# DIETHYLDITHIOLISOPHTHALATE (ETISUL) IN THE TREATMENT OF LEPROSY

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### INTRODUCTION

In 1950 del Pianto reported, it is said, that a mixture of certain thiol compounds was effective against experimental tuberculosis in laboratory animals. This statement had to be modified later, as it was found that the antituberculosis activity was due to sodium ethyl thiosulphate, one of the two thiol compounds which he had used. These observations attracted the attention of other workers to the thiol compounds as possible sources of antituberculosis drugs.

Davies *et al.* (<sup>3</sup>) showed that the activity of sodium ethyl thiosulphate was due to the thiol compound being broken down in the body to ethyl mercaptan. They found that ethyl mercaptan, or any compound which was capable of being broken down in the body to it, possessed antituberculosis activity, and that this property was limited to the ethyl homologues only. Because of the unpleasant odor of ethyl mercaptan it became necessary to prepare derivatives which would release ethyl mercaptan only after absorption. They suggested ethyl thiol esters as the most suitable compounds for treatment of human disease.

After preparing and testing many such compounds, Davies and Driver (<sup>4</sup>) found diethyldithiolisophthalate to be the most promising compound for therapeutic trials in man. This compound is an ester formed from ethyl mercaptan and isophthalic acid, and its smell although still unpleasant—is much less so than that of ethyl mercaptan. It was designated as I.C.I. 15688, and for a while as Etip, but is now called Etisul. It is a pale yellow, oily liquid with a smell suggestive of garlic. It is unsuitable for administration either by mouth or by injection but is readily absorbed after inunction, and it is therefore given by the percutaneous route. Etisul is supplied by the Imperial Chemical Industries Ltd., in the form of a perfumed 75 per cent cream in collapsible tubes containing 5 gm. each.

## PREVIOUS WORK

Both sodium ethylthiosulphate (ET) and diethyldithiolisophthalate (Etip) have been tried and reported on favorably in the treatment of

leprosy. Bertaccini (quoted by del Pianto) and del Pianto ( $^5$ ) found the oral administration of sodium ethylthiosulphate in daily doses of 1.2 gm. to give better results than DDS. Del Pianto concluded that ET is very well tolerated, even when administered over prolonged periods; that it is therapeutically active, the response to daily doses of 1.2 gm. being very quick; and that it is a safe drug, as it does not cause lepra reactions.

Davey and Hogerzeil (<sup>2</sup>) and Davey (<sup>1</sup>) have reported from Nigeria on the use of diethyldithiolisophthalate in leprosy treatment. In the earlier cases, when Etisul was given for a period of 3 to 6 months the initial bacteriologic improvement was better than that with DDS (as compared with standard DDS graphs), and in some cases remarkable. The improvement consisted not only of reduction in the bacteriologic index, but also of degenerative changes producing morphologic changes in the bacilli. However, after the third month of treatment signs suggestive of drug resistance appeared in several cases. Nevertheless, when oral chemotherapy with DDS or DPT was instituted the cases showed a decided acceleration of progress.

This led to further trial of Etisul in combination with DDS in Nigerian patients. The improvement with this combined treatment was definitely better than that with DDS alone, although after the third month there was some slowing down of progress. Further trials of treatment with Etisul in combination with DDS and DPT gave "most satisfactory" results. Davey concluded that combination of Etisul with DDS and DPT gave very encouraging results, and that the progress had been rapid and uniform without any evidence suggestive of drug resistance until after combined treatment had been given for four months. He found the drug well tolerated, without producing any signs of toxicity. He concluded that Etisul "has a limited but very valuable sphere of action." He wrote  $(^1)$ :

The sphere of usefulness of Etisul is clearly at the onset of treatment. Its activity has two aspects. There is in the first place the shortlived but sometimes powerful chemotherapeutic action which has been observed in every group studied, and which appears to last for two or three months, but then diminishes and may disappear altogether. In the second place there is the continued accelerated resolution which has repeatedly been witnessed during standard chemotherapy following a short course of Etisul.

