

CHEMOTHERAPEUTIC TRIALS IN LEPROSY

2. COMPARATIVE TRIAL OF DAPSONE PLUS DITOPHAL (ETISUL) AND DAPSONE ALONE IN THE TREATMENT OF LEPROMATOUS LEPROSY¹M. F. R. WATERS,² M. B., M.R.C.P. and J. H. S. PETTIT, M.D.*The Research Unit, Sungei Buloh Leprosarium
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Perhaps the most controversial of the recently introduced anti-leprosy drugs is the ethyl mercaptan derivative ditophal (Etisul, Etip). This type of compound was first studied in experimental tuberculosis by del Pianto (^{11,12}), who discovered sodium ethyl thiosulfate to be very effective in the treatment of infected mice. Brown *et al.* (¹) showed that other mercaptan derivatives also were active, and Solorovsky *et al.* (³⁰) confirmed that this activity depended upon the *in vivo* production of ethyl mercaptan. Davies *et al.* (⁹) synthesized a series of ethyl thiol esters, the most promising being ditophal (diethyl dithiolisophthalate), which Davies and Driver (⁸) showed to be highly active in murine tuberculosis when given either subcutaneously or by inunction. Naguib and Robson (²³) investigated its activity in intracorneal infection with murine leprosy in mice, and considered it comparable to that of isoniazid.

In man, ditophal has been studied widely, and almost exclusively, in leprosy. The first to report were Davey (^{4,5,6}) and Davey and Hogerzeil (⁷), who concluded that when it was given to untreated patients, ditophal had a definite and sometimes powerful chemotherapeutic action, which lasted two to three months and then diminished. Accelerated resolution continued, however, if standard chemotherapy followed a short course of ditophal. They also claimed that the bacterial index improved more rapidly with ditophal than with dapsone, and that within three months most of the bacilli had become granular. These observations were confirmed by Lechat (¹⁷) and by Ross *et al.* (²⁸). Dharmendra and Noordeen (¹³), however, while agreeing that ditophal was an active drug in the treatment of leprosy, failed to show that it was more active than dapsone either when given alone or in combination with dapsone. Their results were based on clinical assessment and on the bacterial index, and also on a small study of the bacterial morphology, but it was pointed out that the Indian patients were more severely affected, both clinically and bacteriologically than those studied in Nigeria. Similarly Davison (¹⁰), who used ditophal in combination with both dapsone and thiambutazine, concluded that ditophal did not increase the rate of improvement. He deliberately made no study of the bacterial morphology.

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More recently many reports have been published recording the use of ditophal in the treatment of leprosy. Most authors have considered it to be an active drug, if used early in treatment, but its superiority to standard therapy, either alone or in combination, has remained dubious. In particular, in the Leonard Wood Memorial controlled clinical trial, no evidence was obtained that the addition of ditophal to dapsone treatment resulted in added advantage to patients (¹⁴). Although generally considered as a safe drug, it has caused contact dermatitis in some races, e.g., European (^{2, 19}), Iranian (²⁴), and Japanese (¹⁶), but this seems to be rare in other peoples.

At the Research Unit, Sungei Buloh Leprosarium, experience has been gained (³¹) in the application to leprosy of controlled clinical trial methods. In view of the differing reports, it was decided to apply these methods to a study of ditophal. Because of its generally agreed short-lived action it was decided to use the drug in combination with dapsone and to compare progress, clinical, histologic, bacteriologic and morphologic, with that obtained by standard dapsone therapy. In addition, since some of Davey's best results were obtained in patients "with a dimorphous background" (⁶), near-lepromatous, as well as pure lepromatous patients were admitted to the trial, although they were analyzed separately. A "double blind" study was devised, and the trial here reported lasted from April 1961 until March 1964.

ORGANIZATION AND CONDUCT OF THE TRIAL

Outline of the trial.—The general design followed closely that of a previously reported trial (³¹). The research leprologists were responsible for the care of patients, and the clinical assessments were performed by an independent assessor,³ who otherwise had no contact with the patients. Histologic studies (including assessments) were made by D. S. Ridley of London, who was purposely kept unaware of the treatment given. All skin smears were taken by the research leprologists and read by the laboratory technician, whose readings were checked at random intervals. The "double blind" technic was introduced by giving a placebo of inactive liquid to the control group. This was indistinguishable from ditophal (Etisul, liquid formulation) in color, consistency and odor, but could not give an ethyl mercaptan odor to the breath. The drug and the placebo were supplied in similar bottles labeled "Formulation I" and "Formulation II" and no leprologist (indeed, no one in Malaya) was informed which was ditophal until the trial was completed.

Selection of patients.—All new patients entering the leprosarium were considered possible candidates for inclusion in the trial. Only those having lepromatous leprosy, either pure or with few atypical features, were taken, and adults and children of both sexes were admitted to the trial provided they had no other significant organic disease. Previous antileprosy treatment was considered a serious bar to admission, and no patient who was thought to have received more than 3 dapsone injections was included. Pregnant women were not accepted in the trial, nor were any patients, however suitable otherwise, who appeared likely to abscond.

