

## **Influence of sulphone therapy on lepromin reaction**

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*Summary* Sulphones administered in different doses were found to have a modulating effect on lepromin response in TT and BT cases. Twenty-six cases of TT and BT leprosy were initially lepromin tested and included in the study. Eight cases were given orally 100 mg dapsone per day and nine cases were administered a single injection of acedapsone 225 mg. After 4 weeks all cases were retested with lepromin. The treatment was subsequently reversed so that the patients who received acedapsone earlier were placed on dapsone and those who had dapsone earlier were administered acedapsone. After a further 4 weeks the lepromin tests were again repeated. It was found that skin reaction to lepromin was significantly enhanced by small doses of sulphone and was depressed, although not significantly, by larger doses. Therefore, dapsone in full therapeutic doses may be usefully employed from the beginning in TT and BT cases with due care. It is also hypothesized that chemoprophylaxis with acedapsone might possibly enhance CMI against leprosy if already present.

### **Introduction**

In an earlier study at this Institute a depression of phytohaemagglutinin (PHA) induced lymphocyte transformation was observed when human volunteers were administered dapsone in 100 mg doses for one week (Sengupta *et al*, 1979a).<sup>1</sup> Since leprosy patients receive dapsone continuously for long periods in different dosages, the observation on the effect of dapsone on lepromin reaction would be of considerable interest. A prospective study was therefore planned in which a lepromin test was conducted before and following dapsone therapy. It was also felt that different dosages of the drug might induce variation in lepromin reaction. As such the effect of dapsone in 100 mg daily dosage and the effect of a single injection of acedapsone (225 mg/dose) on lepromin reaction were planned. The results of lepromin tests in patients treated by the

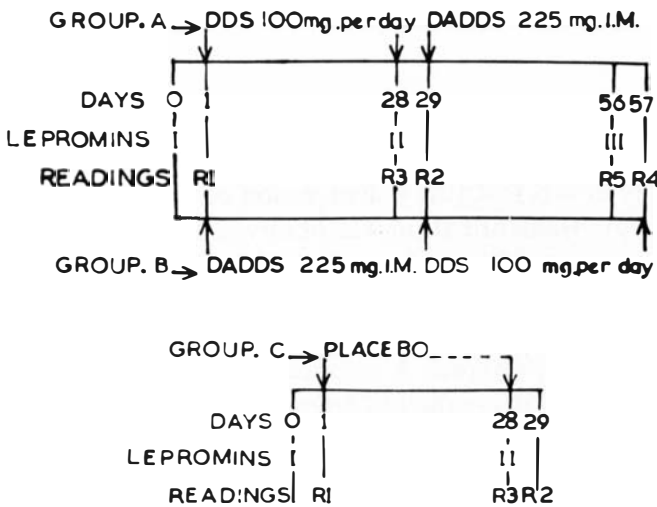
two drugs were compared with each other as also with the results in patients without sulphone therapy.

**Patients and methods**

Twenty-six adult patients suffering from TT and BT leprosy attending the out-patient department of Central JALMA Institute for Leprosy, Agra, formed the subjects of the study. All but one were untreated. The duration of the disease varied from 2 months to 6 years. All the patients were examined clinically and bacteriologically. Biopsy specimens were obtained from representative skin lesions. The cases were classified on the Ridley–Jopling Scale.

The patients were divided in three groups A, B and C. Group A received 100 mg dapsons for 28 days. On day 29 one injection of acedapsons (225 mg) was administered intramuscularly (IM). Group B was administered acedapsons (225 mg) IM on inclusion to the study. After day 28 they received 100 mg dapsons daily. Group C received placebo tablets one daily for 28 days. This group served as control.

Lepromin tests with standardized Dharmendra antigen (Sengupta *et al*, 1979)<sup>2</sup> were conducted on the three groups at different intervals and readings taken as depicted in the flow diagram (Fig. 1). Dharmendra antigen is a chloroform-ether extracted bacilli from lepromas (Dharmendra, 1967)<sup>3</sup> standardized by bacillary count (Sengupta *et al.*, 1979b).<sup>2</sup> The early reaction consisting of induration and erythema seen at 24 and 48 hrs is measured at two



**Figure 1.** Treatment schedules and lepromin tests

diameters at right angles and the average is recorded. The reaction wanes from 48 hrs onwards. The late reaction consisting of an indurated nodule begins after about 7 days and reaches a maximum in 3 to 4 weeks. The diameter of the indurated nodule is measured at 3 weeks. The Dharmendra antigen gives a stronger early reaction than the Mitsuda – Hayashi antigen but gives a less pronounced late reaction. Group A was administered lepromin thrice. Lepromin I was administered on day 0, lepromin II on day 28 and lepromin III on day 56. Reading R1 of the lepromin I is the early reaction prior to therapy. Reading R2 of lepromin II represents early reaction under dapsone therapy. Reading R3 of lepromin I represents late reaction following dapsone therapy. Reading R4 of lepromin III denotes early reaction following acedapsone therapy while reading R5 of lepromin II denotes late reaction following acedapsone therapy.

