THE TREATMENT OF LEPROSY WITH DIAMINO-DIPHENYL SULPHOXIDE: A PROGRESS REPORT

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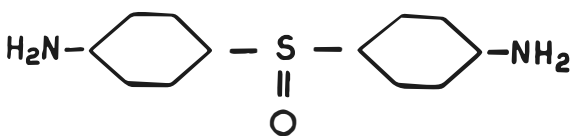
Introduction

During the last few years the great achievements of the sulphones in leprosy treatment have tended to discourage the search for new anti-leprosy drugs. While in a majority of patients sulphone therapy may provide all that is necessary, there remains a sizeable minority, susceptible to one or other of the complications of sulphone treatment, for whom the existence of an effective alternative would be an advantage. Among possible groups of compounds worth studying, those closely related to the sulphones invite interest, and of these the sulphoxides, and in particular, diamino-diphenyl sulphoxide may claim priority. Buu-Hoi and his co-workers have reported on a short term trial of this substance in 34 leprosy patients, and found it comparable in activity with DDS itself. (Buu-Hoi, Nguyen-Ba Khyen and Nguyen-Dat-Xuong, 1955). Through the kindness of Professor Buu-Hoi and of Dr. F. Hawking of the Medical Research Council, supplies of this drug were obtained for a trial in Nigeria, and a progress report is here presented after the trial has been in progress for 15 months. During recent months additional supplies of the drug have been provided by Imperial Chemical (Pharmaceuticals) Ltd.

Chemistry and Dosage

The molecular structure of diamino-diphenyl sulphoxide is very similar to that of DDS, and may be represented as follows:



It is a white or greyish powder, and was received in the form of compressed tablets of 100 milligrammes.

With a molecular weight not far removed from that of DDS, it would appear reasonable to use diamino-diphenyl sulphoxide in a dosage similar to that employed for the parent sulphone. Buu-

Hoi used a dose of 100 mg. daily and it was decided to make this the maintenance dose in adults in this trial. Experience with DDS prompted the starting of treatment at a lower level than this, and 50 mg. was used as the routine initial dose, with an increase to the standard maintenance dose in from three to four weeks from the onset of treatment. Children received an initial dose of 25 mg. daily, raised later to 50 or 75 mg. according to age. All patients had a rest from treatment on one day a week. This system proved entirely satisfactory in practice.

Choice of Patients

A small group of seven patient volunteers was first selected for preliminary trial. All were able bodied, the group consisting of four active tuberculoid cases, one of borderline, and two of indeterminate type. None had had any previous chemotherapy. Under careful laboratory cover these were given treatment with diaminodiphenyl sulphoxide in the dosage indicated above. The drug was well tolerated, and within one month all seven patients showed signs of resolution in their leprosy. On this evidence that the drug was not unduly toxic and was not without activity against *M. Leprae*, the group was expanded as suitable patients became available to form the main trial group of 24 patients, the maximum possible with the supplies available. The 17 patients added were all of lepromatous type, and were representative of this type of leprosy. They included some very severe infections. The group included three children, and neither these nor any others of the patients had had any previous treatment.

In ten cases biopsies were taken to remove any doubt as to classification and to provide a check on progress.

Controls

In a trial of this nature the basis for the assessment of the activity of the new drug is that provided by the expected response of the patients concerned to standard sulphone treatment. The choice of controls is therefore important, but is not an easy matter. A random selection based on the consecutive choice of patients exhibiting the main types of leprosy will almost certainly lead to error. Within the framework of its three or four main types, leprosy presents a variety of forms which differ from one another in the speed with which they exhibit a response to chemotherapy. In view of this fact it appears desirable to choose controls on an individual basis, matching each trial patient as exactly as possible with a control presenting the same type and subtype of leprosy, of

similar duration and extent, and having a comparable Bacterial Index and reaction to lepromin.

In this trial, controls were chosen on such a basis. Some were admitted at approximately the same time as trial patients, found to correspond, and were selected and placed on routine DDS treatment. Others were patients already receiving DDS treatment who at the start of their treatment had fulfilled the necessary conditions. Three had completed their course of treatment, but all the remainder continued under constant observation throughout the period of the trial.

