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An Open Trial of Low Doses of Dapsone in the Management of Lepromatous Leprosy*

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This paper reports the results of treating patients with lepromatous leprosy with low doses of dapsone (5 or 10 mg per day). The incidence of ENL seemed to be little affected but the severity of the reactions was generally less. There was little or no change in the morphological index, but the bacillary index showed a disturbing tendency to rise. The possible significance of these findings and the lesson to be drawn therefrom are discussed.

INTRODUCTION

Leprosy remained the "Cinderella" of medicine for centuries until, some 25 years ago, a specific anti-bacterial agent in the form of a sulphone derivative was first introduced in the treatment of the disease, with striking and spectacular success. Thanks to the early reports of Faget *et al.* (1943) from Carville, the introduction of promin (promanide) as a specific anti-leprosy drug opened a new era for patients with leprosy. Since then, much experience has been gained in the management of all types of leprosy with sulphones and there has been a considerable change in the thinking of leprologists regarding the optimum dose of sulphone in the management of leprosy (Muir, 1944; Faget and Pogge, 1944, 1945; James *et al.*, 1967).

A further refinement was introduced by Shepard and Chang (1967) and later extended by Rees (1967) in the form of the mouse foot-pad technique to test the effectiveness of DDS against *Mycobacterium leprae* and to determine the minimum inhibitory dose of DDS in the mouse foot-pad system which would prevent multiplication of this organism. This technique provided for the first time a system outside man which lends itself to careful quantitative evaluation of therapeutic regimes claimed to be beneficial in the management of leprosy. On the basis of these studies it was suggested that doses of sulphone of the order of 1 to 5 mg per day would be adequate in the treatment of leprosy patients (Shepard, 1967; Waters *et al.*, 1968). During the last 15 years it has been standard practice to treat patients with a maximum dose of 100 mg of dapsone per day or 600 mg per week in divided doses. Further, clinicians have gained the impression that patients treated with sulphones were getting quite severe episodes of erythema nodosum leprosum (ENL) with or without acute neurological catastrophes (Cochrane, 1963). It was also clear that since the introduction of sulphones the incidence of reactions among those with lepromatous leprosy has risen considerably, in contrast to the incidence of such reactions in the pre-sulphone era (James *et al.*, 1967; Shepard, 1967).

It was suggested that the phenomenon of ENL might be dose-related and therefore early trials were initiated to study the effect of small doses of sulphone, in the region of 100 to 200 mg per week in divided doses (Browne, 1965; Ramu and Ramanujam, 1965; Pettit and Rees, 1967). Waters *et al.* (1968), in a pilot trial, demonstrated that when administered in a dose of 1 mg per day, DDS was able to reduce the morphological index (MI) in skin smears from leprosy patients very rapidly, that is, at a

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rate comparable to that seen in patients on 100 mg of DDS, the conventional dose. In the present study at the Schieffelin Leprosy Research Sanatorium, Karigiri, we have investigated the therapeutic efficacy of 2 low dosage levels of DDS in lepromatous leprosy: (1) 5 mg of dapsone 6 times per week (30 mg per week) and (2) 10 mg of dapsone daily (60 mg per week). We were particularly concerned with the change in the MI, the rate of clearance of bacilli, the incidence and severity of ENL in relation to small doses of DDS, the changes in the peripheral nerve functions during treatment, and the over-all clinical improvement or worsening in patients on these small doses. In this paper the changes in the MI and bacterial index (BI), the clinical responses, and the incidence of ENL are presented for patients who have been followed for a minimum period of one year. The results presented here should be considered as still preliminary.

MATERIALS AND METHOD

A total of 20 patients with lepromatous leprosy have so far been carefully followed up for at least one year. Of these, 12 received 5 mg of DDS per day on 6 days per week (total 30 mg per week), and 8 patients were given 10 mg of DDS per day (total 60 mg of DDS per week). The data on MI were recorded according to Shepard's criteria. The BI and the reaction status were determined carefully and recorded periodically, along with the clinical status of the skin lesions and the general condition of the

TABLE 1
Changes in BI and MI for patients on 5 mg of DDS per day

Case no.	*BI*			*No. of days on DDS*	*MI*		
	Initial value	*Final value*	*Initial minus final*		*Initial value* %	*Final value* %	*Initial minus final*
1	3.75	4.12	—0.37	439	0	0.50	—0.50
2	1.37	2.25	—0.88	472	0.50	0	+0.50
3	2.87	3.87	—1.00	567	3	0.37	+2.63
4	4.00	3.87	+0.13	397	3	0.50	+2.50
5	1.75	2.12	—0.37	520	0.50	0	+0.50
6	1.25	2.87	—1.62	492	0.50	0	+0.50
7	3.50	3.00	+0.50	432	0	0	0
8	3.00	3.75	—0.75	540	0.50	0.37	+0.13
9	2.62	3.25	—0.63	596	0.25	0	+0.25
10	3.00	3.25	—0.25	569	1	0.12	+0.88
11	1.37	1.50	—0.13	513	2	0	+2.00
12	2.00	3.12	—1.12	575	1.50	0.25	+1.25

