DDS-resistant Infection Among Leprosy Patients in the Population of Gudiyatham Taluk, South India. Part 3. Prevalence, Incidence, Risk Factors, and Interpretation of Mouse Foot Pad Test Results[1]

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"The wide variation among estimates of the prevalence of secondary dapsone resistance" among leprosy patients was pointed out in October 1980, by the Scientific Working Group of the World Health Organization's THELEP program ([14]). The present study assesses the problem of dapsone (DDS) resistance in the Gudiyatham Taluk of South India. Gudiyatham Taluk, in Tamil Nadu, South India, with an area of about 1320 km^2 and a population of about 480,000 (1981 census), is the leprosy control area of the Schieffelin Leprosy Research and Training Centre, Karigiri, India. Most of the population is engaged in agriculture, and migrations in or out of the area are not common. The area is hyperendemic for leprosy and in December 1977, 6880 patients were on the treatment register at 44 village clinics. DDS monotherapy given as domiciliary oral treatment was introduced in 1955, and has been used throughout the area since 1963. Intensive case detection by repeated house-to-house surveys and health education, and careful maintenance of individual patient records, are features of the program launched in 1963.

The objectives of the present study were: a) to determine the prevalence and incidence of DDS resistance among treated patients in the area, and b) to identify the risk factors associated with the occurrence of DDS resistance.

PATIENTS AND METHODS

All known lepromatous (LL) and borderline lepromatous (BL) patients resident in the area were enumerated on 31 December 1977, from the treatment register maintained by the institution; excluding patients who had previously died or emigrated. Patients had been seen by a physician at the village clinic every three months, if not more often. Individual patient records allowed access to information dating back to the start of treatment for each patient. Data on the patients continued to be assembled up to 28 February 1981. Every patient included had been treated for a minimum of three years by 1981.

Annual skin smears had been taken from apparently active sites as well as four routine sites (earlobe and chin on the right; forehead and buttock or thigh on the left). Reading of smears was done by trained staff who were given no information regarding the patient. In comparing successive smears to decide whether the number of bacilli was rising or falling, the average Bacterial Index (BI) ([13]) of the routine sites was considered, except when this was contradicted by the change in the highest single reading. In the event of such conflict, the comparison was based on successive highest readings.

"Regularity of treatment" is defined as the percentage of months throughout treat-

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ment in which the patient collected DDS tablets. This is based on the assumption that those who collect fewer tablets also ingest fewer tablets, on the average, than those who collect tablets regularly. The "initial dosage" of DDS in a patient is defined as the average dosage of DDS during the first 26 weeks in which tablets were collected by the patient.

Lepromatous (LL) and borderline lepromatous (BL) patients can deteriorate solely through failure to take DDS. Therefore patients who had been absent for >50% of the entire period of treatment ("absentees") were excluded from both the denominator and the numerator in the calculations of prevalence and incidence.

In the remaining patients, DDS-resistant infection was diagnosed when review of skin smear results showed a continuing increase in the number of bacilli in successive smears. Smear results from the start of treatment were reviewed in each patient. It was thus possible to identify the point at which DDS-resistant infection first manifested itself in skin smear readings. This criterion was used to calculate the prevalence and incidence of DDS-resistant infection.

The "duration of smear negativity" in a patient is defined as the single longest period during which the patient remained continuously smear negative at any time from the start of treatment up to 28 February 1981. For example, in a patient who had been smear negative from 1971 to 1975, smear positive from 1976 to 1979, and again smear negative in 1980, only the single period of smear negativity from 1971 to 1975 would be considered, since that was the longest period for which the patient remained continuously smear negative.

The "person-years" of treatment for a patient is the sum of the years of treatment undergone by that patient up to 28 February 1981. In the person-years of treatment for a particular period of treatment, only those years of treatment within the specified period are included.

In addition, a separate approach was used to estimate the frequency with which DDS-resistant *Mycobacterium leprae* occurred in patients, regardless of whether or not the patients responded to DDS monotherapy. Between March 1978 and February 1981, patients with a BI ≥2+ were biopsied for the mouse foot pad test. All other clinical and historical criteria were disregarded in selecting patients for biopsy. (Not all patients with a BI ≥2+ could be biopsied, however, since some refused biopsy, others died or migrated before they had been biopsied and, in some, the BI subsided to <2+ before the biopsy could be taken.) The mouse foot pad test was performed by methods already published ([1, 12]). The detection of $\geq 2 \times 10^4$ *M. leprae* per foot pad ≥6 months after inoculation with 1×10^4 *M. leprae* per foot pad, in mice continuously treated with DDS from the day of inoculation, indicated the presence of DDS-resistant *M. leprae* ([5]). Samples of mouse feed were tested for DDS content to ensure that the required concentration of DDS was achieved in the feed ([4]). Some mouse tests were unsuccessful, failing to grow *M. leprae* in even untreated control mice and, therefore, allowing no conclusion about the drug sensitivity of the *M. leprae* inoculated.