Group B was administered lepromin thrice as in group A. Lepromin I was administered on day 0, lepromin II on day 28 and lepromin III on day 56. Reading R1 of lepromin I is the early reaction prior to therapy. Reading R2 of lepromin II represents early reaction following acedapsone therapy while reading R3 of lepromin I represents late reaction following acedapsone therapy. Similarly reading R4 of lepromin III indicates early reaction following dapsone therapy while reading R5 of lepromin II indicates late reaction following dapsone therapy.

Group C received placebo tablets for 29 days. This group received lepromin only twice on day 0 and day 28. Reading R1 is the early reaction of lepromin I and reading R3 of lepromin I is the late reaction, both the readings being without the influence of sulphone. Reading R2 of lepromin II is an early reaction and this reading was taken to observe the possible effect, if any, of a repeated lepromin test.

## Results

The results are presented in Tables 1, 2 and 3. It could be seen from Table 1 and Fig. 2 that following 4 weeks of administration of dapsone there was a diminution in the size of lepromin reaction, one case becoming even negative. On the other hand following the administration of acedapsone there was an enhancement in the intensity of the lepromin reaction. On statistical analysis, it was found that the depression following dapsone therapy is not significant. However, enhancement of the skin reaction following acedapsone was statistically significant ( $p < 0.01$ ).

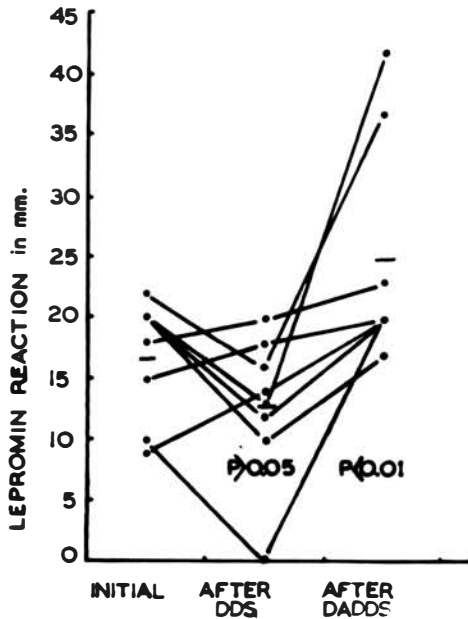
Table 2 and Fig. 3 represent the situation when the sequence of therapy is reversed, patients receiving acedapsone first and dapsone subsequently. It could be seen that administration of acedapsone enhanced the intensity of lepromin reaction and this was found to be statistically significant ( $p < 0.05$ ). Dapsone treatment brought down the intensity of reaction but it was found that the

results are not statistically significant. It could thus be seen that acedapsona whether given initially or following a course of dapsone significantly enhanced lepromin reaction.

**Table 1.** Lepromin reaction following DDS therapy initially and DADDS subsequently (Group A)

Sl No	Reg No	Name	Lepromin reaction before treatment in mm	Lepromin reaction following DDS Therapy in mm		Lepromin reaction following DADDS Therapy in mm	
			Early	Early	Late	Early	Late
1	10656	HL	10	0	0	20	U
2	10762	MP	20	13	6	42	U
3	10849	ML	22	16	U	37	U
4	11007	B	18	20	10	23	U
5	11014	RS	15	18	3	20	U
6	10445	JN	20	12	3	20	7
7	11174	RB	20	10	4	17	U
8	10429	RL	9	14	0	20	U

U = Ulceration

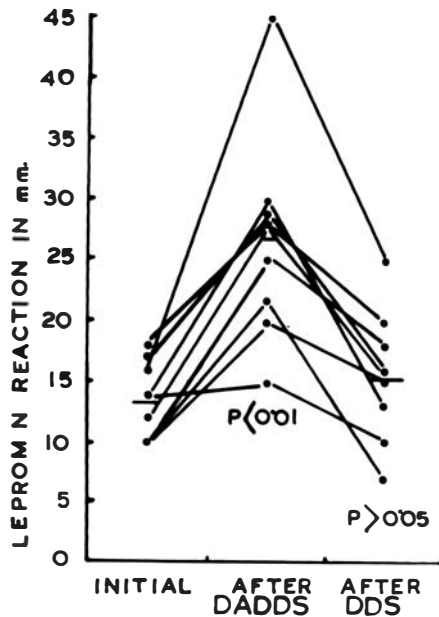


**Figure 2.** Influence on early lepromin reaction after DDS therapy and after subsequent DADDS therapy (·) mm. reaction of each patient. (—) mean value.

