

# Treatment of Moderately Severe Erythema Nodosum Leprosum with Thalidomide — A Double-blind Controlled Trial\*

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This carefully planned, controlled, double-blind trial of the value of thalidomide in the treatment of long-standing, moderately severe erythema nodosum leprosum showed that thalidomide was superior to a placebo, allowed for the concomitant reduction of other anti-ENL drugs, and was clearly preferred by the patients themselves.

Erythema nodosum leprosum (ENL) remains a controversial topic, and its rational treatment is made difficult by the dearth of controlled trials of different managements. For instance, although most workers would advocate reducing or discontinuing antileprosy treatment when ENL develops, there is no study clearly demonstrating the value of this procedure. The place of corticosteroids in therapy is also controversial. There is general agreement that they are best avoided, but it has recently been shown (Karat *et al.*, 1969) that patients with ENL (most of whom were not given steroids) developed more nerve damage than similar patients with no ENL; this might be prevented if steroids were used more freely than is commonly advised. Other drugs, such as chloroquin, antimonials, salicylates, and sedatives are widely used, but none has been adequately tested, and their efficacy requires further evaluation.

Thalidomide is a welcome exception, in that from the time of the accidental discovery (Sheskin, 1965*a*) of its effectiveness against ENL it has been subjected to a number of well planned and adequately controlled studies

(Baccaredda-Boy *et al.*, 1968; Convit *et al.*, 1967; Sheskin, 1965*b*; Sheskin and Sagher, 1968; Waters, 1968). There is now no doubt that it is a highly effective drug which could probably replace steroids in the management of ENL, except in the case of women of child-bearing age. It has also been shown (Magora *et al.*, 1968) to reverse acute nerve dysfunction occurring as part of this reaction. But its known teratogenic properties make close control essential, and its proper place in the management of ENL requires further accumulation of experience. At the Leprosy Research Unit in Sungei Buloh Leprosarium, thalidomide was first used in a double-blind controlled trial carried out in 10 patients with severe ENL, who all required at least 15 to 20 mg of prednisolone daily to control their reaction (Waters, 1968). It was found to be highly effective in such cases, and we therefore decided to undertake a further trial of the drug in patients with less severe ENL.

## ORGANIZATION OF THE TRIAL

### *Selection of patients*

All 12 patients admitted to the trial (11 males and one post-menopausal female (Case 4)) had been suffering from ENL for at least 10 months, and 11 of them for periods of between 1 and 3½

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years. They had all received frequent courses of antimonials ("stibophen") and some required occasional courses of ACTH or corticosteroids in low dosage. All were suffering from lepromatous leprosy (clinically LL (Ridley and Jopling, 1966); there was biopsy confirmation in 11 cases—the twelfth was not subjected to biopsy). The diagnosis of ENL was made on clinical grounds.

#### *Anti-leprosy treatment*

In all cases anti-leprosy treatment was continued and neither drug nor dosage was altered during the study period or for at least 10 months preceding it. The drugs and dosages used are shown in Table 1.

TABLE 1  
Anti-leprosy treatment of trial patients

<i>Treatment</i>	<i>No. of patients</i>	<i>Case nos.</i>
DDS 50 mg twice weekly	6	1, 2, 3, 7, 8, 9
100 mg twice weekly	2	5, 6
200 mg twice weekly	1	4
300 mg twice weekly	1	10
B 663 100 mg daily	2	11, 12

#### *Anti-ENL treatment*

*Thalidomide.* Patients were allotted randomly to treatment with thalidomide, 100 mg 3 times daily (twice daily if weighing less than 35 kg (77 lb), or with a placebo identical in appearance; after 6 weeks the treatment was reversed and continued for a further 6 weeks. Patient and nursing staff were unaware that a placebo was being used, and the research worker did not know which patient was receiving which tablet at any time.

Most of the patients were living in quarters in the hospital grounds; a few were in hospital. Patients in quarters attended the research ward daily, where their temperature was taken and a day's supply of tablets issued. It was not possible to watch each tablet being swallowed.

*Other drugs.* We have found that patients with ENL of this severity require treatment with effective reaction-suppressing drugs: it was

therefore impossible to use a placebo without also allowing the use of additional anti-ENL treatment. It was decided to use only 3 other drugs; namely prednisolone, stibophen, and paracetamol. The first 2 were prescribed by the research worker according to our normal indications; paracetamol was supplied for the patients to take themselves as they wished. The principle of assessing response to treatment by the change in requirement of other anti-ENL drugs has been used successfully for steroids (Pettit, 1967; Waters, 1968) and we expected it would prove satisfactory for stibophen and paracetamol also.