RESULTS

A total of 1580 patients with lepromatous (LL) or borderline lepromatous (BL) leprosy were enumerated from the treatment register. Of these, 1224 patients (77.5%) were fully studied. One hundred forty-nine patients were not screened from 1978 onwards. Another 198 patients were "absentees," having missed >50% of their treatment. The records of the remaining nine patients were not available.

The 1224 fully studied patients were divided into three groups according to their "duration of smear negativity" during treatment. The prevalence of DDS-resistant infection in each of the three groups is shown in Table 1. Among the 76 patients who had remained smear positive throughout treatment, DDS-resistant infection was diagnosed in 18 patients (23.7%). Among the 148 patients who had been smear negative for <3 years during treatment, DDS-resistant infection was diagnosed in ten patients (6.8%). Among the 1000 patients who had been smear negative for ≥3 years during treatment, DDS-resistant infection was diagnosed in 12 patients (1.2%). DDS-resistant infections were significantly more frequent among the patients who remained smear positive throughout treatment than

TABLE 1. *Prevalence of DDS-resistant infections among 1224 patients according to "duration of smear negativity."*

	Remained smear positive	Smear negative for[a]		Total
		<3 yrs	≥3 yrs	
Screened (no.)	76	148	1000	1224
With DDS-resistant infection (no.)	18	10	12	40
Prevalence of DDS-resistant infection	23.7%	6.8%	1.2%	3.3%

[a] Single longest period during which the patient was continuously smear negative; at any time from the start of treatment up to 28 February 1981.

among those who had at some time been smear negative ($p < 0.05$, χ^2 test). A total of 40 DDS-resistant infections were diagnosed among the 1224 patients, yielding an overall prevalence of 3.3%.

In Table 2, the annual incidence of DDS-resistant infection according to the period of treatment is shown for two groups of patients with differing "regularity of treatment." In each period, the incidence indicates the number of persons out of 100 who newly manifested DDS-resistant infection during a year of observation. At no stage is there a significant difference in incidence between the two groups (in each period, $p > 0.05$, χ^2 test). On totalling the various groups, 14,322 person-years of treatment with 40 DDS-resistant infections yielded an average annual incidence of 0.28% per year.

Table 3 shows the incidence of DDS-resistant infection in three groups of patients on differing initial dosages of DDS. All these patients had taken ≥80% "regular treatment," and the respective incidences during successive periods of treatment were calculated independently. At no stage do the differences in incidence between the three groups attain statistical significance (in each period, $p > 0.05$, χ^2 test).

One hundred forty-nine patients had not been screened from 1978 onwards, but an attempt was made to screen these patients in 1981. Of 122 who could be screened, 44 had been absent from >50% of their treatment. Among the remaining 78 patients, only one patient (1.3%) was smear positive in 1981. The prevalence of DDS-resistant infections among these 78 patients appears to be no higher than the prevalence among the 1224 patients who could be fully studied.

Table 4 shows the results of all mouse tests performed up to 28 February 1981, including nine tests performed earlier than 1978. The mouse test was performed only on patients who had a BI ≥2+; all other criteria were disregarded in selecting patients for biopsy. Of 142 tests performed, 108 were successful; 95 (88.0%) out of these

TABLE 2. *Incidence of DDS-resistant infections according to "period of treatment" and regularity of treatment.*

Period after start of treatment (yrs)	Patients with regularity of treatment					
	50%–79.9%			≥80%		
	Person-years of treatment (no. persons)	No. with resistant infection	Annual incidence	Person-years of treatment (no. persons)	No. with resistant infection	Annual incidence
0–2	1216 (608)	0	0.00%	1222 (611)	0	0.00%
3–5	1781 (608)	1	0.06%	1755 (611)	5	0.28%
6–10	2570 (560)	5	0.19%	2215 (514)	2	0.09%
11–15	1647 (430)	14	0.85%	1338 (348)	5	0.37%
16–26	401 (96)	6	1.50%	177 (50)	2	1.13%

TABLE 3. *Incidence of DDS-resistant infection among patients with ≥80% regular treatment, by "initial DDS dosage" and period of treatment.*

