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Chemotherapeutic Trials in Leprosy

7. Trial of 50 mgm. DDS Twice Weekly in the Treatment of Lepromatous Leprosy[1]

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Although 4,4-diaminodiphenyl sulfone (DDS, dapsone) has long been accepted as the drug of choice for the treatment of uncomplicated leprosy, no consensus has yet been reached among leprologists concerning the best dosage to be used. Recently there has been a tendency toward lower doses, particularly in the early stages of treatment; but there is a dearth of evidence that low dosage treatment is as effective or advantageous as its proponents suggest.

We embarked, therefore, on a study using methods of investigation that have been reported previously ([4, 12, 13]) to determine whether or not DDS was therapeutically active in the relatively small dose of 50 mgm. twice weekly (approximately 2 mgm./kgm./week). The first six cases in this study were reported as a "Demonstration Pilot Study" ([4]); we hoped that the validity of our claim concerning the Pilot Trial would be confirmed by the findings of the more extensive (one year) study on 20 cases.

Our second intention was to study whether such low dosage would reduce the incidence or severity of ENL, as it has often been claimed ([2, 10]) that reducing sulfone dosage helps the course of this reaction, and, by analogy, low dosage might perhaps even prevent the onset of reaction in many cases. We were aware that a diminished incidence of ENL could be defined accurately only by a controlled trial on a much larger scale than the present study, but we believed that 20 patients would be sufficient to indicate whether or not there was a marked reduction compared with our previous experience.

This trial differs from the other major trials ([11, 12]) carried out by the Leprosy Research Unit, Sungei Buloh, in being uncontrolled except by comparison with previous cases treated by us using the same criteria of improvement. This policy was forced on us for the practical reason that in the past five years the admission of patients to Sungei Buloh Leprosarium has been halved and the number of patients suitable for trial has been farther reduced by our increasingly rigorous selection policy ([13]). The intake of this 20 patient trial took two and one-half years and even then was incomplete; with such a slow entry it is clearly impracticable for a single center to undertake a large and controlled trial.

METHODS

Selection of patients. All patients were suffering clinically from lepromatous leprosy, and biopsy specimens, taken routinely from two sites, showed the histology to be pure lepromatous leprosy (LL on the scale of Ridley and Jopling ([9])). Patients were rejected if the histology was not pure LL, but a few were included with a histologic diagnosis of LL although clinically there were borderline features. No patient gave any history of previous treatment, and the absence of recent sulfone medication was confirmed by a negative blood sulfone test on admission to hospital. All patients were required also to have an initial morphologic

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index (MI) of 25 or over (average of six sites). We excluded any patients who were suffering from other serious illnesses, particularly tuberculosis. Screening tests routinely carried out included urine and stool examination, chest x-ray, blood count, and Mantoux test, as well as full clinical examination.

Further details, together with clinical histories of the first six patients in this trial (who can be considered as representative of all), have been given elsewhere [4].

Conduct of the trial. All patients remained in the Leprosy Research Unit wards throughout the period of the trial, and received a diet that was higher in protein content (about 80 gm.) than the average in Malaysia. Tablets of DDS containing 50 mgm. were issued twice weekly and seen to be swallowed. Blood DDS levels were taken fortnightly for the first six weeks and occasionally subsequently and indicated that no additional DDS was taken.

Routine investigations during the course of the trial included monthly blood counts and urinalysis, and smears at the start and after 1½, 3, 4½, 6, 9 and 12 months. Biopsies and clinical photographs were taken and the Mantoux test was performed at the start, and after four and one-half and 12 months. Lepromin tests and chest x-rays were repeated after one year's treatment. The smears and biopsies were read blindly by independent observers.

Clinical progress was graded by an independent assessor, who was unaware of the treatment being given. He charted the skin lesions at the start and at four and one-half and 12 months, and at the two later dates, with the help of photographs and his notes, assessed the degree of progress. He was told if corticosteroids were being used, and in what dosage, but was given no other information. The degree of improvement, and the classification and grading of reactions, have been defined in previous reports [4, 11].

RESULTS

An intake of 20 patients was planned, but because of slow entry the trial was closed at 18 patients. Three of these were later rejected, one because of incomplete data, and the other two on histologic grounds. An additional four patients were lost after their four and one-half months assessments; two were discharged home at five months on compassionate grounds, one was withdrawn at eight months because he developed nephritis, and one died at seven months following a subarachnoid hemorrhage. The two latter patients had already developed ENL, and so are included in the 12 months analysis of reactions. The results therefore are for 15 patients followed for four and one-half months and 11 or 13 followed for 12 months.