Toxicity

In dealing with a substance closely related to DDS some degree of toxic action was to be expected, and careful and continuous laboratory control was therefore exercised from the start.

The drug has been well tolerated both by adults and by children. There have been no complaints of any gastro-intestinal disturbance or of any other symptom suggestive of toxic action, and all the patients concerned have been able to continue their treatment throughout the period of trial without interruption. At the dosage tested the toxicity of diamino-diphenyl sulphoxide has thus been of a low order, though abnormalities have been detected by routine examination which might very well become serious at higher dose levels. These call for further comment.

Anaemia

A fall in haemoglobin levels occurred during the early stages of treatment in 13 out of the 24 patients. It was never severe, varying between 10% and 20%, and by the fourth month the loss had been regained in all cases. Thereafter no sign could be detected of any disturbance in normal haemopoiesis. During the first three months moderate doses of iron were given orally to some patients as a precautionary measure, but none was given after the third month, and none was needed, several patients later repeatedly giving values of 100% or a little more, as read by the Grey Wedge Haemoglobinometer.

Leucopenia

In Nigeria, under the influence of such conditions as filariasis and virus infections, white cell counts in apparently healthy individuals are subject to wider variation than is covered by the normal physiological range. This exaggeration of the normal was encountered in several of the trial patients, and would not have deserved mention but for the fact that it was more noticeable

among them than among patients taking part in the trial of thiocarbanilide compound SU1906 which was running concurrently, and also because in three individuals it took the form of a mild but definite leucopenia which occurred between the second and fourth months of treatment. In these patients the white cell count fell to the neighbourhood of 3,000, polymorphonuclears being more affected than the other varieties of cell. Once again, the effect was only temporary and did not demand the cessation of treatment.

Drug fever, hepatitis

No case of dermatitis or drug fever was seen among these patients, and no evidence was obtained of any significant toxic action either on the liver or kidneys. Slight degrees of liver enlargement were encountered in two patients at the second and eighth months respectively during routine examinations, but both then and at other times, tests for urobilinogen were normal.

The impression remains that at the level of dosage used in this trial the toxic effects of diamino-diphenyl sulphoxide were insignificant, but that tendencies were revealed which would call for caution in raising the dosage above that used here. The study of a much larger group is, of course, necessary before any authoritative statement can be made on these matters.

Progress of Leprosy: Comparison with Controls

Of the 24 patients available for study, 18 have had treatment with diamino-diphenyl sulphoxide continuously for 12 months or longer, 22 for 8 months or longer, and all for more than 5 months. The progress made by the various groups is as follows.

(a) *Tuberculoid cases*

All four patients have shown satisfactory clinical improvement and all are now in a residual condition. The time taken for resolution to occur can be compared with that exhibited by controls as follows:

	DDSO	DDS
Becoming residual		
Within 9 months ...	1	2
12 months ...	3	2

(b) *Indeterminate and Borderline cases*

The single borderline case in this series has made very satisfactory progress. After 15 months' treatment skin lesions have become clinically residual and bacteriological improvement has also been marked, with disappearance of bacilli in the nose and in sites in the skin where they were formerly numerous, a few granulated

bacilli persisting at only one of several sites examined. This result is at least as good as that seen in the control patient.

The two indeterminate cases have become residual, one after 10 months, one after 12 months, and in this respect they have resolved more speedily than their controls.

(c) *Lepromatous cases*

The 17 cases may be classified as follows:—

Advanced diffuse or nodular leproma ...	2
Moderately advanced ditto	5
Early diffuse leproma	5
Lepromatous macules	5

Both advanced cases were longstanding and of unusual severity. All the remainder were typical, firmly established examples of their respective types, and all were in a very active progressing phase of their disease. The group included three young children with rapidly advancing infections, and their inclusion brought the average age of the group to the low figure of 23 years.