TABLE 2
Changes in BI and MI for patients on 10 mg of DDS per day

Case no.	*BI*			*No. of days on DDS*	*MI*		
	Initial value	*Final value*	*Initial minus final*		*Initial value* %	*Final value* %	*Initial minus final*
13	1.75	2.75	—1.00	506	0	0.12	—0.12
14	2.37	2.87	—0.50	498	3.50	0	+3.50
15	1.12	0.87	+0.25	1033	0	0	0
16	3.25	3.62	—0.37	513	0	0	0
17	2.37	3.25	—0.88	513	0.50	0.75	—0.25
18	2.50	2.25	+0.25	444	0	0	0
19	3.62	3.62	0	453	0.75	0.25	+0.50
20	2.25	3.25	—1.00	574	0	0.5	—0.50

patient as a whole. When any of the patients in this trial developed a reaction, we attempted to maintain them on the dose of DDS they were getting at the time they went into "reaction", and tried to control the reaction with the conventional anti-inflammatory drugs such as chloroquine, stibophen, aspirin, etc. Unless the clinical condition deteriorated so as to make it necessary for us to intervene with a more potent anti-inflammatory drug we did not change the DDS dosage in these patients. This was a departure from our usual policy of stopping dapsone treatment in patients who developed ENL, but we did so in order to test the opinion that has been expressed that dapsone has probably nothing to do with the precipitation of exacerbation in lepromatous leprosy.

RESULTS

MI and BI

The changes in the MI and BI in the 12 patients receiving 5 mg DDS per day are shown in Table 1, and those in the 8 patients taking 10 mg of DDS per day are shown in Table 2.

TABLE 3
Changes in MI during therapy

Change in MI	*DDS per day*		
	5 mg	*10 mg*	*Total*
Initial value zero, remained at zero	1	3	4
Declined to zero	5	1	6
Declined significantly but did not reach zero	5	1	6
Recorded increases but within 0.5%	1	3	4
Total	12	8	20

The changes in the MI are further summarized and presented in Table 3. It is obvious from this table that the MI declined, and in many instances become zero, in patients treated with these small doses of DDS. The changes in the BI recorded at the last follow-up examination were compared with the initial values at the beginning of therapy and are presented for patients on 5 mg DDS per day (Fig. 1 (a)) and on 10 mg DDS per day (Fig. 1 (b)).

The increases or decreases from the initial value are summarized and presented in Table 4.

TABLE 4
Changes in BI during therapy

Changes in BI from initial value		*DDS per day*		
		5 mg	*10 mg*	*Total*
Increased or same	0.5 and less	4	3	7
	0.6 to 0.9	3	1	4
	1.0 and more	3	2	5
	No. increased	10	6	16
Decreased	0.5 and less	2	2	4
	No. decreased	2	2	4
Total studied		12	8	20

From this table it can be seen that 16 (80%) of the patients showed either no significant change or an increase in the BI from the initial value. Whatever decreases there were are rather small, considering the duration of therapy.

It is interesting to observe the changes in the BI during therapy. While there are considerable variations in the individual responses, one

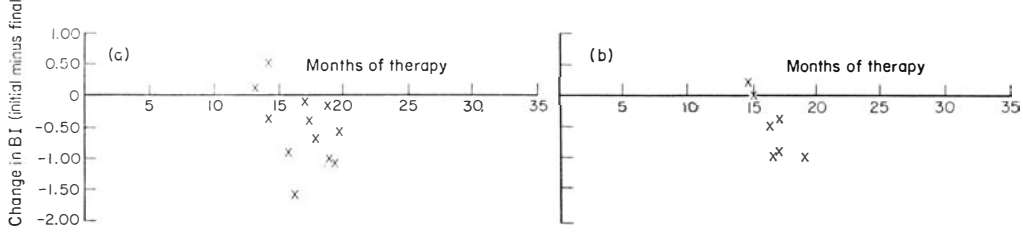

FIG. 1
Change in BI at the last follow-up treatment: (a) DDS 5 mg; (b) DDS 10 mg.

might try to fit the changes into one of the following 4 categories: (1) fluctuations throughout the course of therapy, with no change in the BI at the time of reporting; (2) an initial decline in the BI followed by an increase, with some fluctuations; (3) a continual increasing BI with minor fluctuations; and (4) a constantly declining index with some fluctuations.