Full clinical notes were made of each possible patient, color photographs were taken, and two biopsy specimens were obtained from typical active lesions (²⁶), and classified histopathologically as "pure lepromatous" (LL), in 38 patients, or "near-

³The assessor was unable to complete the trial, resigning when 74 per cent of clinical assessments had been completed. The remaining assessments were made in his absence by one of us (J.H.S.P.).

lepromatous" (BL), in 12 patients (27). The average pretreatment biopsy index for each patient always exceeded 0.5. Smears, which were taken from both ear lobes and from 4 active selected skin lesions, were examined for the bacterial index (BI), which was recorded on a logarithmic scale of 0 to 6+ (26), and for the proportion of solid-staining and irregularly-staining bacilli (32). The percentage of solid-staining acid-fast bacilli is hereafter called the morphologic index (MI) (term suggested by C. S. Goodwin). Before any patient was treated, additional investigations were performed, including lepromin and tuberculin tests, hemoglobin estimation, total and differential white blood counts, and serum protein estimation (total, albumin/globulin ratio and paper electrophoresis).

Pairing of patients.—Selected patients were paired by race (Malay 5, Chinese 17, Indian 3 pairs), sex (21 male and 4 female pairs), age (above 15 years 23 pairs, or below 15 years 2 pairs); and intensity and type of leprosy infection, BL patients being paired together (6 pairs).

As suitable pairs were formed, the patients were examined individually by the independent assessor, who made detailed notes and charts of their lesions. Photographs and bacterial indices were shown to the assessor, but not the morphologic indices nor the biopsy reports. Next the patients were submitted in their pairs and the assessor was required to reject any pair that he considered unsatisfactory. He then recorded differences between the members of each pair, and the relative severity of their disease.

When a pair was accepted the patients' names were placed in alphabetic order, the first being designated "A," and the second "B." A letter ("A" or "B"), determining which patient was to receive Formulation I, was contained in the next sealed envelope in a numbered series based on random sampling. In all, 25 matched pairs were accepted for treatment in the research wards for one year.

Treatment.—All patients received intramuscular injections of dapsone in refined coconut oil twice weekly. The initial dose was 200 mgm. and after 6 weeks (12 injections) the dosage was raised to 300 mgm. twice weekly, for the remainder of the 12 months. In addition, one patient from each pair received ditophal (treatment group DE) by percutaneous inunction in a dose of 5 ml. 3 times a week for one year. The oil was applied to the back, chest, arms, and thighs (nonhairy areas), and each inunction lasted at least 10 minutes. Thereafter the patients rested for 1 hour before washing or showering. The other member of the pair (treatment group DP) was treated with placebo in the same way. In children the dosage was adjusted according to age and weight.

Progress of trial.—Smears were taken from the original 6 sites every month and a half for the first 6 months, and then every 3 months. The urine was checked each week, and blood counts were made monthly; serum proteins were estimated every 3 months, and on 3 occasions (after 3, 6 and 12 months' treatment) special assessments were made.

After 3 months each patient was given a general clinical examination, which included smears, tuberculin test and color photographs comparable to the pretreatment photographs. The biopsies were repeated in sites adjacent to the sites of the previous biopsies and clinical assessment was performed.

To avoid the slight possibility of the ability of the independent assessor to detect which patients were receiving the active drug by the mercaptan smell on the breath, all patients undergoing assessment ceased receiving percutaneous treatment 48 hours beforehand. The assessor first examined each patient individually, making detailed notes and charts of lesions, and then the photographs were shown to him, after which he passed an opinion as to the change, if any, in the patient's condition as follows: No change; Improvement, Slight, Moderate or Marked; or Deterioration, Slight, Moderate or Marked (31). Having completed the individual assessments of the two members of a pair, the assessor then examined both of them together. First he decided which patient was in the *better clinical condition*, stating whether the difference was slight, moderate or marked, and then he decided which member of the pair had made the *greater progress* since the start of treatment, again recording the difference. Finally,

the assessor carefully recorded differences between the members of each pair, and, in particular, the presence (including type and severity) of any reaction. In all assessments care was taken to distinguish as far as possible between reaction and the underlying lepromatous state.

After 6 months' treatment, pulmonary radiographs were repeated and also the lepromin test. Otherwise the investigations and assessment resembled those at 3 months, but the assessor also had to decide, using the same standards as before, which member of each pair had made the *greater progress during the second 3 months of treatment*.

Finally, at the end of a year's treatment, all the investigations performed at 6 months were repeated and the patients were then reassessed as at 3 months. In addition the assessor had also to decide which member of each pair had made the *greater progress during the second 6 months of treatment*, and to assess the scale of difference.

As the trial progressed a number of patients developed reactions. These were treated with any or all of the standard drugs, including corticosteroids as required, but the doses of the trial drug were not altered. The protocol followed allowed any patient to be removed from treatment when it was clinically indicated, but in practice this was not found to be necessary. Drugs used in the treatment of reactions included stibophen, calcium levulinate, chloroquine, antihistamines, prednisolone and corticotrophin. As the independent assessor was required to judge the clinical progress of the disease, he was told if a patient at assessment was receiving steroids, but he was never told the results of further smears and histologic studies.

