Chemotherapy of Leprosy[1]

D. L. Leiker[2]

DIAMINODIPHENYLSULFONE, DDS

DDS is, and probably for some time will be, at least in developing countries, the standard drug for routine treatment of uncomplicated leprosy, because of its low cost and the low incidence of drug resistance to it. The existence of resistance to DDS has, however, been established (Rees 1967) ([6]). It is not yet exactly known how frequently resistance occurs. As it appears to develop stepwise [Rees 1967 ([6]), Morrison 1968 ([5])] partial resistance may already be more common than at present is known.

The optimal dosage of DDS has not yet been established. There is, however, definitely a trend toward the use of lower dosages, which, theoretically, increases the risk of development of more drug-resistant strains of *M. leprae*. The advantages of lower dosages (50-300 mgm. weekly) are that side effects such as hemolytic anemia and insomnia, which may persist for one or two days after intake of DDS, are lessened. Furthermore, on the average, the incidence of reactions appears to decrease after administration of lower initial dosages, slow increase of dosage, and a low maintenance dosage.

On the other hand, in many lepromatous patients who have been treated with DDS until most bacilli have become granular, and the bacterial index (B.I.) has already significantly decreased, and who suffer from repeated reactions, lowering of the dosage fails to reduce the incidence of reactions. Many of these patients do not tolerate even very low dosages (25-50 mgm. weekly), nor low dosages of most other antileprosy drugs. It seems that in these patients the choice and the dosage of the drug are less important than other reaction-provoking factors. Such patients can be treated successfully only if the reactions are suppressed by steroids or with thalidomide. The question remains whether the advantages of lower dosages counterbalance the theoretical risk of development of drug resistance.

This risk does not seem to be great, for it has been found that the bacteriologic effect of these lower dosages is not significantly less than of higher dosages (Table 1). The differences between the three groups of patients cited are not significant. Waters *et al.* (1968) ([8]) have reported that dosages even of 1 mgm. DDS daily are only bacteriologically effective, atlhough they do not claim an optimal effect.

The subject is somewhat complicated by the finding that in patients lacking natural resistance DDS does not always destroy all bacilli. Harman (1968 ([1]) and Leiker

[1] Most trials reported in this article have been carried out in cooperation with Dr. M. FitzHerbert, P.O. Box 2677, Addis Ababa, Ethiopia and Dr. C. S. Goodwin, Public Health Laboratory, St. Mary's General Hospital, East Wing, Milton Road, Portsmouth, England, in the A.L.E.R.T. Centre, Addis Ababa, Ethiopia.

[2] D. L. Leiker, M.D., Royal Tropical Institute, Amsterdam, The Netherlands.

TABLE 1. *Bacteriologic effect of different dosages of DDS in lepromatous leprosy*[a].

Weekly dosage	Percentage of granular bacilli				
	Onset	3 months	6 months	9 months	12 months
250 mgm.	50	47	75	85	90
50 mgm.	62	68	79	83	93
20 mgm.	60	64	78	89	93

[a] The bacteriologic assessment has been based on examination of serial biopsies of the same lesion.

(1969) ([2]) have found intact bacilli in histopathologic sections from patients who had been treated until all bacilli in smears had become granular and the B.I. had become very low, even in some patients with negative routine smears. Such intact bacilli have been found in smooth muscle tissue in the skin (arrector pili, bloodvessel walls) and in superficially located striated muscle (scrotum, extremities). It appears that, in spite of prolonged treatment, viable bacilli may survive. Because the bacilli had not been phagocytized by macrophages, nor had a local lymphocytic response been found, it was assumed that the bacilli were in a dormant phase. It is likely that, as in tuberculosis, the drugs act on metabolically active or multiplying bacilli only. It is not likely that such dormant bacilli will easily produce a drug-resistant strain.