# PRESENT INVESTIGATIONS

Following the very encouraging reports of Davey from Nigeria, a trial of diethyldithiolisophthalate in Indian patients was started in this Institute.<sup>1</sup>

Trials have been completed with three series of patients (12, 18, and

<sup>&</sup>lt;sup>1</sup> The Etisul used in the investigation was supplied free of cost by the Imperial Chemical Industries, Ltd., England.

25, respectively); totaling 55. In these trials only lepromatous cases with no previous treatment have been included. The results obtained in these three series are reported here separately.

In all instances DDS was given by mouth, Etisul by inunction. During the periods of observation Etisul did not cause any untoward side effects, except that one patient in the third series developed an allergic dermatitis due to that drug. Routine blood and urine examinations did not show any noticeable changes. Although Etisul has a strong odor, esthetic acceptability of the preparation was not a problem among our patients.

### FIRST SERIES

The first series comprised 12 lepromatous cases, divided into two groups. One group was given Etisul and DDS (Etisul group), and the other, control, group was given DDS alone (DDS group). The trial was continued for 7 months and discontinued thereafter, all the patients being continued on DDS alone.

All of the 12 cases were typical lepromatous, fairly advanced with diffuse infiltration. Two of them in addition had nodulations, and one of them was put into each of the two groups. All the cases were strongly positive bacteriologically, the bacteriologic index varying from 3.00 to 5.43 (using the method of 14 smears and 6 degrees of positivity). Great care was taken to make the two groups comparable in most respects. This was achieved by matching pairs of cases and putting one of the pair in each group. The result was that the two groups were comparable as regards age, duration of the illness, clinical appearance and bacteriologic index. Comparing the Etisul and DDS groups, the average age of the former was 28, and of the latter 31; the average duration was 5 years in the former, and 6 years in the latter; the average bacteriologic index was 3.91 in the former, and 3.90 in the latter. All the cases were fresh, without any previous treatment, although 6 of the cases were put on DDS for 10 to 12 weeks before starting the actual investigation with Etisul. It was proposed to put 3 of these into each of the groups, but in trying to match other factors 2 were ultimately put in the Etisul group and 4 in the DDS group.

DDS was started with an initial dose of 25 mgm. 3 times a week, and was increased in the course of 6 weeks to a maximum of 200 mgm. 3 times a week. The Etisul inunctions of 5 gm. each were given 3 times a week. The cream was rubbed over the trunk, thighs and arms for a period of about 20 minutes, avoiding the face and hairy parts. The patients were then allowed to rest for about an hour, after which they bathed using soapnut powder.<sup>2</sup>

<sup>&</sup>lt;sup>2</sup>Soapnut powder is obtained from the dried fruits of *Acacia concinna*, which belongs to the Mimosoideae or soapnut subfamily of the Leguminosae. Soapnut is popularly used in South India to remove oil after the oil bath, for which purpose it is found to be better than soap.

#### RESULTS, FIRST SERIES

Clinical improvement.—During the 7 months of the trial, the 12 cases all showed clinical improvement, in varying degrees. However, the improvement was more or less similar in both of the groups, except in one case under Etisul which showed marked subsidence of the nodular lesions; but in this case the subsidence of the nodules was not sustained, and after about 5 months fresh nodules began to appear in spite of continuation of the treatment with Etisul.

Bacteriologic improvement.—Bacteriologic examinations were repeated every 2 weeks during the first 3 months, and later once a month, to note any changes in the bacteriologic index and in the morphology of the bacilli. During the 7 months of the observation, decrease in the indices were very small, and both the groups behaved similarly, no accelerated reduction in the indices being seen in the Etisul group. This is shown in Fig. 1 which shows the results of monthly determinations of the average indices of the groups.



1

FIG. 1. Changes in the monthly average of the bacteriologic indices of the two groups of the first series, over the seven-month period of experimental treatment. (Indices by the method of 14 smears and 6 degrees of positivity.)