RESULTS

The results have been analyzed in two ways. First, the assessments of individuals in one treatment have been compared with those obtained in the other and, secondly, the relative progress of the members of each pair has also been analyzed.

Three patients were removed from the trial during its course and have been excluded from all analyses. One LL patient (Group DE) developed severe dapsone sensitivity after 4 weeks and his partner~~s~~ asked to be released from the trial. The third case (female BL from Group DE) was found to be pregnant 2 months after commencing treatment, and was also excluded, but her partner was continued on treatment and has been included in the "treatment group," but not the "pair" analysis. The analyses are therefore based on 18 LL pairs, 5 BL pairs and 1 unpaired BL patient.

Clinical findings.—After 3, 6 and 12 months' treatment the independent assessor classified the progress of the patients, which was scored as follows:

Improvement:	Marked	3
	Moderate	2
	Slight	1
No change:		0
Deterioration:	Slight	-1
	Moderate	-2
	Marked	-3

Although 5 of the 47 patients were thought to have deteriorated during the first 3 months, usually in association with lepra reactions, at the end of the year all patients showed clinical improvement.

TABLE 1.—Assessment of clinical progress.

Type of disease	Period (months)	Treatment series ^a	No. of patients	Clinical assessment ^b								
				6	5	4	3	2	1	0	-1	-2
LL	0-3	DP	18	0	0	0	0	2	9	4	2	1
		DE	18	0	0	0	1	4	7	6	0	0
	3-6	DP	18	0	0	0	1	10	6	1	0	0
		DE	18	0	0	0	1	10	5	2	0	0
	0-6 ^c	DP	18	0	0	1	8	4	2	3	0	0
		DE	18	0	0	5	5	4	3	1	0	0
	6-12	DP	18	0	0	0	0	12	5	1	0	0
		DE	18	0	0	0	0	11	7	0	0	0
	0-12 ^d	DP	18	0	5	8	1	3	1	0	0	0
		DE	18	2	6	5	3	2	0	0	0	0
BL	0-3	DP	6	0	0	0	0	2	4	0	0	0
		DE	5	0	0	0	0	0	2	1	2	0
	3-6	DP	6	0	0	0	0	4	2	0	0	0
		DE	5	0	0	0	0	3	1	1	0	0
	0-6 ^c	DP	6	0	0	2	2	2	0	0	0	0
		DE	5	0	0	0	1	0	4	0	0	0
	6-12	DP	6	0	0	0	0	4	2	0	0	0
		DE	5	0	0	0	0	3	2	0	0	0
	0-12 ^d	DP	6	2	1	2	1	0	0	0	0	0
		DE	5	0	1	0	2	2	0	0	0	0

^a DP = treatment with dapsone and placebo.

DE = treatment with dapsone and ditophal.

^b Scored as follows: Improvement: slight, 1; moderate, 2; marked 3.

No change, 0.

Deterioration: slight, -1; moderate, -2; marked, -3.

None of the differences above, in mean clinical progress between the two treatment series, attains statistical significance.

^c Sum of reading for 0-3 and 3-6 months.

^d Sum of reading for 0-3, 3-6 and 6-12 months.

Table 1 shows the analysis of individual improvement; none of the differences in the mean clinical progress between the two treatment groups attains statistical significance at the 5 per cent level.

The relative clinical condition of the paired patients at each successive examination is shown in Table 2. At 3 and 12 months the LL patients in treatment group DE were in significantly better clinical condition (at the 1 per cent and 5 per cent levels respectively) than the paired patients on treatment DP. In contrast, the results for the BL patients were significantly in favor of treatment DP at 3 and 6 months (at the 5 per cent level on each occasion). However, the comparison of the clinical progress of the paired patients in the various trial periods (Table 3) shows no obvious benefit of one treatment over the other.

TABLE 2.—Comparison in paired patients of clinical condition at successive examinations.

Type of disease	Examination	Patient on DP better than patient on DE ^a			No difference	Patient on DE better than patient on DP ^b		
		Marked	Moderate	Slight		Slight	Moderate	Marked
LL (18 pairs)	Pretreatment	0	0	3	10	4	1	0
	3 months	0	2	1	0	8	7	0
	6 months	1	2	1	0	7	7	0
	12 months	0	1	3	1	10	3	0
BL (5 pairs)	Pretreatment	0	0	2	2	1	0	0
	3 months	0	4	0	1	0	0	0
	6 months	0	3	1	1	0	0	0
	12 months	0	2	2	0	1	0	0

^aDE = treatment with dapsone and ditophal.

^bDP = treatment with dapsone and placebo.

At 3 and at 12 months the LL patients in Group DE were in significantly better clinical condition (at the 1% and 5% levels, respectively) than the paired patients in Group DP. In contrast, the results for the BL patients were significantly in favor of Group DP at 3 and 6 months (at the 5% level on each occasion).

TABLE 3.—Comparison in paired patients of clinical progress in various periods.