In some tables the results of the first six patients are quoted separately to allow easy comparison between this group, already reported as a demonstration pilot study [4], and the complete group of trial patients.

Clinical improvement. (Table 1) Most patients showed slight or moderate improvement at four and one-half months, and marked improvement at 12 months. No patient deteriorated, and comparison of columns 1 and 2 shows that the first six patients were reasonably representative of the whole group. Improvement continued for the whole period of 12 months.

Bacteriologic improvement. (a) *Bacterial index (BI).* Changes are shown in Table 2. As might be expected, the fluctua-

TABLE 1. *Assessment of clinical improvement during the trial period.*

	Number of patients		
	0–4½ months		0–12 months
Degree of improvement	Cases 1–6	Cases 1–15	(11)
Slight	4	4	
Sl./Mod.	2	6	
Moderate		3	2
Mod./Mk.		2	1
Marked			7
Very marked			1

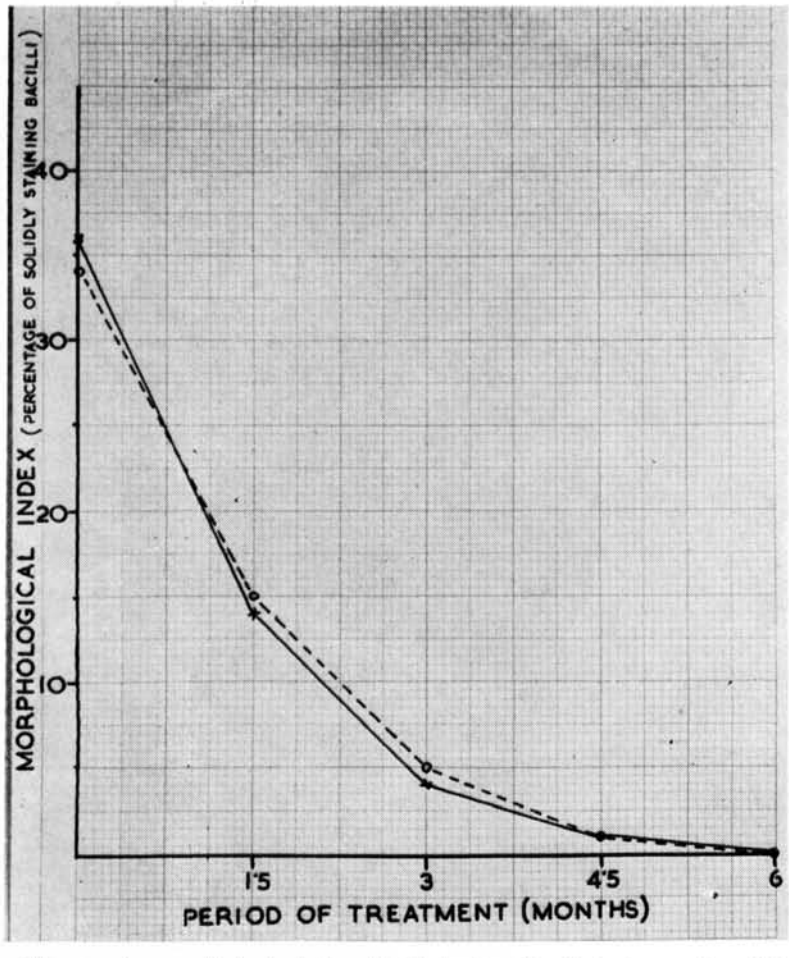

FIG. 1. Changes in morphologic index (MI) during the first six months of treatment. O---O = Cases 1-6; X—X = Cases 1-15.

tions of the first six patients are evened out in the whole series, and there is only a slight fall (from 4.2 to 3.9) over one year.

(b) *Morphologic index (MI).* This is shown graphically in Figure 1. It is clear that the curve for the first six patients is identical with that for the whole series. No patient showed more than occasional solid staining bacilli (less than 1 per cent)after six months.

Histologic improvement. The average figures for the logarithmic biopsy index ([7, 8]) are shown in Table 3. The index falls steadily and at the rate we have found in our previous studies. The biopsies also were assessed for activity, and all were reported quiescent or regressive at 12 months unless reaction was present.

Reactions. The reactions that developed are shown in Table 4.

(a) *ENL.* During the first four and one-half months four of our 15 patients developed ENL that was visible clinically. A fifth patient (who at no time in the 12 month trial period showed clinical signs of ENL) was reported as showing it on his four and one-half month biopsies. Between four and one-half months and 12 months these four patients' ENL continued, in two cases severely (Grade 3 or 4), while four more patients had transient attacks of mild ENL (Grade 1 or 2). Thus, in all, eight out of 15 patients developed clinical ENL during the period of the trial. Details of the individual patients are given in Table 5.