During the period of treatment all the lepromatous cases without exception have shown satisfactory clinical signs of resolution, with flattening of nodules, reduction in infiltration, and loss of erythema and thickening in macules. Clinically their progress as a group has been as good as would have been expected under DDS treatment, and equalled that displayed by their controls. In a number of cases it has been very gratifying.

Clinical improvement is also reflected in the histological findings. The resolution occurring in two cases in this group, one adult and one child, is illustrated in Figures 1 to 4.

Bacteriological progress: Comparison with controls

A decline in numbers of bacilli in routine smears has occurred in every case, and has been accompanied by the changes in morphology of bacilli now familiar in satisfactory chemotherapy. In Tables I and II bacterial indices are presented for each trial patient and the corresponding control, calculated at three monthly intervals. Each figure is the average of all smear results obtained on that individual during each period of three months, the maximum in all cases being 4.0. This provides a satisfactory basis of comparison both between individuals and between groups, and was found useful in a similar trial of this nature. (Davey and Currie, 1956.)

TABLE I

BACTERIAL INDEX: TREATMENT WITH DIAMINO-DIPHENYL SULPHOXIDE

Maximum 4.0

Trial Patient Ref. No.	Months of Treatment						Decrease
	0	3	6	9	12	15	
1	3.5	2.5	1.9	1.0	1.0	1.0	2.5
2	2.8	2.0	2.0	2.0	1.8	2.4	0.4
3	1.8	1.5	1.8	1.5	2.0	1.7	0.1
4	4.0	2.8	3.1	2.5	2.8	2.6	1.4
5	0.7	0.3	0.2	0.2	0.4		0.3
6	2.5	2.3	1.7	1.3	1.8		0.7
7	2.6	2.7	1.7	2.0	2.1		0.5
8	1.4	1.0	0.6	0.3	0.6		0.8
9	0.8	0.8	0.6	0.2	0.1		0.7
10	1.7	0.7	0.6	0.9	0.8		0.9
11	0.5	0.1	0.1	0.1			0.4
12	3.0	2.0	1.0	1.0	0.9		2.1
13	3.0	2.7	2.0	2.7	1.9		1.1
14	2.8	2.0	2.8	2.6			0.2
15	1.7	1.5	0.7	1.0			0.7
16	3.4	2.4	2.6	2.5			0.9
17	3.0	2.0	1.5				1.5
						Group decrease	15.2
Group average	2.3	1.7	1.5	1.4			

TABLE II

BACTERIAL INDEX: CONTROLS ON DDS TREATMENT

Maximum 4.0

Control Patient Ref. No.	Months of Treatment						Decrease
	0	3	6	9	12	15	
1	3.3	2.8	2.8	2.5	2.3	2.0	1.3
2	2.5	2.5	2.5	2.0	2.0	2.0	0.5
3	1.8	1.3	1.0	0.5	0.3	0.3	1.5
4	4.0	4.0	3.3	3.5	3.5	2.5	1.5
5	1.1	1.1	1.2	0.4	0.7		0.4
6	2.5	2.5	1.5	2.0	1.5		1.0
7	2.2	2.5	1.8	1.8	1.5		0.7
8	1.2	1.2	1.0	0.8	0.5		0.7
9	0.9	1.0	0.8	0.6	0.8		0.1
10	1.8	2.5	2.0	2.0	1.0		0.8
11	0.6	0.4	0.2	0.2			0.4
12	3.0	3.2	2.3	2.3	1.3		1.7
13	3.0	3.3	1.5	2.5	2.0		1.0
14	2.5	2.5	2.3	1.8			0.7
15	1.7	1.0	0.4	0.2			1.5
16	3.5	4.0	3.5	3.0			0.5
17	2.5	1.9	2.0				0.5
						Group decrease	14.9
Group average	2.2	2.2	1.8	1.6			

The improvement in bacterial index displayed by the trial patients as a group is thus a little better than that shown by their controls.

