INTERNATIONAL JOURNAL OF LEPROSY

Volume 49, Number 4
Printed in the U.S.A.

The Problem of Dapsone-Resistant Leprosy[1]

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The purpose of this paper is to review the available information on dapsone-resistant leprosy from 1964, when the first proven cases were reported, until 1980. In addition, background information on the methods used to detect dapsone-resistant leprosy, and also on the rationale of the use of dapsone in antileprosy treatment, will be presented.

Methods to study dapsone-resistant leprosy. Resistance to dapsone appears to develop in the same way as resistance to other antimicrobial drugs; monotherapy with dapsone selectively allows dapsone-resistant mutants of *Mycobacterium leprae*, present in any large population of the organisms, to survive, multiply, and ultimately cause recrudescence of active leprosy. Thus, the condition may be suspected if a patient says that he is taking dapsone, but his disease, although previously improving under treatment, is now getting worse. Clinical examination will show new, active skin lesions superimposed on signs of old, quiescent leprosy. Skin smears and biopsies will confirm that the disease is active, and that the bacillary load is higher than expected at this stage of his treatment.

Such patients may be considered to have *prima facie* evidence of dapsone-resistant leprosy. The suspicion may be confirmed by testing the sensitivity of the patient's organisms to dapsone, using the mouse foot pad technique ([14]). *M. leprae* obtained from the patient are inoculated into the foot pads of mice. Multiplication (which, however, cannot be detected for many months) in mice fed dapsone in the diet confirms the diagnosis of dapsone-resistant leprosy. Different degrees of dapsone resistance can be defined by feeding different concentrations of the drug in the diet. 0.01 Percent is roughly equivalent to 100 mg daily in man, which is the maximum in normal clinical use; but fully sensitive strains of *M. leprae* are inhibited by concentrations of dapsone as low as 0.0001 percent, the equivalent of 1 mg daily in terms of therapy in man.

Because of the limited availability of the mouse foot pad test, dapsone-resistant leprosy has usually been diagnosed clinically. Patients with *prima facie* evidence of dapsone-resistant leprosy are given a trial of dapsone in full dosage under as full supervision as possible. If the patient is taking the medication, and if the disease deteriorates, he must have dapsone-resistant leprosy. Careful supervision is required to prevent serious and possibly irreversible deterioration during the course of the trial. The patient may well also be a source of infection to others during the trial period.

The use of dapsone against leprosy. The use of sulfones began in 1943 and of dapsone in about 1948; thus, effective chemotherapy of leprosy predates that of tuberculosis. By the time that the need for multiple-drug therapy to prevent drug-resistant tuberculosis was established, the absence of cases of dapsone-resistant leprosy in patients receiving dapsone as monotherapy was well recognized, although not explained at that time. The first cases were recognized in the early 1960s; but it was not until about 1975 that it became clear that dapsone-resistant leprosy was more than an infrequent and rather insignificant problem.

The use of dapsone also antedates by more than 10 years the description of the mouse foot pad technique for obtaining limited multiplication of *M. leprae*. Thus, for more than a decade dapsone was used without knowledge either of the very slow doubling time of *M. leprae* (about 2 weeks) or of the extreme sensitivity of *M. leprae* to dapsone (the minimal inhibitory concentration is <0.01 microgram/ml). It is clear now that these two factors account for the fact

[1] Received for publication on 30 June 1981. This article is based on a presentation made at the October 1980 meeting of the Scientific Working Group of THELEP in Geneva. We have been asked to note that information contained in the article by Balraj, *et al.* (IJL **48** [1980] 397–401), accepted on 7 August 1980, was also presented at this meeting. It is our understanding that similar publications will be printed in the December issue of LEPROSY REVIEW.—RCH

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that dapsone-resistant leprosy usually emerges only after 10–20 years of treatment. Indeed, it was a fortunate coincidence that the mouse foot pad technique that made laboratory proof of dapsone resistance possible was described at almost the same time that the first cases of dapsone-resistant leprosy were observed.