Type of disease	Period in months	Patient on DP better than patient on DE ^a			No difference	Patient on DE better than patient on DP ^b		
		Marked	Moderate	Slight		Slight	Moderate	Marked
LL (18 pairs)	0-3	0	1	5	3	5	4	0
	3-6	1	3	4	0	7	3	0
	0-6	1	1	3	1	6	6	0
	6-12	0	1	10	3	3	1	0
	0-12	0	1	4	1	9	3	0
BL (5 pairs)	0-3	0	2	1	1	1	0	0
	3-6	0	2	0	1	3	0	0
	0-6	0	0	3	1	1	0	0
	6-12	0	0	2	0	2	1	0
	0-12	0	0	3	0	2	0	0

^aDE = treatment with dapsone and ditophal.

^bDP = treatment with dapsone and placebo.

There is no obvious benefit of one treatment over the other in terms of clinical progress in paired patients.

Histologic findings.—All except 2 patients showed histologic improvement in 12 months. The mean decrease of the biopsy index was estimated for the periods 0-3 months, 0-6 months, and 0-12 months, for the LL and BL patients. None of the mean differences between the two treatment groups attains statistical significance (Table 4).

Although no retrospective reclassification of patients in their LL and BL groups has been permitted, it is pertinent to note that only one of the 38 LL patients showed a change in classification during the year's treatment. This patient (in Group DE) was histologically pure lepromatous on admission, and her clinical appearance was compatible with LL or BL. However, the smears from the ears were negative, and the BI was only 2.7 (all other LL patients were 3.7 or higher), and this finding may indicate that she was not suffering from true polar lepromatous leprosy. Following a mild lepra reaction, her 6 months' biopsy was graded borderline (BB), and after 12 months the histology was near-tuberculoid (BT). During this time there was a dramatic fall in the BI so that only one smear site remained positive at 1 year. In general, however, the results confirm the stability of pure lepromatous leprosy. On the other hand, the near-lepromatous patients proved unstable in their classification, 4 of the 11 (2 DP, 2 DE) changing histologically in one direction or the other.

TABLE 4.—Percentage decrease in biopsy index.

Type of disease	Treatment series ^a	Number of patients	Mean decrease after stated periods of treatment		
			3 months	6 months	12 months
LL	DP	18	14.4	22.5	47.6
	DE	18	23.1	31.6	56.3
BL	DP	6	25.0	54.5	67.8
	DE	5	3.0	37.5	58.1

^aDP = treatment with dapsone and placebo.

DE = treatment with dapsone and ditophal.

None of the mean differences above, between the two treatment series, attains statistical significance.

Bacteriologic findings.—Throughout the study, on every occasion that smears were taken from a patient, the results were averaged to give the bacterial index at each treatment time. The group averages for the pretreatment smears were as follows:

Group DE:	LL patients	4.6 (range 5.5 - 2.7)
	BL "	3.4 (range 4.7 - 3.0)
Group DP:	LL patients	4.7 (range 5.5 - 3.8)
	BL "	4.2 (range 5.2 - 2.7)

At the end of 12 months' treatment, the bacterial indices of 42 patients had improved with the pretreatment results, 2 (1 DE and 1 DP) were unchanged, and 3 (1 DE and 2 DP) had deteriorated. However, all these 5 showed satisfactory improvement in the MI and were also considered to have improved both clinically and histologically.

The mean decrease in the BI throughout the treatment period is shown in Table 5. None of the differences between the two treatment groups attains statistical significance.

TABLE 5.—Decrease in bacterial index.

Type of disease	Treatment series ^a	Number of patients	Mean decrease after stated periods of treatment					
			1½ months	3 months	4½ months	6 months	9 months	12 months
LL	DP	18 ^b	-0.06	0.16	0.20	0.47	0.47	0.55
	DE	18 ^b	0.14	0.32	0.41	0.77	0.79	0.94
BL	DP	6 ^c	0.03	0.16	0.28	0.48	0.75	1.17
	DE	5 ^d	0.06	0.22	0.30	0.58	0.92	1.28

^aDP = treatment with dapsone and placebo.

DE = treatment with dapsone and ditophal.

^bAt 1½ months, 17 patients; and at 9 months, 16 patients.

^cAt 3 months, 5 patients.

^dAt 3 months, 4 patients.

None of the mean differences above, between the two treatment series, attains statistical significance.

On all occasions when smears were taken the MI also was estimated, and the present trial has confirmed our previous finding (^{31, 32}) that a dramatic decrease of the MI occurs in lepromatous patients following the commencement of dapsone therapy. The pretreatment average morphologic indices for the two groups were as follows:

Group DE:	LL patients	36	(range 59 - 3)
	BL "	39	(range 56 - 6)
Group DP:	LL patients	33	(range 55 - 1)
	BL "	45	(range 72 - 32)

At the end of 6 months' treatment the average MI was only 2 per cent in each of the four groups (overall range was 0-8 per cent).