The average reduction in the B.I. in the Etisul group in the 7 months of treatment was 0.40, ranging from an increase of 0.36 in one case to a maximum decrease of 0.79 in another. In the DDS group the average B.I, reduction was 0.41, ranging from an increase of 0.07 in one case to a maximum reduction of 0.64. The initial and final indices in the individual cases in both groups are shown in Table 1. As regards morphologic changes, irregular staining and beading of bacilli were found in both the groups to nearly the same extent.

37

$\begin{array}{c} \text{Etisul group} \\ \text{(DDS + Etisul)} \end{array}$			Control group (DDS alone)			
Patient	Initial B.I.	B.I. after 7 months	Patient	Initial B.I.	B.I. after 7 months	
KT	3.79	3.36	Vd	3,64	3.50	
AH	3.00	3.36ª	JB	3.07	2.57	
AM	3.50	2.71	Pr	3.00	3.07	
RM	4.86	4.29	Pg	5.43	4.79	
Db	4.43	4.07	Nt	4.21	3.57	
Ar	3.86	3.14	Rg	4.07	3.43	
Average	3.91	3.51	Average	3.90	3.49	

TABLE 1.—Variations in bacteriologic indices in Series 1 (using the method of 14 smears and 6 degrees of positivity).

<sup>a</sup>This B.I. of 3.36 in this patient was at the end of 4 months, after which he left the sanatorium and discontinued treatment.

#### SECOND SERIES

The second series comprised 18 lepromatous cases, divided into 3 groups. One group was given Etisul alone, the second group DDS alone, and the third group both Etisul and DDS. The trial was continued for 6 months and then discontinued, after which all of the patients were continued on DDS alone.

All the 18 cases were typical lepromatous, with diffuse infiltration. Three of them in addition had nodulations, and of these 1 was put into each of three groups. All the cases were strongly positive bacteriologically. As in the first series, great care was taken to make the three groups comparable in most respects, by matching sets of 3 cases and putting one into three each of the three groups. The result was that the groups were comparable as regards age, duration of illness, clinical appearance, and bacteriologic index. The average age of the patients in the Etisul-alone and the combined groups was 21 years, and in the DDS alone group 22-1/2 years; the average duration of illness was 3-1/2 years in all three groups; the average bacteriologic index was 2.33, 2.39 and 2.67 in the first, second and third groups, respectively. In this series the bacteriologic indices were arrived at by using the method of 6 smears and 4 degrees of positivity; the indices were therefore lower than in the first series, varying from 1.0 to 3.33. The dosage and mode of administration were as in the previous trial (first series).

Although to begin with there were 6 patients in each group, 1 patient in the DDS-alone group left the sanatorium after 4 months, and 2 cases dropped out of the combined group at the end of 1 and 2 months, one because of active pulmonary tuberculosis and the other because he left the sanatorium. For the purpose of assessing the results the 2 cases in the combined group are excluded because of the very short duration of observation, but the one case in the DDS-alone group is included as it was under treatment and observation for four months. Thus in the analysis of results only 16 cases have been taken into account.

### RESULTS, SECOND SERIES

Clinical improvement.—During the period of trial the 16 cases all showed clinical improvement in varying degrees. The improvement was least marked in the Etisul-alone group, in which two cases showed some deterioration of their condition. In the other two groups (DDS-alone and DDS plus Etisul) the improvement was appreciable and more or less similar, except that the one nodular case in the combined group showed marked subsidence of many of the nodular lesions within 3 to 4 weeks, and—unlike the similar case in the first series—the nodules had not reappeared at the end of the trial.

Bacteriologic improvement.—As in the first series, the bacteriologic examination (by the modified method indicated above) was repeated every 2 weeks during the first three months, and every month afterward. During the 6 months under observation the decreases in the bacteriologic indices were very small, except in one case in the Etisul-alone group; in that case the index decreased from 1.33 to 0.17 (i.e., a decrease of 1.16).