Results of studies of dapsone-resistant leprosy. Since 1964, individual cases of clinically proven dapsone-resistant leprosy have been observed in the majority of countries in which leprosy is endemic. Mouse foot pad proven cases have been reported from many countries, including Malaysia, UK, Singapore, Tanzania, Malawi, Australia, Thailand, Burma, Zambia, Nigeria, Sierra Leone, Ethiopia, Jamaica (R. J. W. Rees, personal communication, 1980) and Mali, Morocco, Senegal, Upper Volta, Burundi (S. R. Pattyn, personal communication, 1980). However, there have been only a few studies including 10 or more patients. These studies may be grouped as either "limited studies," in which patients were drawn from undefined populations, or surveys in which all patients in a defined area were studied.

LIMITED STUDIES (See Table 1)

America. In 1941 a group of 22 patients were treated with the sulfone drug, Promin®, at the Public Health Service Hospital, Carville. These were the first leprosy patients to receive sulfone therapy; their treatment was probably equivalent to dapsone 10 mg daily. Jacobson and Trautman ([6]) followed up this group of patients. They found that 13 were still alive, and 10 still had active leprosy, 8 cases being considered dapsone resistant. Mouse foot pad tests, however, were not performed in all cases.

Dapsone-resistant leprosy was also diagnosed in 75 patients attending the same hospital during the period 1960–1973 ([4]). Although the size of the population from which these cases were drawn is uncertain, and not all were confirmed by mouse foot pad tests, the figure indicated that dapsone resistance was by no means uncommon in patients treated at Carville.

Of these 75 patients, 33 appear to have developed dapsone resistance outside the continental U.S., Alaska, and Hawaii. The patients had received prolonged treatment with dapsone in their countries of origin, and their dapsone-resistant strains of *M. leprae* were isolated within one year of their arrival in the U.S. (R. R. Jacobson, personal communication, 1981). Included in this group of 33 patients are patients from American Samoa, Cuba, Mexico, Okinawa, Philippines, Puerto Rico, Suriname, Taiwan, Trinidad, Vietnam, and the Virgin Islands.

TABLE 1. *Results of limited studies of dapsone-resistant leprosy.*

Country	Number of patients		Reference
	Tested	Resistant	
USA	13	8	([6])
USA	—	75	([4])
India	39	14	([17])
Philippines	12	11	([1])

India. Taylor, Chacko, and Job ([17]) identified 39 patients attending the Schieffelin Leprosy Research & Training Centre, Karigiri, with *prima facie* evidence of dapsone-resistant leprosy; in 19 cases, mouse foot pad tests confirmed the diagnosis; 14 were proved dapsone sensitive.

Philippines. Fajardo and Abalos (1) identified 12 patients with *prima facie* evidence of dapsone-resistant leprosy. In all cases the diagnosis was confirmed by mouse foot pad tests; one was proved to be dapsone sensitive.

In India and the Philippines, the populations from which the patients were drawn were not defined, but the numbers of patients tested, and the high proportions proved dapsone resistant served to draw attention to the need for further studies to be undertaken in these areas.

SURVEYS (see Table 2)

The first seven suspected cases of dapsone-resistant leprosy, in which mouse foot pad proof was undertaken, were reported from Malaysia by Pettit and Rees ([14]), this paper being later amplified ([15]) to include nine patients, four of whom showed foot pad proof of resistance. These patients were said to be drawn from a pool of some 5000 cases at risk, giving a prevalence of about 1 per 1000. However, all mouse foot pad tests were performed using a high concentration of dapsone in the diet (0.1 percent or 0.025 percent), which gave blood levels in the

TABLE 2. *Results of surveys of dapsone-resistant leprosy.*

Country	Number at risk	Minimal prevalence (per 1000)	Incidence (percent per year)	Reference
Costa Rica	200	68	1.0	(13)
Ethiopia	1500	100	3.0	(9)
Israel	100	37	—	(7)
Malaysia	5000	25	0.3	(18)

mice considerably higher than are found in human therapy. When subsequently retested at lower dapsone dosages, the remaining five patients all proved to be dapsone resistant. Thus the true prevalence in 1964 was about 2 per 1000, and the incidence about 0.1 percent of cases at risk per year. If continued at this level for 10 years, the forecast prevalence could have been taken as at least 10 per 1000 cases at risk.

Subsequent papers from the same center (11,18), where all suspected cases were tested in mouse foot pads, showed that by 1977 the prevalence was about 25 per 1000. However, groups of patients receiving dapsone in low dosage (25 mg weekly) or solapsone as initial therapy (in dosage equivalent to dapsone 10 mg daily) showed a prevalence of dapsone resistance of about 75 per 1000 (8). The incidence was about 0.3 percent per year.