The mean decrease in the MI has been studied for the periods 0-1½, 0-3, 0-4½, 0-6, 0-9, and 0-12 months (Table 6) as well as the mean decrease between successive examinations during the course of treatment. The results for LL patients are shown graphically in Figure 1. There is a statistically significant greater decrease (at the 1 per cent level) in the percentage of solid-staining bacilli in the smears of LL patients treated with ditophal and dapsone, than occurred with placebo and dapsone, for the period 0-1½ months. None of the other mean differences for LL patients, and none for those for BL patients, attains statistical significance. There is, therefore, clear evidence that the combination of ditophal and dapsone kills leprosy bacilli more rapidly than dapsone alone during the first 6 weeks of treatment in LL patients.

Reactions.—Careful clinical notes, in which the same standards as in the previous trial (³¹) were used, recorded the incidence and severity of "lepra reactions" and of erythema nodosum leprosum (ENL).

In pure lepromatous (LL) patients, lepra reactions were mild and

TABLE 6.—Decrease in percentage of solid-staining bacilli.

Type of disease	Treatment series ^a	Number of patients	Mean decrease after stated periods of treatment					
			1½ months	3 months	4½ months	6 months	9 months	12 months
LL	DP	18 ^b	1.24	22.2	28.0	30.5	30.2	31.1
	DE	18 ^c	14.94 ^f	30.4	33.4	34.1	32.3	32.6
BL	DP	6 ^d	9.33	25.8	39.3	43.3	43.3	43.7
	DE	5 ^e	13.80	29.5	32.6	36.8	36.0	37.4

^aDP = treatment with dapsone and placebo.

DE = treatment with dapsone and ditophal.

^bAt 1½ months, 17 patients; and at 9 months, 16 patients.

^cAt 1½ months, 17 patients; at 9 months, 15; and at 12 months, 17 patients.

^dAt 3 months, 5 patients.

^eAt 3 months, 4 patients.

^fOver the period 0-1½ months, smears from patients in Group DE showed a statistically significant (at the 1% level) greater mean decrease in the percentage of solid-staining bacilli than those from Group DP. None of the other mean differences above attains statistical significance.

infrequent (16%), and developed before or during the first 6 months of treatment. ENL, which occurred in 19 (53%) of this group, developed later than the lepra reactions; only 3 patients had ENL in the first 3 months of treatment and in 2 of these the pretreatment MI was less than 10. Eight patients required treatment with prednisolone

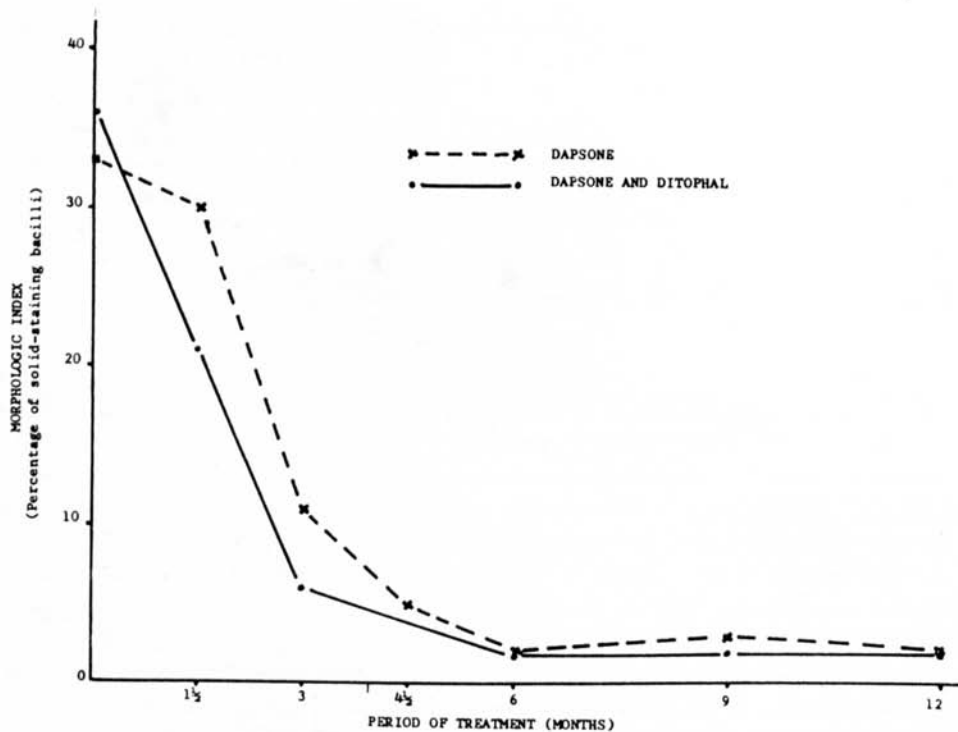


FIG. 1. The effect of treatment with dapsone compared with dapsone and ditophal on the morphologic index (MI) in lepromatous leprosy.

and in 3 of these the reaction was severe, including one in which necrotizing ENL developed. The overall incidence of ENL was similar to that of previous experience at Sungei Buloh Leprosarium (³¹).

Five of the 11 near-lepromatous (BL) patients developed lepra reactions which tended to be more severe and persistent than those seen in LL patients. Serial biopsies showed that the histology of 2 of these patients changed toward the tuberculoid end of the spectrum.

In neither the LL nor the BL patients is there any significant difference in the incidence or severity of reactions in the two treatment groups.