Intact bacilli have been found also in patients who had been treated with higher dosages (600-800 mgm. weekly) and not less frequently as compared with patients treated with lower dosages. Up to the present time there is no evidence that relapses are more frequent in patients treated with the lower dosages. Until evidence to the contrary has been produced, there is no reason to use dosages of more than 200-300 mgm. DDS weekly for routine treatment. The possibility of development of partial resistance or of poor resorption of the drug should, however, always be kept in mind if bacteriologic progress is not satisfactory. A careful follow-up of the morphologic index is indicated.

THIAMBUTOSINE (DPT)

This drug has the advantage of producing, on the average, fewer and less serious reactions, and of few other side effects, but the disadvantage of development of drug resistance after a few years of treatment and of higher cost than DDS. Although some patients tolerate thiambutosine better than the sulfones, there are many reaction-prone patients who do not tolerate thiambutosine in the conventional dosage of 1.5-2 gm. daily. In practice such patients are frequently treated with lower dosages of thiambutosine, though the effect of lower dosages has not been adequately assessed.

Table 2 shows that 500 mgm. thiambutosine daily has a rapid effect on the morphology of bacilli, and that this effect is not significantly different from the effect of 100 mgm. DDS weekly. Lower dosages of thiambutosine are therefore recommended for patients who do not tolerate low dosages of DDS, nor higher dosages of thiambutosine, and for patients at risk of complications after DDS treatment. No evidence has been found that the thiambutosine has more effect on the dormant bacilli than DDS.

LAMPREN

Numerous reports have shown that Lampren is a very effective drug against leprosy. Table 3 shows that 100 mgm. Lampren daily has a rapid effect on the morphology of the bacilli, comparable with the effect of DDS. Lampren appears to have major advantages over other antileprosy drugs. The side effects are mild, the most inconvenient one being of a cosmetic nature, hyperpigmentation of the skin. In 30 patients treated in the Netherlands for periods of 2-4 years, thus far no signs of drug resistance have been found. In 20 patients receiving steroids because of serious reactions, after treatment with Lampren the steroids could be gradually with-

TABLE 2. *Bacteriologic effect of 500 mgm. thiambutosine (DPT) daily in lepromatous leprosy.*

Treatment	Percentage of granular bacilli				
	Onset	1 month	2–3 months	4–5 months	6–7 months
500 mgm. DPT daily	37	58	85	92	95
100 mgm. DDS weekly	37	54	73	93	96

TABLE 3. *Bacteriologic effect of 100 mgm. Lampren daily in lepromatous leprosy.*

Dosage	Number of patients	Percentage of granular bacilli				
		Onset	3 months	6 months	9 months	12 months
100 mgm. daily	44	52	82	94	94	94

drawn in all but a few patients. The latter occasionally require brief courses of steroids or thalidomide for suppression of the reactions, which are as a rule only mild.

In all patients the treatment with Lampren has been continued during the reactions and no evidence has been found that the reactions were aggravated by Lampren. These findings are in favor of the concept of a reaction-suppressive effect of Lampren. It has not been found that this effect, even with dosages of 300-400 mgm. daily, is sufficiently rapid to make Lampren suitable for the treatment of acute reactions. Also, the period after which withdrawal of the steroids was possible, was not significantly shorter in patients treated with 300-400 mgm. Lampren daily, as compared with 100-200 mgm. Lampren daily.

It is concluded that Lampren is the drug of choice for patients presenting reactions and for patients who are likely to develop complications after treatment. In most countries where leprosy is highly endemic the use of Lampren on a large scale is limited, however, by the need for daily treatment and by the relatively high cost of the drug. Because of the deposit of Lampren in the skin, in particular in leprosy lesions, and the slow excretion of the drug, it has seemed likely that Lampren can be used as a long acting drug. Table 4 shows that the bacteriologic effect of 100 mgm. Lampren twice weekly and of 800 mgm. once monthly is not significantly less than of 100 mgm. daily.