All patients in these studies had been treated for many years as inpatients, and their treatment had been regular and well supervised; in most cases dapsone was used in full dosage, most commonly 400 mg twice weekly by injection. These figures for prevalence and incidence of dapsone-resistant leprosy can therefore be taken as the best results that can be achieved by dapsone monotherapy.

Israel. Levy, Rubin, and Sheskin (7) reviewed all cases at risk in the national control program. Of 94 patients, 20 appeared possibly resistant. Mouse foot pad tests showed 3 resistant and 2 sensitive, giving a prevalence of 37 per 1000. Incidence figures cannot be derived from the paper.

Costa Rica. Peters, *et al.* (13) reviewed all patients at risk in this compact and well-documented leprosy control program. Out of about 200 patients, 25 cases appeared possibly dapsone-resistant. The diagnosis was confirmed in 12 cases by mouse foot pad tests, and clinically in two more, giving a prevalence (in about 1973) of about 70 per 1000. However, only three cases were proved sensitive; if the patients were randomly selected for testing and 12 out of 15 were resistant, the probable true prevalence would be about 100 per 1000. The incidence appears to be about 1 percent per year.

Ethiopia. Pearson, *et al.* (9) studied all patients in the Addis Ababa area with *prima facie* evidence of dapsone-resistant leprosy during the period 1973 to 1977. From about 1500 patients at risk, 254 cases were seen; 41 more cases had been diagnosed prior to the start of the study. Mouse foot pad tests in a random sample of 53 patients showed only two strains sensitive to dapsone, giving a probable prevalence of about 190 per 1000. At the end of the study, a total of 154 patients had been proved by mouse foot pad tests or clinical trial to have dapsone-resistant leprosy, giving a minimal prevalence of about 100 per 1000.

In each year of the study, about 50 new cases were seen with *prima facie* evidence of dapsone-resistant leprosy. The probable incidence was thus about 3 percent per year among patients at risk; if continued, this would have lead to a prevalence of about 300 per 1000 by 1980 (12).

PRIMARY DAPSONE-RESISTANT LEPROSY (see Table 3)

The major risk of acquired dapsone-resistant leprosy is that it will cause new cases that show primary dapsone resistance. Thus the primary resistance rate can be considered as indicating the epidemiological significance of the cases of acquired dapsone-resistant leprosy. This rate can be readily determined by undertaking mouse foot pad tests on randomly selected cases of previously untreated leprosy. Such tests can only be performed consistently in lepromatous leprosy (in which patients have a large bacillary load); but the rate of primary dapsone resistance may be expected to be similar in all types of leprosy.

Results of such tests have been reported from India (2), where one patient was resistant out of three tested, and from America, (5) where nine cases were discovered during the period 1973–1977.

In Ethiopia, Pearson, Haile, and Rees (10) reported five cases resistant among eight

TABLE 3. *Results of studies of primary dapsone-resistant leprosy.*

Country	Number of patients		Prevalence (per 1000)	Degree of resistance	Reference
	Tested	Resistant			
USA	—	9	—	Majority low	(5)
Ethiopia (Addis Ababa)	9	5	550	Majority low	(9)
Ethiopia (excluding Addis Ababa)	15	11	700	—	(9)
Philippines	47	1	20	Low	(3)
India	3	1	300	—	(2)
Malaysia	22	6	270	Majority high	(Rees, personal communication, 1980)

tested. This program was continued, and the final results (9) showed that, in the Addis Ababa areas, five out of nine patients tested were resistant, and that 11 of 15 from other parts of Ethiopia were resistant. Most cases showed low-grade resistance and would be expected to show initial improvement to dapsone used in full dosage as monotherapy.

The high proportion of primary resistant cases found in this study was unexpected at the time. Nevertheless, in Addis Ababa during that period, only half the active lepromatous cases were untreated or starting treatment; the other half had relapsed with probable dapsone-resistant leprosy. One might therefore have predicted that about half the new cases would show primary dapsone resistance. The possible value of primary resistance surveys as indicators of the problem of secondary dapsone resistance requires further study. The variations in prevalence in different countries also indicate the possible value of dapsone-resistant leprosy as a marker for epidemiological studies.

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