#### *Assessments*

Patients were seen twice weekly by the research worker, who graded the severity of their ENL and prescribed treatment as indicated. Points were allotted for the severity of ENL, maximum temperature since previous assessment, requirement of other anti-ENL

TABLE 2  
Classification and scoring for each half-week period

<i>Parameter</i>	<i>Definition</i>	<i>Score (points)</i>
Clinical (severity of ENL*)	No ENL	4
	Mild ENL	3
	Moderate ENL	2
	Steroids required on one day	1
	Steroids on more than one day	0
Fever (maximum temperature recorded)	< 98.8°F (37.1°C)	2
	98.8 to 99.9°F (37.1–37.75°C)	1
	> 100°F (37.8°C)	0
Stibophen requirement	0	2
	1 to 5 ml	1
	> 5 ml	0
Total WBC (when done)	< 8000 per ml	4
	8000 to 16,000 per ml	2
	> 16,000 ml	0

\*Definitions of ENL—*mild*, few or moderate number of lesions, indolent or slightly active, causing no discomfort; *moderate*, lesions mild or moderately active, causing some discomfort.

drugs, and total leukocyte count (performed every 2 weeks) as shown in Table 2. It will be noted that the higher the score, the less severe is the ENL. The scoring was designed with the following aims:

(a) To give greatest weight to the clinical assessment, which is scored higher than the other parameters.

(b) To compensate for the effects of treatment. Thus a patient with active ENL but no additional anti-ENL treatment might score ENL 2 + fever 1 + treatment 2 = 5. If treated, say with stibophen daily, his score could be expected to be ENL 3 + fever 2 + stibophen 0 = 5.

At each assessment the number of paracetamol tablets taken by the patient was also recorded, as it was considered possible that this would give objective evidence of the patient's opinion of the severity of his reaction. It is clear that the method of scoring is highly subjective. Nevertheless we consider that this technique will give reliable results in relatively short trials when clinical assessments are all performed by the same workers.

## RESULTS

### *Side-effects*

There were few complaints of side-effects during the course of the trial. During the first week 3 patients complained of drowsiness and of these, 2 were receiving thalidomide and one the placebo. In all cases the drowsiness cleared after a few days and there were no complaints when the treatments were interchanged after 6 weeks. Constipation and dryness of the mouth were not observed. One patient developed mild dermatitis after 10 day's treatment with thalidomide; this subsided with local treatment, but recurred for a week when treatment was changed to the placebo. One patient complained of temporal headaches for a week during the placebo treatment. The one female patient (Case 4) developed intestinal obstruction of uncertain cause after 9 weeks and was withdrawn from the study. She was receiving treatment with thalidomide at the time. (Her average scores for the first 3 weeks of thalidomide have been

inserted for weeks 10 to 12; this makes it possible to compare figures for drug and placebo treatment periods directly.)

### *Overall results*

These are shown in Table 3.

TABLE 3  
Total scores of all cases according to parameters during drug and placebo treatment

Parameter	Treatment	Weekly scores (total of all cases)	
		Range	Average
Clinical condition	Drug	59 to 70	65
	Placebo	47 to 55	50
Fever	Drug	40 to 47	43
	Placebo	34 to 43	39
Stibophen requirement	Drug	40 to 46	42
	Placebo	26 to 43	31
Total white blood count	Drug	20 to 26	22
	Placebo	14 to 22	18
Paracetamol requirement (no. of tablets)	Drug	114 to 160	142
	Placebo	212 to 282	246

*Clinical assessments.* These show a clear difference between the 2 treatment periods. The lowest weeks' score during thalidomide treatment was greater than the highest during placebo treatment; i.e. the most severe ENL during thalidomide treatment was less than the mildest during placebo treatment.

*Degree of fever.* There was little difference between figures for the thalidomide and placebo periods; this might be expected as patients in the placebo group were receiving other effective anti-ENL drugs.

*Stibophen treatment.* Here the difference between the 2 groups was very clear cut, as during 5 out of the 6 weeks of placebo treatment patients needed more stibophen than the maximum required in any one week of thalidomide treatment.

*White blood cell counts.* There was little difference between the 2 sets of figures. As in the case of the degree of fever this probably reflects the effectiveness of the additional anti-ENL treatment that was prescribed.

*Paracetamol requirements.* There was a most striking difference between the 2 groups, in that the patients took almost twice as many tablets during treatment with the placebo. Since these tablets could be taken as and when the patients wished, these figures make it clear that the patients found thalidomide more effective than the placebo, even allowing for the extra stibophen injections they received during placebo treatment.

TABLE 4

**Steroid requirements during the trial period**

<i>Case no.</i>	<i>Total amount of prednisolone prescribed (mg)</i>	
	<i>Thalidomide treatment</i>	<i>Placebo treatment</i>
3	0	35
4	10	135
8	400	630
10	35	0
12	500	345

*Steroid requirement.* Five patients received steroids during the trial; Table 4 shows that 3 of the 5 required less prednisolone when treated with thalidomide. Of the other 2, one (Case 10) received it for a few days only at the start of the thalidomide period; the other (Case 12) is discussed later.

The usual dosage of prednisolone was 5 to 10 mg daily; larger doses than this were required by Case 8 for almost all the placebo period (15 to 20 mg daily) and by Case 12 for the second half of the thalidomide period (12½ to 15 mg daily).