Other findings.—The average serum protein figures were estimated at 0, 6 and 12 months. In both treatment groups there was a significant decrease in total protein and in the percentage of gamma globulin, and a significant increase in the percentage of albumin, over the 12 month period, but there is no significant difference between the two treatment groups.

The average pretreatment hemoglobin for all patients was 13.95 gm. per cent (range 8.7-16.8), and at the end of the study 12.95 gm. per cent (range 10.0-16.1). Both treatment groups showed similar falls (Group DP from 14.1 on admission to 13.1 gm. per cent at 12 months, and Group DE from 13.8 to 12.8). No leucopenia was detected, but leucocytosis often occurred in ENL and occasionally in response to intercurrent infection.

There were no significant changes in the lepromin test during treatment. Changes in the tuberculin test will be reported elsewhere.

Throughout the trial, patients showed little adverse reaction to any form of treatment. One patient, who has been mentioned above developed a severe sulfone sensitivity 4 weeks after the onset of treatment, but none of the 23 patients who anointed their bodies with ditophal 3 times a week for one year developed any form of sensitization dermatitis and only a very few complained passingly of the odor. No patient refused to take this treatment.

DISCUSSION

Under the conditions of this trial, none of the standard methods of assessment, i.e., individual clinical progress, the bacterial index, and the biopsy index, revealed any differences between the two treatment groups. However, the study of the bacterial morphology reveals advantages at the 1 per cent level of significance, in the ditophal-treated group (DE) over the control group (DP) of pure lepromatous (LL) patients in the early stages of treatment. This study was included because of Davey's reports, confirmed by Molesworth (²⁰), and also because a quantitative method of its assessment had recently been introduced (³²). The fall in the morphologic index (MI) in Group DP LL patients at 3 and 6 months closely corresponds with previous experience, and shows that the effects of dapsone on bacterial mor-

phology are reproducible under standard conditions. It also confirms the lack of chemotherapeutic activity of the placebo.

The use of ditophal concurrently with dapsone therapy, is clearly shown at 1½ months to result in a more rapid "fragmentation" of the bacilli. Plentiful evidence that irregularly-staining bacilli are dead has now been produced (^{25, 29, 32}), and we conclude that combined therapy with ditophal and dapsone at the beginning of treatment kills off *M. leprae* faster than does dapsone alone.

If an analogy can be drawn with the sulfonamides, dapsone is probably bacteriostatic. The earlier change in the MI in Group DE compared with Group DP may support Davey's suggestion that ditophal is bactericidal, but further evidence is needed. This very rapid killing of bacilli did not have any detectable adverse effect on our patients, and none of them suffered from any Herxheimer-like reaction, such as is seen frequently when mice with advanced experimental murine leprosy commence isoniazid treatment (¹⁵).

Many previous studies of the value of ditophal in combination with sulfone followed Davey's suggestion (⁶) to withhold the ditophal until the dapsone dose had been built up to a full maintenance level. Such an initial build-up of dapsone was used in the Leonard Wood Memorial trial of ditophal (¹⁴). In the trial reported by Dharmendra and Noordeen (¹³), half the patients in the group whose bacterial morphology was studied received 10 to 12 weeks of dapsone treatment before ditophal was commenced; the failure to detect any morphologic difference between their two treatment schedules is thereby almost certainly explained. Davison (¹⁹) also states that nearly all his ditophal trial patients had had previous treatment with dapsone. We may therefore infer that the pre-ditophal smears consisted almost entirely of irregularly-staining bacilli, and it has recently been suggested (³³) that such patients are unsuitable for standard leprosy drug trials. In the series reported here, however, dapsone and ditophal were given concurrently to the patients and we believe that this enabled us to demonstrate the differential changes in the bacterial morphology in the first few weeks of treatment which had been overlooked by some previous workers. Nevertheless, there was no significant difference in the rate of fall of the bacterial index in our two treatment groups, and therefore we have no evidence that ditophal aids the destruction and removal of dead bacilli (²²).

Although, in LL patients, the study of the bacterial morphology has revealed a definite difference between the two treatment groups, the clinical assessments are difficult to evaluate. The analyses of clinical progress in which patients were assessed individually or in pairs did not favor one treatment schedule more than the other, but both assessments depend upon a retrospective comparison. The third method of assessment, viz., the comparison of the actual clinical condition of a pair, contains no retrospective element, and analysis of