Clinical and histological improvement was thus borne out by bacteriological progress, but similarities and differences between Tables I and II should not be pressed too far. No matter how accurate the technique of bacteriological examination may be, there remains an element of uncertainty which cannot be overcome. In the advanced florid lepromatous case the skin may be sufficiently saturated with bacilli everywhere to make it immaterial where smears are taken, and in such a patient if multiple sites are selected on each occasion, consecutive smears will give a fair picture of progress. In all other cases, although bacilli may be very numerous, the skin is not uniformly invaded by them. At the onset every site examined may display innumerable bacilli, but as treatment progresses, the decline in bacilli first makes itself felt at sites where their density was least. Such sites may be small and scattered all over the body, and cannot be detected clinically until the process of resolution is gaining momentum. An element of luck in the choices of sites for bacteriological examination therefore exists, and although it is minimised by making multiple smears, it is not overcome. As a result, even though a patient may be making steady progress, some irregularity may appear in successive bacteriological findings, according as to whether sites of great or lesser bacteriological density happen to have been chosen.

This accounts in part for the variations in the progress of individuals in these Tables. The difference in progress between one individual and another is also noticeable. It serves to emphasize the care needed in the choice of controls, and is also a reminder that in any case there is an element of irregularity in the progress of leprosy patients, the causes of which still need to be clarified. In this trial there was a definite seasonal variation in progress, noticeable both among trial patients and among controls. One other feature needs comment. Although clinically and histologically there was little to choose between the progress shown by children and by adults, where bacteriological progress was concerned adults were at an advantage. At a later stage in the trial this finding may no longer apply, but it has applied during the first year.

Complications during Treatment

Erythema Nodosum Leprosum

Erythema nodosum occurred in one individual, a severe

nodular case, at the twelfth month. It was not sufficiently severe to interrupt treatment.

Neuritis

Three lepromatous cases experienced neuritis for short periods after treatment had been in progress for from nine months to one year. One tuberculoid case experienced neuritis of moderate severity at the fifth month. In none of these cases was neuritis of sufficient severity to interrupt treatment. All four of them had extensive nerve involvement before treatment was started. Others, also with marked nerve involvement, had no neuritis, and at this stage of the investigation it may be said that neuritis has not been a prominent feature.

Increased activity in lesions

None of the trial patients has so far exhibited any change in the form of the disease.

Complications of treatment have thus been few and unimportant.

Discussion

The findings in this trial confirm and extend those of Buu-Hoi and his colleagues. On its showing during the first fifteen months of observation there is evidence that diamino-diphenyl sulphoxide possesses activity against *M. Leprae* of the same order as that displayed by DDS, and that at a dosage of 100mg. daily it has been found safe to use.

Wider and more prolonged trials will be needed before any realistic assessment can be made of the place of this drug in leprosy treatment. Much will depend in the first place on whether its administration on a twice weekly basis is practicable. Its toxicity obviously calls for further study. The remarkable improvement shown by individiual patients, and the general freedom from complications shown by the trial patients as a group are, however, facts of interest. The drug is not a proprietary preparation and may possibly be manufactured quite cheaply. It therefore invites further study, and if progress is maintained, and late complications do not arise, it may very well be a potential rival to the sulphones.

Summary

A progress report is presented of a clinical trial in leprosy treatment of diamino-diphenyl sulphoxide.

This substance was administered in doses of 100 mg. daily to a representative group of 24 leprosy patients, none or whom had had any previous chemotherapy. Patients were matched individually against controls receiving routine DDS treatment, and a