Except for this one case, no accelerated reduction in the bacteriologic index was seen either in the combined group or in the Etisul-alone group. The average reduction in the bacteriologic index in the Etisul-alone group was 0.38; in the DDS-alone group, 0.45; and in the combined (Etisul plus DDS) group, 0.42. The average indices in the three

Group	Patient	Initial B.I.	B.I. after 6 months	Reduction or increase
I, Etisul alone	Vl	2.33	1.50	0.83
	Sb	2.83	2.50	0.33
	Gr	1.33	2.00	+0.67
	Gn	1.33	0.17	-1.16
	Ks	3.17	3.00	·0.17
	Ar	3.00	2.50	0.50
Average	11	2.33	1.95	0.38
II, DDS alone	Vs	2.67	2.33	0.34
	MR	2.67	2.00	0.67
	PI	1.00	1.00 <sup>a</sup>	-0.00
	KP	1.67	0.83	-0.84
	JK	3.00	2.33	-0.67
	KN	3.33	3.17	-0.16
Average		2.39	1.94	0.46
III, Etisul				
$+ DDS^{b}$	GG	3.17	2.83	0.34
	VK	1.83	1.00	0.83
	KV	2.50	2.00	-0.50
	Kl	3.17	3.17	-0.00
Average		2.67	2.25	-0.42

TABLE 2.—Variations in bacteriologic indices in Series 2 (using the method of 6 smear• and 4 degrees of positivity).

\* In this case the final B.I. was taken at the end of the fourth month, after which he left the sanatorium.

<sup>b</sup> In this group only 4 patients are included for analysis, since 2 left before the end of the second month.

International Journal of Leprosy

1961



FIG. 2. Course of the monthly averages of the bacteriologic indices of the three groups of the second series, 6 months of treatment. (Indices by the method of 6 smears and 4 degrees of positivity.)

groups at monthly intervals are shown in Fig. 2. The initial and final indices and the extent of reduction are given in Table 2.

## THIRD SERIES

The third series comprised 26 lepromatous cases, divided into two groups of 13 each. As in the first series, one group was given Etisul and DDS, and the other, control, group DDS alone. Soon after the trial was started 1 case in the Etisul group had to be dropped, due to the development of an allergic dermatitis, and 1 case in the DDS group left the sanatorium. This left 12 cases in each group. The trial was continued for 5 months, after which treatment of all the patients was continued on DDS alone.

All the 24 cases were typical lepromatous, with diffuse infiltration. In addition 8 of them had nodulation of varying degrees, and they were equally divided between the two groups. Bacteriologically, most of the cases were strongly positive. As in the previous series great care was taken to make the two groups comparable in most respects. The average age in both groups was about 20 years; the average duration of illness was 5 years in the Etisul group, and 4 years in the DDS-alone group; the two groups were comparable as regards clinical appearance; the average bacteriologic index (using the method of 6 smears and 4 degrees of positivity) was 2.47 in the Etisul group and 2.53 in the DDS-alone group.

## RESULTS, THIRD SERIES

41

Clinical improvement.—During the period of 5 months of trial all the 24 cases showed clinical improvement, in varying degrees. However, the improvement in the two groups was more or less similar. Even the tendency for quicker subsidence of nodular lesions under Etisul treatment seen in 1 case in each of the previous series was not evident in this one.

Bacteriologic improvement.—The decrease in the bacteriologic indices was usually very small. The variations in the indices in the Etisul group were from an increase of 0.33 to a decrease of 0.84, the average for all the cases being a reduction of 0.29; the variations in the DDS-alone group were from an increase of 0.33 to a decrease of 1.00, the average reduction in all the cases being 0.35. The initial and final indices and the extent of differences between the two in all the cases in both the groups are shown in Table 3. The average indices in the two groups at monthly intervals are shown in Fig. 3.

Allergic dermatitis due to Etisul.—In the first two series there was seen no evidence that Etisul had produced any untoward side effects. In the present series, however, one case showed—as has been said—the development of an allergic dermatitis due to Etisul. A brief account of this case is given here.