these results shows that although the LL pairs were well matched before treatment, the DE-treated cases were in a significantly better clinical condition (at the 1 per cent level) after 3 months' treatment than their DP partners. The differences, however, were not significant at 6 months, and only significant at the 5 per cent level after a year. One possible explanation of this discrepancy between the first two methods of clinical assessment and the third, is that combined therapy did not result in any clinical advantage, and that the "significant" results obtained by the third method arose only by unlikely chance. We suggest, however, that a far more probable explanation is that combined treatment with ditophal does result in an increased rate of clinical improvement early in treatment, but that this advantage is only slight. Therefore it is not detected in the more difficult and more subjective retrospective assessment of progress, but only in the more objective simultaneous comparison of two matched patients in a "like pair." Moreover, the latter explanation is in keeping with the results of the bacterial morphology. Death of the bacilli results in a decrease in the signs of disease activity, i.e., the "immediate" results of treatment described by Muir⁽²¹⁾. The improvement in these signs is easier to assess and compare than the slow decrease in lepromatous infiltration that occurs during Muir's "intermediate" phase. Since combined therapy has been found to kill off the bacilli more rapidly than dapsone alone, it is to be expected that DE patients would show fewer signs of active leprosy at 3 months than their DP partners. But dapsone alone, under our conditions, has a highly significant effect on the bacterial morphology within 3 months. Therefore the difference between the signs of clinical activity in the two treatment groups could not be expected to be very great. The gain of perhaps 3 to 4 weeks at the beginning of treatment would be even more difficult to detect clinically at 6 and 12 months. Such an explanation is not only in accord with our findings, but corresponds with the prediction of Lowe, made as long ago as 1948⁽¹⁸⁾.

The results obtained from the small number of near-lepromatous (BL) patients included in the trial were inconclusive. There was no significant difference between the two treatment groups in the rate of fall of the bacterial index, and although at 1½ months the average MI for Group DE was 25 per cent and for Group DP 36 per cent, this similarity to the findings in pure lepromatous cases is not statistically significant in such a small number of patients. Clinically, the two methods of assessing progress failed to reveal any advantage in either treatment, but comparison of the clinical condition of paired patients showed that at 3 and 6 months those receiving the placebo were in a better clinical condition than their partners, but only at the 5 per cent level of significance. This result not only differs from our finding in LL patients but also from that of Davey⁽⁶⁾, who included a number of lepromatous patients "with a dimorphous background." As

only 5 BL pairs were included in the trial, it is possible that the slight favoring, by one method of clinical assessment only, of the control treatment is due to chance selection. Alternatively, a study of the progress of the 5 pairs reveals that in 3, the DE patient had a more severe lepra reaction than his partner; in the remaining 2 pairs, no or only mild reactions occurred, and possibly the assessment of clinical conditions was influenced by the presence of the reaction. It has recently been suggested (³³) that only pure lepromatous patients should be included in formal clinical drug trials, because of the instability and variability of BL cases, and this trial underlines the difficulties of assessing such patients.

Currie (³) has suggested that although ditophal does not decrease the incidence of erythema nodosum leprosum (ENL) in lepromatous patients, yet such reactions are less severe and less prolonged. The incidence of ENL, 53 per cent in this trial, is similar to our past experience in Malaya, and indeed, to figures reported from many other parts of the world. Detailed analysis of the severity of ENL reaction fails to reveal any significant difference in the 2 treatment groups.

As the combination of ditophal and dapsone resulted in the significantly faster killing of *M. leprae* (as measured by morphologic changes in stained skin smears) than did dapsone alone, we believe that ditophal is an active antileprosy drug under these conditions, and that it may cause a slightly greater rate of clinical improvement in the first 3 months of treatment. The general value of ditophal remains difficult to determine. It can be argued that in any infectious disease the patient is best served by the rapid killing of the organisms, provided no allergic response or Herxheimer reaction results. Therefore some may consider the addition of ditophal to standard therapy during the first 6 to 12 weeks of treatment to be advantageous, especially should a patient develop sulfone sensitivity. But if the cost of the ditophal, its odor, and the time needed for treatment are considered, it is probable that the slight advantages obtained are insufficient to justify its large scale use.

SUMMARY

A controlled clinical trial, using the "double blind" technic, is reported of combined dapsone and ditophal therapy compared with dapsone and placebo in the treatment of pure lepromatous and near-lepromatous leprosy. Twenty-five untreated, matched pairs were admitted, and the final analysis was made on 23 pairs and 47 patients studied for one year.

Dapsone and ditophal were commenced simultaneously, and over the treatment period 0-1½ months, a statistically significant (at the 1 per cent level) greater decrease in the percentage of solid-staining bacilli occurred in the smears of pure lepromatous patients treated with ditophal and dapsone than occurred in the smears of patients treated with placebo and dapsone. Therefore, it is evident that com-

bined therapy resulted in a faster rate of killing of leprosy bacilli than did dapsone alone. However, only one method of clinical assessment of the pure lepromatous pairs favored combined therapy; the two other methods of clinical assessment used, and the bacterial index and biopsy index results, all failed to reveal any significant differences between the two treatment groups. In addition, the incidence and severity of erythema nodosum leprosum did not differ in the two groups. Since the more rapid death of bacilli early in treatment had little effect on the rate of improvement of patients after 12 months, the widespread use of ditophal with dapsone does not appear to be justified. Special circumstances are envisaged, however, in which ditophal would be a useful adjunct to treatment.

The small number (11) of near-lepromatous patients studied showed a high incidence of lepra reactions, and 4 underwent histologic change during their year in the trial. There was no evidence that the addition of ditophal to dapsone treatment increased the rate of improvement, clinically, histologically or bacteriologically, in this type of leprosy, which, because it is so unstable, appears unsuitable for formal clinical drug trials.