Period after start of treatment (yrs)	Patients with initial DDS dosage								
	≤70 mg/week			71–200 mg/week			>200 mg/week		
	Person-years of treatment (no. persons)	No. with resistant infection	Incidence (%/yr)	Person-years of treatment (no. persons)	No. with resistant infection	Incidence (%/yr)	Person-years of treatment (no. persons)	No. with resistant infection	Incidence (%/yr)
0–2	188 (94)	0	0.00	368 (184)	0	0.00	654 (327)	0	0.00
3–5	282 (94)	0	0.00	545 (184)	0	0.00	913 (327)	5	0.55
6–10	447 (93)	0	0.00	768 (176)	2	0.26	992 (241)	0	0.00
11–15	332 (84)	1	0.30	415 (110)	1	0.24	592 (153)	3	0.51
16–26	15 (6)	0	0.00	9 (4)	0	0.00	141 (39)	2	1.42

108 successful tests detected DDS-resistant *M. leprae*. It is interesting to compare the proportion of successful tests which detected DDS-resistant *M. leprae* in the different groups of patients tested. Patients in the first column showed an increase in the number of *M. leprae* in successive skin smears preceding biopsy, even though they had not been absent from treatment. In contrast, patients in the third column showed a definite response to DDS as manifested by a decrease in the number of *M. leprae* in successive smears preceding biopsy. Among those in the first column, 26 (100%) out of 26 successful tests detected DDS-resistant *M. leprae*; however, among those in the third column, 5 (83.3%) out of 6 tests also detected resistant *M. leprae*. The difference is not statistically significant ($p > 0.10$, Fisher's exact test).

The occurrence of tests failing to grow *M. leprae* in untreated mice is significantly more

TABLE 4. *Results of all mouse tests performed.*

	Number of patients			
	Successive smears show number of bacilli			
	Increasing		Decreasing	Total
	Not absentees	Absentees[a]		
BI ≥2+[b]	31	111	46	188
Biopsied	29	99	14	142
Failure to grow *M. leprae*	3	23	8	34
Test successful[c]	26	76	6	108
Only DDS-sensitive bacilli grown	0	12	1	13
DDS-resistant bacilli detected	26	64	5	95
Highest concentration at which bacilli grew (g% DDS in mouse diet)				
0.0001	3	1	0	4
0.001	3	6	0	9
0.01	20	57	5	82

[a] Patients absent from >50% of their treatment.
[b] Bacterial Index ≥2+ at any time during the period 1 March 1978 to 28 February 1981.
[c] *M. leprae* grew in untreated control mice.

frequent among patients showing a decrease in the number of *M. leprae* in skin smears than among the rest of the patients biopsied ($p < 0.05$, χ^2 test).

DISCUSSION

The prevalence of DDS-resistant infections among the patients studied was found to be 3.3% (33 per 1000), and the average annual incidence was 0.28% per year. Comparable figures for prevalence and incidence were reported from a study in Malaysia—2.5% (25 per 1000) and 0.30% per year ([8, 10]). The prevalence in Costa Rica was found to be 6.8% ([11]); in Israel, 3.7% ([7]) and in Bamako, Mali, 5.7% ([2]). All of the patients in the present study had been treated for a minimum of three years by 1981.

An important additional observation has been brought to light. DDS-resistant infections do not appear to be uniformly distributed among all LL and BL patients. Instead, the small group of patients (76 out of 1224) who remained smear positive throughout their treatment included 18 patients with DDS-resistant infection, a prevalence of 23.7% DDS-resistant infections. In marked contrast, the vast majority of patients (1000 out of 1224) had been smear negative for ≥3 years during treatment; only 12 of them were found to have DDS-resistant infection, a prevalence of only 1.2%. The attainment of smear negativity in a patient appears to be a favorable prognostic sign, indicating a significantly reduced risk of DDS-resistant infection. Identification of the small proportion of LL and BL patients at high risk of showing drug-resistant infection is likely to be of practical importance in areas with financial and operational constraints.

From the data shown in Table 1, ≥80.0% regular treatment is not statistically significantly different from 50.0%–79.9% regular treatment with regard to the incidence of DDS-resistant infections. Table 3 shows that among patients on ≥80% regular treatment, an initial DDS dosage of >200 mg/week is not statistically significantly different from lower initial DDS dosages with regard to the incidence of DDS-resistant infection. Thus these data do not support the views that irregular DDS treatment or low initial dosages of DDS result in an increased incidence of DDS-resistant infection.