*Results for individual patients*

A clear-cut benefit from thalidomide was shown in the over-all figures, but individual patients showed marked differences in their responses. Table 5 shows results for each of the patients arranged according to the severity of the ENL (i.e. their scores during placebo treatment, mildest cases first). As might be expected the more severe cases show the most definite responses; this finding, however, reflects the system of scoring rather than the efficacy of the drug. The 2 exceptions (Cases 8 and 12) are considered in detail in the discussion below.

TABLE 5

**Scores of individual patients during drug and placebo periods**

<i>Case no.</i>	<i>Total score during placebo treatment</i>	<i>Additional score during thalidomide treatment</i>
6	89	+8
11	82	-1
1	82	+13
5	81	+12
10	78	+11
9	60	+31
2	56	+32
4	56	+25
7	55	+32
12	50	-7
8	46	+1
3	39	+23

*Rapidity of action of thalidomide*

The total scores of all patients for individual weeks are shown in Table 6. It is clear that thalidomide was fully effective after only one week, and that it affected the score even in the first week.

TABLE 6

**Total weekly scores of all patients during drug and placebo treatment periods**

<i>Week</i>	<i>Total scores of 12 patients</i>	
	<i>Placebo</i>	<i>Thalidomide</i>
1	132	146
2	138	160
3	123	166
4	139	158
5	119	156
6	123	168

**DISCUSSION***Method of study*

It is difficult to over-emphasize the importance of adequately controlled trials in the evaluation of drugs used in the management of ENL. There are obvious difficulties in performing drug trials in a condition which shows spontaneous fluctuations and has a variable but self-limiting course; even so it is surprising that so few satisfactory studies have been undertaken. The detailed technique and scoring of this trial could probably be improved, and will in

any case require amendment according to the particular regimen undergoing trial. But it is considered that the methods of this study could readily be applied to testing any drug or other treatment of ENL, and would give reliable results even in a trial based on a relatively small number of patients over a short time.

#### *Selection of patients*

This is critical to any study of the treatment of ENL. Patients with very severe reaction will probably show no detectable response to a weakly active drug; and those with very mild ENL may not give a clear-cut response even to a highly effective drug. Patients with continuous severe reaction are suitable for trials of powerful anti-ENL agents: but cases such as the majority of patients in this study who had had fairly continuous ENL for some months but did not usually need steroids, are more suitable for the assessment of less effective drugs. Selection of cases may well prove to be the most important part of trials of drugs used to treat ENL.

Three of our patients apparently failed to respond to thalidomide. One of them (Case 12) had little visible reaction, but considerable bone pain and ulceration of the legs. Biopsy specimens were reported to show "reversal reaction" ("lepra reaction") rather than ENL. A second patient (Case 11) had what were, clinically, definite ENL lesions, though mild and rather persistent: but biopsy examination showed evidence of a "reversal" reaction. The third patient (Case 8) had definite ENL, clinically and on biopsy; he needed less prednisolone when treated with thalidomide, and this response could be shown if the scoring system were modified. Cases 11 and 12 were included as being probably suitable and in order to make up numbers; but this was a mistake. It is strongly recommended that there should always be histological confirmation of the diagnosis of ENL in studies of its treatment: and it is clear that small numbers of well selected patients will give a more clear-cut result than will a large group of less satisfactory cases.

#### *Clinical assessments*

These should always be carried out without previous results being available. They are not difficult to perform quickly and reproducibly once the worker has gained the habit of recording, each time he sees a patient, the number of ENL lesions (few, moderate, many) and their degree of "activity" (indolent, slightly active, active, ulcerating). It is unlikely that scoring could be standardized between different units; but in any single unit uniformity could easily be achieved.

#### *Anti-ENL treatment other than thalidomide*

The decision to prescribe prednisolone or stibophen was made on clinical assessment, and so these scores were determined on as subjective a basis as were the clinical assessments. But this does not mean that they are either irreproducible or unreliable. Any leprosy worker develops, in the course of time, his own indications for treatment. And providing he is not influenced by previous knowledge (by knowing, for instance, that an active and powerful anti-ENL drug is being taken), a short trial conducted by a single worker should give valid results.

#### *The patients' verdict*

The most surprising finding of this study was the clear preference of patients for thalidomide, shown by the amount of paracetamol they consumed. It is clear from this that thalidomide is effective to a greater degree than is revealed by the figures for the clinical and other assessments.

#### **SUMMARY**

Twelve patients with long-standing ENL, but not usually requiring steroid treatment were subjected to a double-blind controlled trial of thalidomide in a dosage of 100 mg 3 times daily. Their response was assessed clinically and by the reduction of their requirement of other anti-ENL treatment (stibophen and/or prednisolone). Thalidomide was shown to be superior to the placebo, and was also preferred by the patients, who consumed less paracetamol during the period of thalidomide treatment.

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