(b) *"Lepra reaction" ("Exacerbation"*

TABLE 2. *Average bacterial index (BI) during treatment.*

Group	Time in study (months)						
	0	1½	3	4½	6	9	12
Cases 1–6	3.9	4.3	4.0	4.4			
Cases 1–15	4.2	4.3	4.2	4.2	4.0	3.9	3.9

TABLE 3. *Average logarithmic biopsy index (LIB) during treatment.*

Group	Start	4½ months	12 months
Cases 1–6	4.9	4.9	4.0
Cases 1–15	5.0	4.9	4.0

TABLE 4. *Reactions occurring during treatment.*

Group	No. pts.	Period (months)	ENL	"Lepra reaction" ("Exacerbation" reaction)
Cases 1–15	15	0–4½	4 (+1)[a]	2 (+2)[a]
Cases 1–15	13[b]	4½–12	8	3

[a] Figures in brackets ( ) represent patients in whom reaction was diagnosed histologically but not seen clinically.

[b] The two patients discharged at 5 months have been excluded.

reaction). During the first four and one-half months two patients developed signs of this type of reaction, and it was reported in the four and one-half month biopsies of another two, although not apparent clinically. During the second part of the trial (four and one-half to 12 months) one patient continued to suffer from the reaction, and two other patients (including one of the two with biopsy evidence only at four and one-half months) developed it for the first time.

Two of these patients changed their histologic classification during the trial period. One, who had obvious and prolonged "exacerbation" starting very early in the trial, had reached BB-BL histologically at four and one-half months, and showed little change at 12 months. The other was reported as reacting on his four and one-half month biopsies, although the reaction was not evident clinically then or later. He had reached BL-BB by 12 months. Table 6 shows that both patients had clinical borderline features; i.e., they were suffering from a pattern of lepromatous leprosy that reverts fairly commonly to borderline during the course of treatment.

DISCUSSION

So far as the first aim of this study is concerned, little discussion is necessary. Our findings confirm previous reports ([1, 3, 6]) that doses of DDS of the order of 100 mgm. per week bring about clinical improvement at least as rapidly as 100 mgm. per day. Over a study period of one year there was good improvement in all patients by all criteria (clinical, bacteriologic and histologic). It is gratifying to see how closely the fall in the MI (which is the most sensitive index of early response) for the whole group matches that for the first six patients, thereby fully confirming our contention that the response of six properly selected patients provides reliable evidence as to the initial effectiveness of a drug treatment.

The question of reaction and its relation to the dose of DDS needs full discussion. It has been common clinical practice for many years to reduce the dose of DDS when a patient develops reaction; but the evidence that this procedure is effective is unsatisfactory, and in any case it will not necessarily have the same result as treating patients from the start with a small dose. The few reports of the incidence of ENL in patients treated with low doses of DDS are inconsistent. Leiker and Carling ([3]) treated a group of 20 carefully selected pure lepromatous patients, half with DDS, 200 mgm. weekly, and half with 800 mgm. weekly for a year. They found reaction was no less frequent or severe in the low dose patients during this period, even though the dose of DDS was lowered during the reactions. Ramu and Ramanujam ([6]), on

TABLE 5. *Severity of ENL occurring during treatment.*

Patient No.	Time in months											
	1	2	3	4	5	6	7	8	9	10	11	12
15196	Biopsy only											
15197									1+			
15210												±
15301								1+	2+			
15324				1+	1+	1+	2+	2+	2+	2+	2+	2+
15325[a]				2+	3+	4+	4+	4+	(4+	3+	3+	3+)
15483									1+		1+	1+
15517[b]			1+	1+	2+	3+	2+					
16059	1+	1+	1+	1+	1+	1+	1+	1+	1+	1+	1+	1+

[a] Removed from trial at 8 months because of nephritis but continued treatment under trial conditions.
[b] Died of subarachnoid hemorrhage at 7 months.
Grading of ENL is after Waters (11)
1+ = mild, causing little discomfort and responding to standard therapy.
2+ = moderate, usually persistent, and not easily controlled by standard therapy; requiring occasional steroids or ACTH.
3+ = severe, persistent, causing very considerable discomfort, and requiring regular steroids and/or ACTH.
4+ = very severe, usually necrotic, requiring high doses of steroids and/or ACTH for long periods.

the other hand, found that the incidence of reactions was reduced from 40 per cent on 600 or 500 mgm. weekly to 15 per cent on 200 mgm. weekly, despite reduction of the dose during reaction to the extent that the 400 and 600 mgm. groups received only about 65 per cent of the prescribed dosage. They used 96 patients who were less rigidly selected than Leiker's, but arranged them into well matched groups and followed them for one and a half to two years. Browne (1) also states that he found both the incidence and severity of episodes of exacerbation less than usual in a small uncontrolled group of severe lepromatous patients treated with 50 or 100 mgm. DDS twice weekly for several years, and this is commonly stated (though poorly documented) clinical experience.

