimental wastage should act as a warning that small piecemeal campaigns against filariasis in Fiji will run into difficulties. The relapse of a number of apparently successfully treated subjects has been seen before, but results from our examination of larger blood samples indicate that the number of true relapses was more or less balanced by the subsequent spontaneous remission of those still positive after treatment. Even after 4 years the mean mf.d. of the 507 people present throughout the experiment was reduced by *92.8* per cent. (Table I) with a profound effect on transmission, although only 401 (79 per cent.) received the full treatment (Table V gives details of treatment). Among those uncured (including 9 not detected until the 4th survey) the reduction is a very useful *85* per cent., accompanied by a reported cessation of all symptoms of filariasis, except in one man.

Table V. Showing the number of people participating, to different extents, in the experiment. Number of positive cases in brackets—a subject is shown as positive even if he was not detected until the last survey.

No. of courses of drug taken	Present at all four surveys	Present at 1st and 4th surveys	Others	Total
Two	401 (79)	149 (10)	328 (30)	878 (119)
One	97 (13)	78 (7)	247 (29)	422 (49)
One, incomplete	6 (2)	32 (6)	134 (7)	172 (15)
Untreated	3 (1)	22 (6)	104 (12)	129 (19)
Total	507 (95)	281 (29)	813 (78)	1601 (202)
			Died	51 (13)
			Untested and untreated	120
			Total	1772 (215)
			New Arrivals (after Survey 3)	439 (14)
			Grand Total	2211 (229)

The highly significant inverse relationship between initial mirofilarial density and cure is interesting. There may be some direct relation between intensity of microfilaraemia and number of adult filariae, such as was found by Bertram (1958) with *Litomosoides carinii* in the cotton rat. All populations of animals show variation in the susceptibility of individuals

to unfavourable factors, including drugs (which is the basis of all standard tests of susceptibility), and the larger the population the greater the number of resistant individuals likely to be present. This may explain the persistence of originally heavy infections after treatment with a given dosage and the need for more drug to obtain equal effects in groups with high mf.d. than in those with low mf.d. It is likely that in populations originally more highly infected the relapse rate will be higher than it was in Rewa.

Summary

An account is given of the follow-up blood survey made 4 years after the mass administration of a double course (total dosage 4.8 grammes) of diethylcarbamazine citrate to a population of about 1700 people in Fiji. The pre-experimental microfilarial infection rate and mean density in 20 c.mm. were 12.2 per cent. and 4.05.

The follow-up (4th) survey included 1430 people. The microfilarial infection rate had risen from 2.7 per cent. to *5.5* per cent. in 4 years. The mean microfilarial density had risen from 0.36 to *0.50*. For 507 people present at all four blood surveys the corresponding rates rose from 1.2 per cent. to *6.9* per cent. (originally 16.0 per cent.) and from 0.012 to *0.51* (originally 7.08). It is concluded that disease transmission on a significant scale is unlikely to have resumed yet.

When known positive cases are considered alone, the proportion not cured by treatment with two courses of drugs appears to have risen from 7 per cent. to *35* per cent. in the 4 years since treatment. It is known, however, that about 40 per cent. of those apparently cured were still harbouring microfilariae in numbers too small for detection by the routine method used, and there has not been any significant increase in the true infection rate. The records of individual subjects show that some had become positive but these were balanced by others who had become negative. The mean mf.d. had, however, increased about 30 times.

The pre-treatment mean microfilarial density among those cured by either one or two courses of drug was very highly significantly lower than among those not cured.

A high proportion, 74 per cent., of subjects were lost to the experiment through population movement.

REFERENCES

Bertram, D. S. (1958). *Proc. 6th Int. Congr. trop. Med. Malar.*, **2,** 437 (seen only in abstract).
Burnett, G. F. (1960a). *Filariasis Research in Fiji.* Tropical Pesticides Research Institute, Arusha, Tanganyika, Misc. Rep. 262.
——— (1960b). *J. trop. Med. Hyg.*, **63,** 153.
——— & Mataika, J. E. (1961). *Trans. R. Soc. trop. Med. Hyg.*, **55,** 178.
Jordan, P. (1959). *Ibid.*, **53,** 54.
Kessel, J. L. (1957). *Bull. World Hlth. Org.*, **16,** 633.
Symes, C. B. (1956). *Observations on the Natural History of Filariasis in Fiji.* Report to Secretary of State for the Colonies, London. H.M.S.O.
——— (1960). *J. trop. Med. Hyg.*, **63,** 31.