Etisul group (DDS + Etisul)				Control group (DDS alone)			
Patient	Initial B.I.	B.I. after 5 months	Variation	Patient	Initial B.I.	B.I. after 5 months	Variation
Bs	3.17	2.67	0.50	Gs	3.00	3.00	Nil
Ap	3.00	2.67	0.33	Rn	3.00	2.83	-0.17
Sg	3.17	2.83	-0.34	VI	3.33	2.83	-0.50
Dr	2.33	1.83	0.50	Dp	2.67	2.83	+0.16
Ny	3.00	2.67	0.33	Br	2.33	1.50	-0.83
Gn	1.50	0.83	-0.67	Gr	1.83	1.17 .	-0.66
Jn	2.83	3.00	+0.17	Am	2.83	2.33	0.50
Pm	2.67	3.00	+0.33	Sr	3.33	3.00	0.33
Sd	2.17	1.83	-0.34	Kp	2.17	1.17	-1.00
Vt	2.17	1.83	-0.34	Rk	2.00	2.33	+0.33
Nr	1.17	0.33	-0.84	PV	0.83	1.00	+0.17
Kp	2.50	2.67	+0.17	MG	3.00	2.17	-0.83
Average	2.47	2.18	-0.29	Average	2.53	2.18	-0.35

TABLE 3.—Variations in the bacteriologic indices in Series 3 (using the method of 6 smears and 4 degrees of positivity).

The case was a highly bacteriologically positive one, with a B.I. of 3.00 (maximum 4.0). In the first two weeks of the combined treatment the patient showed no signs of intolerance. After two weeks—i.e., after sixth application of Etisul—he developed a generalized erythematous eruption, located particularly over the face, trunk and upper extremities. The eruptions were symmetrical, and there was a certain amount of exfoliation. The treatment with both drugs was immediately stopped, the patient was hospitalized, and he was treated with antihistaminic drugs and local application of zinc cream. He recovered in about a week, and was rested for another 3 weeks.

After this period another application of Etisul was given, and immediately the erythematous lesions appeared again. No further application of Etisul was given, and the patient was hospitalized and treated as before, the erythematous lesions again disappearing in about a week. Then, after a rest period, the patient was put on treatment

# International Journal of Leprosy

1961



FIG. 3. Course of the monthly averages of the bacteriologic indices of the two groups of the third series, 5 months of treatment. (Indices by the method of 6 smears and 4 degrees of positivity.)

with DDS alone. This time there was no allergic reaction, and since then he has tolerated DDS quite well. It has therefore been concluded that the allergic dermatitis in this case was caused by Etisul and not by DDS. Out of the 31 cases treated with Etisul, allergic dermatitis was seen only in this single case; all the others tolerated Etisul well, without any side effects.

### DISCUSSION

The findings reported herein and the conclusions to be drawn therefrom are not in keeping with the very favorable results with Etisul reported by Davey in Nigeria, whether the drug was given in combination with DDS or alone. It is difficult to explain the discrepancy in the results in the two places. It could not possibly be due to inadequate dosage, as we used 5 gm. of Etisul thrice weekly, and Davey had used 3-6 cc. twice weekly. Nor could the difference have been due to any difference in the method of inunction, as in our cases the Etisul cream was vigorously rubbed over large areas of the body, the patients helping each other in rubbing on the back. One obvious difference is that a fair proportion of the cases in the trials in Nigeria were earlier and less advanced, and bacteriologically less strongly positive, than our cases, which were of longer duration, well-established, and bacteriologically more strongly positive. It is difficult to say how far the observed differences in the results could be attributed to the difference in the

degree of advancement of the disease. Another obvious difference is that in Nigeria the bacteriologic results were compared with a standard graph showing the average decline in the bacteriologic index during DDS treatment in previous years, while in our trials there were comparable groups of cases on DDS to serve as controls. This fact also does not appear to afford a plausible explanation for the observed differences in the results with Etisul in the two places.