The number of patients falling into each of the 4 patterns in the 2 treatment groups is shown in Table 5.

TABLE 5

Patterns of change in BI during therapy

Pattern of change	*DDS per day*		
	5 mg	*10 mg*	*Total*
(1) No significant change	5	1	6
(2) Initial decline, later rise	3	4	7
(3) Continual rise	4	3	7
(4) Constant decline	–	–	–
Total	12	8	20

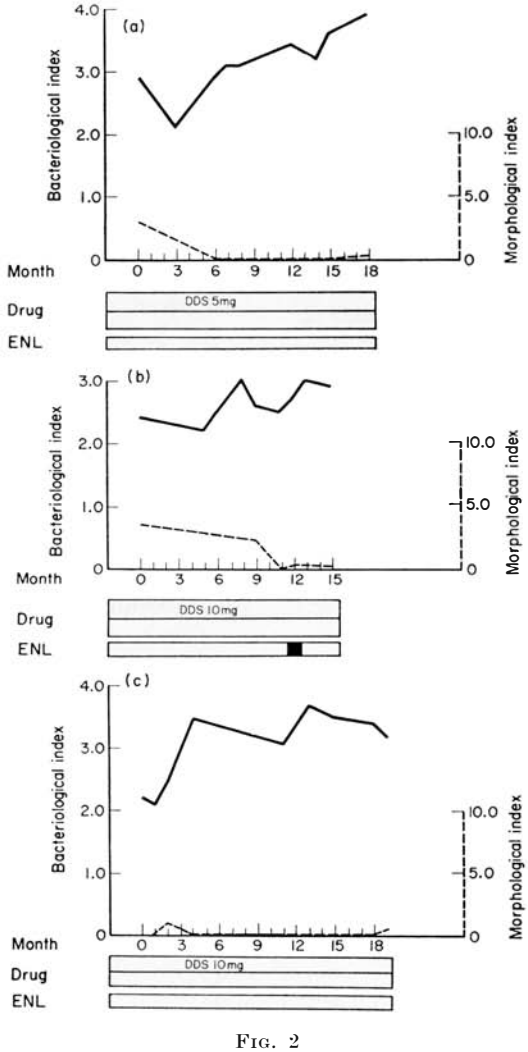

FIG. 2
Response to low dose DDS. Case no. (a) 3; (b) 14; (c) 20.

All the responses fall in patterns 1, 2 or 3, depicting either no change or an increase in the BI. No patient showed the fourth pattern of a constantly declining bacterial index. However, there was one patient in the DDS 10 mg per day group for whom a decline in the BI to zero was recorded, but this case has subsequently shown increases even while continuing the therapy. The changes in BI and MI in 3 sample cases are depicted in Fig. 2 (a, b, c).

Changes in clinical features

In this study none of the 20 patients has shown any significant improvement in the appearance of skin lesions. On the other hand, none of the patients showed any striking deterioration in terms of the clinical appearance of skin lesions and of systemic disturbance.

ENL

The episodes of reactions (ENL syndrome) observed in the 20 patients while receiving treatment with low doses of DDS are summarized in Table 6, which shows that out of the 20 patients 7 had "reactions" (ENL). These reactions, however, responded fairly satisfactorily to anti-inflammatory therapy without discontinuing the DDS therapy, and except for 3 cases in the 5-mg group the "reactions" did not recur.

TABLE 6

Reactions during therapy

Reactions	*DDS per day*		*Total*
	5 mg	*10 mg*	
0	8	5	13
1	1	3	4
2	2	–	2
3	1	–	1
Total	12	8	20

DISCUSSION

The changes observed in patients receiving small doses of DDS could be considered under the following headings.

Changes in the MI

In almost all the cases in which the MI was available throughout the period of follow-up, it was obvious that the fall in this index was comparable to that observed in patients on conventional doses of DDS. Practically all the cases showed a reduction to zero or near zero in the solid to non-solid ratio in the skin smears.

It is, however, worthy of mention that while the BI was beginning to rise or was steadily rising, there was no corresponding rise in the MI in the cases under review. This is somewhat surprising in view of the currently held opinion that granulated bacilli and non-solid bacilli are not viable (Water and Rees, 1962; Rees and Valentine, 1964). If this be the case, the persistent rise in the BI with a consistently zero or near zero solid : non-solid ratio would be difficult to explain. It is worth emphasizing that at this state we are not able to correlate exactly the MI with the rising BI in patients receving low doses of DDS.