Of the 13 patients in this study who were followed for seven months or more, eight developed definite clinical ENL. In four cases it was mild and transient (1 to 3 episodes only) and in two mild but persistent for nine months or more. The other two cases suffered from severe ENL requiring continuous corticosteroids. The incidence and severity of reaction in this study are therefore as great as in our previous experience (5) using higher doses of DDS (300 mgm. twice weekly) and we do not consider that treatment with DDS at 50 mgm. twice weekly markedly reduces either the incidence or severity of ENL.

TABLE 6. *Details of patients whose histologic classification changed during the trial period.*

Patient No.	Biopsy classification			Clinical features
	Start	4½/12	12/12	
15256	LL	BL-BB	BL-BB	Borderline features. Prolonged lepra reaction.
15250	LL	LL	BL-BB	Borderline features. Reaction not clinically apparent.

SUMMARY

Fifteen patients with pure lepromatous leprosy were treated for 12 months with DDS at 50 mgm. twice weekly. The drug was fully effective in this dose, and the incidence and severity of ENL were not less than on larger doses.

RESUMEN

Quince pacientes con lepra lepromatosa pura fueron tratados por 12 meses con DDS a una dosis de 50 mgm. dos veces por semana. La droga fué ampliamente efectiva en esta dosis, y la incidencia y severidad del ENL no fué menos que en dosis mayores.

RÉSUMÉ

Quinze malades atteints de lèpre lépromateuse pure ont été traités pendant 12 mois par la DDS, à raison de 50 mg. du produit deux fois par semaine. Le médicament a été pleinement efficace à cette posologie; l'incidence et la gravité de l'ENL n'ont pas été moindres qu'avec des doses supérieures.

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REFERENCES

1. Browne, S. G. Low dose oral dapsone: interim report. Leprosy in India **37** (1965) 299-302. (Suppl. No. 3A)
2. Jopling, W. H. Treatment of acute phases (reactional states) in lepromatous leprosy. *In* Leprosy in Theory and Practice. R. G. Cochrane and T. F. Davey, Eds., Bristol, John Wright & Sons, Ltd.; Baltimore, Williams and Wilkins Co., 2nd ed., 1964, pp. 418-424.
3. Leiker, D. L. and Carling, D. Low dosage of DDS. Leprosy Rev. **37** (1966) 27-29.
4. Pettit, J. H. S. and Rees, R. J. W. Chemotherapeutic trials in leprosy. 4. Dapsone (DDS) in low dosage in the treatment of lepromatous leprosy. Internat. J. Leprosy **35** (1967) 140-148.
5. Pettit, J. H. S. and Waters, M. F. R. The etiology of erythema nodosum leprosum. Internat. J. Leprosy **35** (1967) 1-10.
6. Ramu, G. and Ramanujam, K. Lower dosage sulphone regimen in leprosy. Leprosy in India **37** (1965) 293-299. (Suppl. No. 3A)
7. Ridley, D. S. A logarithmic index of bacilli in biopsies. 2. Evaluation. Internat. J. Leprosy **35** (1967) 187-193.
8. Ridley, D. S. and Hilson, G. R. F. A logarithmic index of bacilli in biopsies. 1. Method. Internat. J. Leprosy **35** (1967) 184-186.
9. Ridley, D. S. and Jopling, W. H. Classification of leprosy, according to immunity: a five-group system. Internat. J. Leprosy **34** (1966) 255-273.
10. Trautman, J. R. The management of leprosy and its complications. New England J. Med. **273** (1965) 756-758.
11. Waters, M. F. R. Chemotherapeutic trials in leprosy. 1. Comparative trial of Macrocyclon plus dapsone and dapsone alone in the treatment of lepromatous leprosy. Leprosy Rev. **34** (1963) 173-192.
12. Waters, M. F. R. and Pettit, J. H. S. Chemotherapeutic trials in leprosy. 2. Comparative trial of dapsone plus ditophal (Etisul) and dapsone alone in the treatment of lepromatous leprosy. Internat. J. Leprosy **33** (1965) 280-296.
13. Waters, M. F. R., Rees, R. J. W. and Sutherland, I. Chemotherapeutic trials in leprosy. 5. A study of methods used in clinical trials in lepromatous leprosy. Internat. J. Leprosy **35** (1967) 311-335.