### CONCLUSIONS

In the investigations here reported, Etisul, whether alone or in combination with DDS, was not found to produce any accelerated improvement in the bacteriologic status of the patients under treatment, except in one case in Group I (Etisul alone) of the second series. It was also not found to produce any accelerated clinical improvement, except in the 2 cases with nodulations under combined (Etisul plus DDS) treatment in which marked subsidence of nodular lesions was seen, but the nodules began to reappear after 5 months treatment in the case in the first series. In the case in the second series, relapse of the nodules was not observed up to the end of 6 months, when the trial was discontinued and all the patients were continued on DDS alone.

### CONCLUSIONES

Según se observó en las investigaciones aquí descritas, el Etisul, ya solo o combinado con DDS, no produjo aceleración de la mejoría en el estado bacteriológico de los enfermos bajo tratamiento, excepto em un caso del Grupo I (Etisul solo) de la segunda serie. Tampoco produjo aceleración de la mejoría clínica, excepción hecha de los 2 casos con nódulos bajo tratamiento combinado (Etisul más DDS) en los que se observó acentuada atenuación de las lesiones nodulares, pero los nódulos comenzaron a reaparecer al cabo de 5 meses de tratamiento en el caso de la primera serie. En el caso de la segunda serie, no se observó recidivación de los nódulos hasta al cabo de 6 meses, cuando se abandonó el ensayo y se continuó en todos los enfermos con DDS sola.

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#### ADDENDUM

When this paper was submitted for publication, a fourth group of patients was in the course of treatment. This having been finished, a brief statement of the results is added.

#### FOURTH SERIES

In this series 16 cases of lepromatous leprosy was divided, as before, into 2 groups, one given Etisul and DDS, the other DDS alone as control. The period of treatment was 6 months, after which the patients were continued on DDS alone. One case in each group suffered from lepra reaction during the entire period and treatment had to be discontinued for most of the time, so they are not included in the assessment.

*Material.*—All of the 14 cases were typical lepromatous cases with diffuse infiltration; none had nodulations. As before, the 2 groups were comparable in most respects: the average age in the combined-treatment group was 16 years and in the DDS group 15 years; the average duration of illness in the former group was 4 years, and in the latter group 3 years; the average bacteriologic indices were 2.07 and 2.00, respectively.

*Results.*—Clinical improvement: During the six-months period all cases showed varying degrees of clinical improvement, more or less similar in both the groups.

Bacteriologic improvement: The decrease in the bacteriologic indices was usually small, except in 3 cases on DDS-alone group in which the reduction was more than 1.0. The average reduction in the combined-treatment group was 0.40, varying from an increase of 0.16 in one case to a maximum decrease of 0.67 in another. The average reduction in the DDS-alone group was 0.74, ranging from a decrease of 0.16 in one case to 1.5 in another.

*Conclusion.*—The results in this series therefore confirm our earlier conclusion that Etisul given in addition to DDS has generally been found not to produce any accelerated bacteriologic or clinical improvement beyond that produced by DDS alone.

*Comment.*—The findings reported herein are not in keeping with the favorable results with Etisul reported by Davey in Nigeria. While in some cases with nodulations and thickened lepromatous lesions Etisul has been helpful in bringing about early subsidence of the lesions, the accelerated bacteriologic clearance attributed to it has not been observed.

It is difficult to explain the discrepancy. One obvious difference is that a fair proportion of the cases in the trials in Nigeria were earlier and less advanced, and bacteriologically less strongly positive, than

our cases which were of longer duration, well established, and bacteriologically more strongly positive. Another difference appears to be with regard to the nature of the lepromatous lesions: while in India the diffuse infiltration is the commonest lesion, this is not so in Nigeria. It is difficult to say how far the observed difference in the results could be attributed to these differences in the cases. Then one is to surmise about any possible racial differences in the response of the patients to the drug, or any possible regional differences in the strain of the bacillus.