Changes in BI

As demonstrated in the graphs for individual patients shown above (Fig. 2) and from Tables 4 and 5, a significantly higher proportion of patients showed either no change or a BI higher than the initial value even after one year of treatment. Comparison between patients on 30 mg and those on 60 mg of DDS per week revealed that a large proportion of patients on 30 mg showed either no change, or an increase in the BI at the end of 12 months. On the other hand, of the patients on 60 mg, some showed an initial decline in BI at the end of the same period, with a tendency for the index to rise as the duration of treatment was prolonged.

Clinical response

In this admittedly small series it is interesting that the clinical improvement generally seen in patients treated with 600 mg of dapsone a week during the initial 6 to 12 months was not seen in patients taking 30 mg DDS per week. Further, we could not record any significant alteration in the skin infiltration and nodular lesions of patients on these small doses during the period of trial.

Incidence of ENL

Seven out of the 20 patients under study developed one or more episodes of ENL while receiving the small doses of DDS. We have personally observed that one-third of all the patients with lepromatous leprosy treated with 100 mg of DDS per day developed ENL during the clinical course of their disease while on treatment (unpublished observation). It appears as though the incidence of ENL is not greatly influenced by the dose of DDS the patient is receiving, to judge by the equal distribution of patients with ENL in the 5, 10 and 100 mg per day dosage-groups in this study.

It should, however, be mentioned that the severity of the ENL on the whole was much less in the smaller-dose group of patients than in patients on the usual dosage of 600 mg per week. In fact, in none of the patients under report was it necessary to terminate the treatment with dapsone because of reaction. In all of them the episodes of reaction could be brought under control either with oral chloroquine or with parenteral stibophen. This is in distinct contrast to our experience in the management of ENL appearing in patients on a dosage of 600 mg of DDS per week. From the limited data available in this study it appears as though the *severity* of ENL may be dose-related, while the *incidence* of ENL may be unrelated to dosage. At this point, it is worthy of mention that if ENL were simply a manifestation of "drug reaction" to sulphone, then the vast majority of our patients with non-lepromatous leprosy, who are taking 600 mg of dapsone per week, should have shown evidence of ENL since they are derived from the same population. It seems as though the appearance of ENL is, in part, a response of the bacillated forms of leprosy, in contra-distinction to the exacerbation that one sees in non-bacillated forms of leprosy under treatment with dapsone. To date, as far as we are aware, there is no record of ENL appearing in patients with non-bacillated types of leprosy. We are therefore unable to substantiate the concept that ENL can be eliminated, or its existence substantially reduced, by reduction in the dosage of sulphone. We are also unable to confirm the expected finding of improvement in the clinical status and bacterial status of patients on small doses of DDS, namely 30 and 60 mg per week.

The long-term results of this study would indeed be disturbing if they suggested the appearance of resistant strains of bacilli. One fervently hopes that this will not happen because it would be a major disaster in the natural history of leprosy as a whole. In countries where there is no other drug available other than dapsone for the general management of leprosy, appearance of resistance to this "sheet-anchor" of treatment would be an unmitigated diaster! Therefore it would be in order for us to sound a word of caution against the general recommendation of the use of very small doses of dapsone in the routine management of leprosy. If one could restrain the therapeutic enthusiasm dictated by changing fashions, one might obtain more satisfactory long-term results! It is hoped that this presentation might help us all to see the need for more intensive, carefully followed-up, long-term studies to establish the efficacy or otherwise of smaller doses of dapsone, as well as to demonstrate clear-cut advantages of dropping the existing doses of dapsone. In the present state of our knowledge, therefore, one cannot recommend with confidence the small doses of DDS that have been recommended in the past.

SUMMARY

This paper presents our experience of the use of 30 and 60 mg of dapsone per week in 20 leprosy patients. It appears that the bacterial load tends to increase gradually but progressively in patients treated with small doses of dapsone, in contrast to the gradual decline in bacillary load seen in patients on conventional doses of the drug.

It is interesting to observe that under the conditions of this study, while the BI slowly but steadily increased, there was no corresponding rise in the MI. From the data presented here, one is unable to substantiate the concept that all non-solid bacilli are non-viable.

No significant reduction in the incidence of ENL among patients on 30 and 60 mg DDS per week could be demonstrated; it has been observed that the severity of "reaction" (ENL) appears to be significantly reduced in patients on smaller doses of dapsone, as compared with patients receiving 600 mg of DDS per week.

A word of caution is offered regarding the widespread use of smaller doses of DDS. It is suggested that adoption of this policy be deferred until further studies in small groups of patients on a long-term basis have confirmed the advantages of such a regime and have dispelled the fear of possible development of resistance to dapsone on a mass scale.

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