The costs of treatment are significantly reduced by the use of these lower dosages, and the intermittent administration of the drug simplifies the outpatient treatment. Thus far no evidence has been found that Lampren has a greater effect on dormant bacilli than other antileprosy drugs. If the results of this trial are further confirmed; this drug may be recommended as a first alternative to DDS treatment, even in countries with a small budget for health. The higher costs of the drug are counterbalanced by the lesser need for inpatient treatment.

RIFADIN

Recent trials [Leiker 1969 ([3]), 1970 ([4]), Rees *et al.* 1970 ([7])] have shown that Rifadin has a very rapid effect on the morphology of *M. leprae* (Table 5). Rifadin is an antibiotic acting on the ribonucleinic acid synthesis of mycobacteria. Its rapid

TABLE 4. *Bacteriologic effect of different dosages of Lampren in lepromatous leprosy.*

Dosage	Number of patients	Percentage of granular bacilli				
		Onset	1 month	2–3 months	4–5 months	6–7 months
100 mgm. daily	7	46	60	75	88	97
100 mgm. twice weekly	10	45	56	65	83	89
800 mgm. once monthly	6	42	52	71	93	95

TABLE 5. *Bacteriologic effect of Rifadin in lepromatous leprosy.*

Dosage	Number of patients	Percentage of granular bacilli						
		Onset	1 month	2 months	3 months	6 months	9 months	12 months
600 mgm. daily	7	49	80	85	95	97	98	99

effect on the morphology of *M. leprae* is in favor of the concept of a bactericidal action.

Serious side effects of the drug have not been found in this trial. In the first year of treatment four out of seven patients have shown mild to moderately severe reactions. Treatment with Rifadin has been continued during the reactions. No conclusive evidence has been found that the reactions were aggravated by continuation of the treatment. In the second year of treatment in three patients the reactions became more severe and these patients were switched over to Lampren. In two patients who have now been treated for two years and three months respectively so far signs of drug resistance have not been found. The effect of Rifadin on dormant bacilli has not yet been assessed.

In conclusion, several effective and relatively rapidly acting antileprosy drugs are available. The differences in bacteriologic effect of these drugs are not significant. Further research should be directed primarily toward solving the problem of the dormant bacilli, responsible for relapses, rather than toward the search for more similarly acting drugs, and toward methods of promoting the elimination of the dead bacilli, which play a role in reactions, rather than toward the search for more reaction-suppressive drugs.

SUMMARY

DDS in a dosage of only 100 mgm. weekly is highly effective against *M. leprae*. Little difference in bacteriologic effect has been found between 100 mgm. DDS weekly, 500 mgm. thiambutosine daily, 100 mgm. Lampren daily, 100 mgm. Lampren twice weekly and 800 mgm. Lampren once monthly. Even after only one month of treatment each drug produced a significant change in the morphologic index. After about three months of treatment the great majority of *M. leprae* had become granular.

The most rapidly acting drug known so far is Rifadin. This drug may have a bactericidal effect on *M. leprae*. In preliminary trials it was found, however, that the incidence of reactions was not lower than with DDS treatment, and was higher than with Lampren treatment. In lepromatous patients treatment with Lampren has been continued during reactions. No evidence has been found that the reactions were aggravated by the drug. On the contrary, in most steroid-dependent patients it has been possible to withdraw the steroids gradually.

A serious problem in the treatment of leprosy is that even after many years of treatment small numbers of *M. leprae* may survive. In clinically inactive lepromatous patients with bacteriologically negative routine smears, intact bacilli, not surrounded by a lymphocytic reaction, have been found in muscle tissue in the skin. It is possible that *M. leprae* remains dormant in these tissues for prolonged periods, and that the present antileprosy drugs act on multiplying bacilli only. Another problem is the slow elimination of the dead bacilli from the body, which prolongs the period of reactions.

Thalidomide, in a dosage of 100-600 mgm. daily is as effective against all types of leprosy reactions as the steroids are. Caution in the use of the drug is indicated because of its teratogenic effect and the occurrence of neuritis.

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