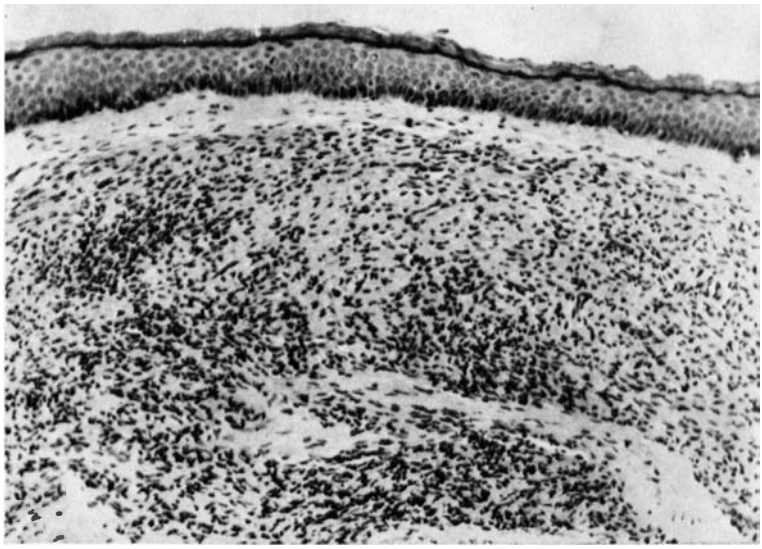


Fig. 1.—Trial Patient No. 1. Moderately severe lepromatous leprosy in a middle aged adult male. The section shows the typical features, flattened epidermis, subepidermal clear zone, and fairly extensive infiltration in the corium lepromatous in nature. The foamy appearance of the infiltration can be seen. X 195. Slide H75/55.

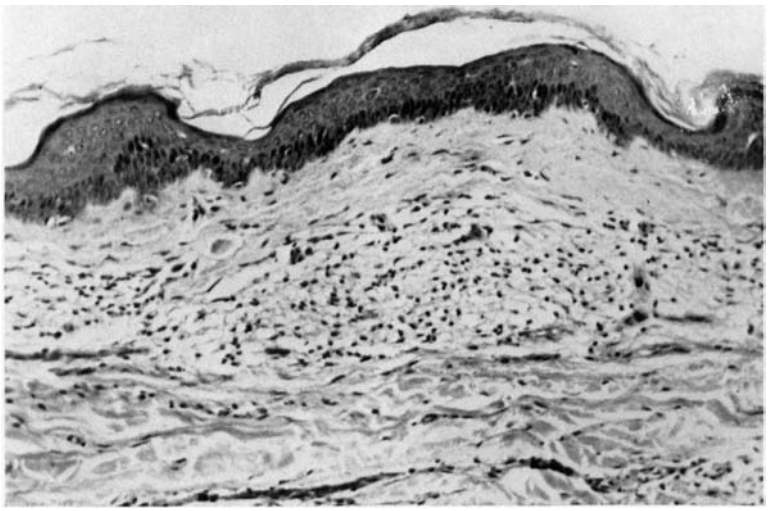


Fig. 2.—Trial Patient No. 1. Section from a site immediately adjacent to that shown in Fig. 1, and taken seven months later. Resolution is apparent. The epidermis is regaining its normal contour, and marked shrinking has occurred in the area of infiltration, with loss of cellularity, a vacuolated appearance, and dilatation of capillaries. X 195. Slide H24/56.

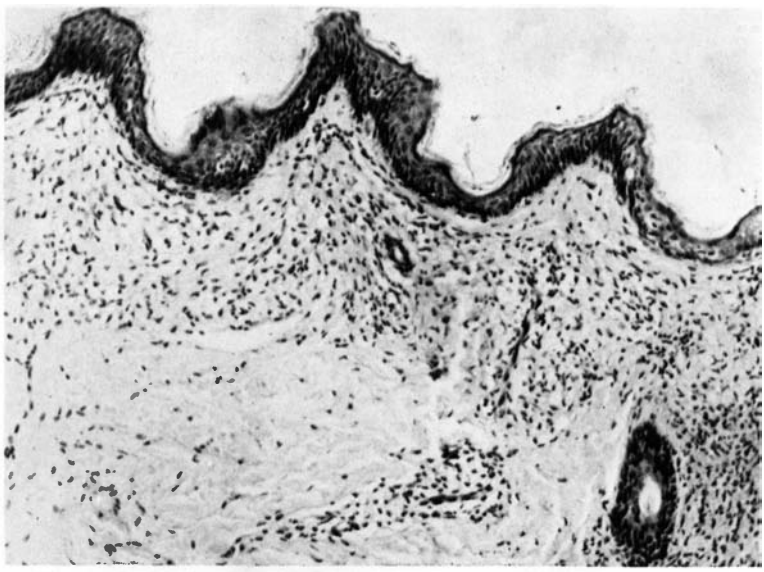


Fig. 3.—Trial Patient No. 3. Rapidly advancing lepromatous leprosy in a young child of six years, showing the typical features of a lesion of recent origin. The foamy nature of the infiltration can be seen especially in relation to a hair follicle. X 195. Slide H85/55.