Although the majority of the patients included were light-skinned Chinese, no contact dermatitis or other toxic effects of ditophal were observed.

RESUMEN

Se comunica un ensayo clínico controlado, usando la técnica "double blind," de terapéutica combinada dapsona y ditophal, comparada con dapsona y placebo en el tratamiento de la lepra lepromatosa pura y la cerca-lepromatosa. Fueron admitidas veinticinco parejas no tratadas, y los análisis finales fueron hechos en 23 pares y 47 pacientes estudiados durante un año.

Dapsona y ditophal fueron comenzados simultáneamente, y durante el periodo de tratamiento, 0-1½ meses, una gran disminución en el porcentaje de bacilos fuertemente teñidos ocurrió en los extendidos, estadísticamente significativa (al nivel de 1 por ciento), de los pacientes lepromatosos puros tratados con ditophal y dapsona que en los pacientes tratados con placebo y dapsona. Por lo tanto, es evidente que la terapéutica combinada resulto de mayor velocidad para matar a los bacilos leproso que la dapsona sola. Por lo tanto, solamente un método de catastro clínico de los pares lepromatosos puros favorece la terapia combinada; los otros dos métodos de catastro usados, y el índice bacteriológico y los resultados de los índices biópsicos, todos fallaron en revelar una significativa diferencia entre los dos grupos de tratamiento. En adición, la incidencia y severidad del eritema nudoso leproso no difirió en los dos grupos. Desde que la mas rápida muerte del bacilo, tempranamente en el tratamiento, tiene efecto menor en el nivel de mejorías de pacientes después de 12 meses, el uso extenso de ditophal con dapsona no parece ser justificado. De cualquier manera son contemplados las circunstancias especiales en las cuales ditophal podría ser una ayuda útil en el tratamiento.

El pequeño número (11) de pacientes cerca-lepromatosos estudiados, mostraron una alta incidencia de reacciones leprosas, y 4 llegaron a cambios histológicos durante el primer año del ensayo. No hay evidencia de que el tratamiento adiciendo ditophal a dapsona aumente la mejoría, clínica, histológica o bacteriológica en este tipo de lepra, la cual, debido a su inestabilidad, aparece inadecuada para ensayos clínicos formales con drogas. Aunque la mayoría de los pacientes incluidos fueron Chinos de piel clara, no se observaron dermatitis por contacto u otros efectos tóxicos del ditophal.

RÉSUMÉ

On relate ici un essai clinique contrôlé par la technique du double inconnu et portant sur la thérapeutique combinée dapsoné plus ditophal comparée à la thérapeutique par la dapsoné accompagnée d'un placebo, cet essai visant à comparer les deux méthodes pour le traitement de la lèpre lépromateuse pure et de la lèpre pré-lépromateuse. Vingt-cinq paires de malades non traités et semblables (matched) furent inclus dans cette étude, et l'analyse finale des résultats a porté sur 23 paires de malades (sur 47 malades au total), ces malades ayant été observés durant un an.

Le traitement par la dapsoné et le ditophal furent commencés au même moment. Au cours des six premières semaines de traitement, on a enregistré dans les frottis obtenus chez les malades traités par le ditophal et la dapsoné un abaissement dans le pourcentage de bacilles à coloration uniforme plus prononcé que celui noté dans les frottis des malades traités par la dapsoné et un placebo. La différence était statistiquement significative au seuil de probabilité de 1%. Dès lors, il est évident que la thérapeutique combinée entraîne une destruction plus rapide des bacilles de la lèpre que ne le fait la dapsoné seule. Toutefois, l'avantage de la thérapeutique combinée chez les malades lépromateux purs n'a pu être mis en évidence que par une seule méthode d'évaluation clinique; les deux autres méthodes d'évaluation clinique qui ont été utilisées, de même que l'index bactériologique et l'index basé sur la biopsie, n'ont pas permis de mettre en évidence une quelconque différence qui soit significative entre les deux groupes traités. De plus, l'incidence et la gravité de l'érythème nodosum leprosum n'ont pas témoigné de différences entre les deux groupes. Du fait que la destruction plus rapide des bacilles au début du traitement a peu d'effet sur l'amélioration lointaine des malades après douze mois, l'adjonction généralisée de ditophal à la dapsoné ne paraît pas justifiée. On admet cependant qu'il existe des circonstances particulières où le ditophal pourrait constituer un appoint thérapeutique utile.

Le petit nombre (11) de malades pré-lépromateux qui ont été étudiés ont témoigné d'une incidence élevée de réactions lépreuses, et 4 ont subi des changements au point de vue histologique au cours de l'année de traitement. Il n'a pas été possible de démontrer que l'addition de ditophal au traitement par la dapsoné ait accru le taux d'amélioration, qu'il s'agisse de l'amélioration clinique, histologique ou bactériologique, dans ce type de lèpre qui, du fait de son instabilité, se prête mal aux essais cliniques médicamenteux systématiques.

Quoique la majorité des malades inclus dans cette étude aient été des Chinois à la peau claire, aucune dermatite de contact ou autre effet toxique du ditophal n'ont été observés.

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