**Table 2.** Lepromin reaction following DADDS therapy initially and DDS subsequently (Group B)

Sl No	Reg No	Name	Lepromin reaction before treatment in mm	Lepromin reaction following DADDS treatment in mm		Lepromin reaction following DDS treatment in mm	
			Early	Early	Late	Early	Late
1	10857	RS	10	25	6	18	4
2	10748	GS	16	45	10	25	3
3	11002	D	14	15	7	10	0
4	10719	RL	18	28	U	20	U
5	10346	B	14	30	U	13	2
6	10759	S	12	28	U	16	6
7	11104	J	17	29	10	16	2
8	4477	B	10	25	6	18	4
9	11145	RN	10	20	8	15	3

U = Ulceration

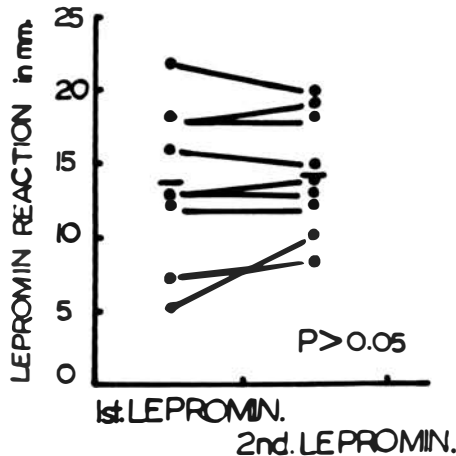


**Figure 3.** Influence on early lepromin reaction after DADDS therapy and after subsequent DDS therapy. (·) mm reaction of each patient; (—) mean value..

As could be seen in Tables 1 and 2 the late reaction following acedapsona therapy was quite severe resulting in ulceration in most of the cases. A peculiar phenomenon was observed in the cases treated with acedapsona. In many of the cases receiving this drug either initially or following dapsona therapy it was found that the second lepromin test after 4 weeks brought about an erythematous flare around the late lepromin nodule of the previous lepromin test resembling an exacerbated early response. This was not noticeable in cases receiving dapsona or placebo.

**Table 3.** Lepromin reaction in control subjects (Group C)

Sl	Reg	Name	Results of first lepromin test		Results of repeated lepromin test
			Early	Late	Early
1	12437	BD	16	7	15
2	12426	H	7	3	8
3	12472	R	18	5	18
4	12475	CS	22	8	20
5	12334	D	12	4	12
6	12111	YMK	13	5	14
7	12333	D	13	4	13
8	12468	KS	18	5	19
9	12352	W	5	0	10



**Figure 4.** Effect of two lepromin tests on the size of early lepromin reaction. (•) mm. reaction of each patient. (—) mean value.

The object of administration of placebo in the control group was to observe whether the second lepromin test had a boosting effect on the lepromin response. It could be seen in Fig. 4 and Table 3 that earlier lepromin injection does not influence the response to the latter.

## Discussion

The results of the study show that the intensity of lepromin test is influenced by administration of sulphone. There is a depression by the therapeutic dose of 100 mg daily. However, this was not statistically significant. Doses higher than 100 mg were not tried. On the other hand, sulphones in small doses were found to stimulate the lepromin test. Acedapstone, 225 mg IM administered in a single dose releases 2.5 mg daily into the blood stream. With such a small dosage the lepromin response was found to be significantly heightened. The comparison was made on the same patients who first received dapstone and were subsequently switched over to acedapstone or vice-versa. Individual variations were thus ruled out by repeating the test on a separate control group without treatment with sulphone. The conclusions therefore bear testimony to the influence of sulphone in different doses upon the lepromin test.

The implications of these findings on sulphone therapy need to be considered. Although the optimum recommended dose is 10 mg per kg body weight per week, which works out to 100 mg per day for the adults, much smaller doses are frequently used. For example, it has been a practice to start therapy with a small dose (Dharmendra, 1967;<sup>3</sup> Bryceson and Pfaltzgraff, 1973).<sup>4</sup> Jopling (1971)<sup>5</sup> advises a small dose in tuberculoid and borderline cases since, according to him, reactions could be precipitated in these cases with the recommended doses. Further, it is an accepted practice to withhold the drug during reaction and administer in small graded dosage after its subsidence. It is thus evident that sulphones are administered in different doses and the possible influence of such varied doses on the immune system deserve a careful study.

In view of the results of the present study it would appear that the sulphones have a modulating effect on the immune system. *In vitro* studies of Beiguelman and Pisani (1974)<sup>6</sup> and of Sengupta *et al* (1979)<sup>1</sup> have shown the depressive effect of dapstone to PHA-induced blastogenesis. If these *in vivo* and *in vitro* tests indicate cell-mediated immunity (CMI), it would appear that dapstone in high doses depresses CMI, while small doses would stimulate it. There is clinical evidence that TT and BT reactions are correlated with the increase in delayed hypersensitivity. The results of the present study would indicate that dapstone in normal clinical doses would be beneficial, and small doses might have a deleterious effect. Barnetson *et al* (1976)<sup>7</sup> have presented some evidence that 1–2 mg per kg body weight, might prevent reaction in

borderline cases. The results of the present study support the view of some of the workers that sulphone should not be discontinued or reduced during reaction. However, it needs to be emphasized that treatment during reaction is to be viewed very carefully in view of the risk of precipitating nerve damage and deformity. Physicians should proceed cautiously while interpreting the results of experimental observations.

Another important implication of the present study is that if small doses have an enhancing effect on skin delayed hypersensitivity the use of acedapsone in the chemoprophylaxis of leprosy might have an additional advantage. In addition to its inhibitory effect on *Mycobacterium leprae* it could also have a boosting effect on the immunity of the host.

## References

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