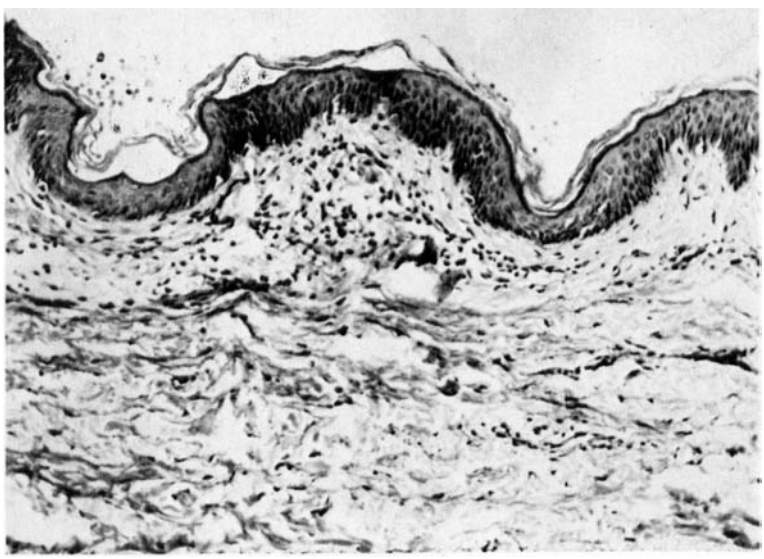


Fig. 4.—Trial Patient No. 3. Section from a site immediate adjacent to that shown in Fig 3, and taken seven months later. The features of resolution are again evident, with shrinking in the area of infiltration, a vacuolated appearance and loss of cellularity in the lesion, and dilatation of capillaries. X 195. Slide H33/56.

progress report written when the trial had been in progress for 15 months, by which time 18 of the patients had received the drug for one year or longer.

The drug was found to be active during the first year against *M. Leprae*, and to be comparable in this respect with DDS itself. The findings of Buu-Hoi and his colleagues are thus confirmed. Clinical progress was satisfactory in all cases, and indeed very gratifying in some. Decline in bacilli as evidenced by routine tests took place in all cases, but was irregular in degree, adults on the whole showing more progress than children. Toxicity was not of a high order at the dosage used in this trial. A mild degree of anaemia encountered in the early stages of treatment was self-limiting and called for no interruption in the treatment schedule. Complications of treatment were insignificant. The drug is considered worthy of wider trials.

Acknowledgements

This trial was suggested by Dr. F. Hawking of the Medical Research Council, and thanks are due to him for his encouragement and assistance in obtaining supplies of the drug used and in the preparation of photomicrographs. Thanks are also due to Professor Buu-Hoi, who obtained supplies of diamino-diphenyl sulphoxide before the drug was available in Britain, and also to Imperial Chemical (Pharmaceuticals) Ltd. for generous supplies later.

Grateful thanks are also due to Mr. S. E. Drewett, F.I.M.L.T., Laboratory Superintendent, and the laboratory staff of the Unit, especially Mr. G. Okezie, Senior Technician. The laboratory cover of this trial has so far called for over 2,000 laboratory procedures, and the promptitude and complete reliability with which these have carried out have been extremely valuable.

It is a pleasure to acknowledge the assistance given by the patient staff of the Research Unit, and also the patients themselves who cheerfully volunteered to take part in the trial and thus exposed themselves to many tests and no little inconvenience.

Thanks are also due to Dr. Onwu, Acting Director of Medical Services, Ministry of Health, Eastern Region, Nigeria, and to Dr. A. Zahra, Acting Leprosy Adviser, for permission to publish.

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