Ninety-five of the 108 successfully completed mouse tests (88.0%) detected DDS-resistant *M. leprae*. This high proportion of tests detecting DDS-resistant *M. leprae* confirms reports from five previous studies. Ninety-six out of 96 successfully completed tests in Malaysia detected DDS-resistant *M. leprae* ([10]). In Costa Rica, the corresponding figure was 12 out of 15 ([11]); in Israel, 3 out of 5 ([7]); In Ethiopia, 88 out of 93 ([9]) and in Mali, 5 out of 6 ([2]). Since the only criterion applied in selecting patients in the present study for the mouse test was BI ≥2+, it seems that the majority of treated LL and BL patients with a BI ≥2+ harbors DDS-resistant *M. leprae*. Patients deteriorating on DDS treatment are likely to harbor a greater proportion of DDS-resistant *M. leprae* than those improving on DDS treatment. The mouse test as presently used does not seem to discriminate between the two groups, as shown in Table 4; perhaps because it is not designed to measure the proportion of resistant *M. leprae* in the sample under test.

It has been shown by Levy ([6]) that five viable *M. leprae* can produce growth in the mouse foot pad. A sample of organisms growing in mice treated with DDS is therefore likely to have included at least five viable DDS-resistant *M. leprae*. However, five DDS-resistant organisms do not form a majority among the 10,000 organisms in the foot pad inoculum. As many as 30% (3000) of the 10,000 inoculated organisms may be viable. Further, if only 30% of these 3000 viable organisms remain in the foot pad 24 hr after inoculation ([5]), then no more than 1000 viable *M. leprae* are available to initiate bacterial growth. If these 1000 viable organisms contain five DDS-resistant organisms, growth can probably occur in mice treated with DDS. Five out of 1000 (0.5%), therefore, may well be the "threshold proportion" above which the mouse foot pad test can detect DDS-resistant *M. leprae*.

In the present study, five patients yielded DDS-resistant *M. leprae* in the mouse test even though they were responding to DDS monotherapy. In these patients, therefore, the "threshold proportion" for the foot pad test was exceeded; yet they did not show a

corresponding failure of response to DDS monotherapy. Pearson, *et al.* (9) reported uninterrupted response to DDS monotherapy in patients who yielded DDS-resistant *M. leprae* in the mouse test, even when patients were observed for a further 4½ years. It appears difficult to maintain that every patient who yields DDS-resistant *M. leprae* in the mouse test will fail to respond to DDS monotherapy. The explanation is likely to be as follows.

The frequency of DDS-resistant *M. leprae* in an untreated population of *M. leprae* is believed to be about 1 in 10^6. Since every untreated LL or BL patient is likely to have $>10^6$ *M. leprae*, every such patient probably harbors DDS-resistant organisms. During treatment with DDS, approximately 99.9% of the *M. leprae* are "killed" within four months (15). Only 10^3 out of 10^6 *M. leprae* survive, including all of the DDS-resistant *M. leprae*. The frequency of DDS-resistant *M. leprae* among the surviving bacilli would have now reached ≥ 1 in 1000. With the continuation of DDS monotherapy, the frequency of DDS-resistant *M. leprae* in the steadily diminishing total bacillary population can only increase. It appears, therefore, that the "threshold proportion" above which the mouse test can detect resistant bacilli may be exceeded at some stage of DDS monotherapy in every LL and BL patient. Yet no more than 3.3% of such patients failed to respond to DDS monotherapy. In the remaining 96.7% of patients, unknown factors must have operated to avert DDS-resistant infection. The demonstration of DDS-resistant *M. leprae* by the mouse test (Almeida, *et al., Leprosy Review,* in press) should not be regarded as synonymous with failure of response to DDS monotherapy. Estimates of DDS resistance based on the mouse test are likely to indicate the frequency of DDS-resistant *M. leprae,* rather than the frequency with which patients fail to respond to DDS monotherapy.

Because the mouse test has a low "threshold" for the detection of DDS-resistant *M. leprae,* areas where relatively many mouse tests were done are likely to report higher estimates of resistance than areas where relatively fewer tests were done. This is reflected in the estimated prevalence of 2.5% (25 per 1000) in Malaysia, the lowest of all available estimates (8). A carefully supervised trial of DDS monotherapy had been used in that study to exclude from the mouse test patients who responded to DDS. In contrast, one study in Ethiopia reported a prevalence of 19% (190 per 1000) and an incidence of 3% per year (8). Patients with predominantly DDS-sensitive *M. leprae* can deteriorate solely through failure to take DDS. It appears difficult to avoid the inflation of DDS-resistance estimates with such patients unless they are given a well-supervised trial of DDS treatment before being subjected to the mouse test.

These findings merely confirm what has long been known in the related field of tuberculosis chemotherapy. In a report on the Geneva international consultation of specialists, Canetti, *et al.* (3) stated that "all strains of tuberculosis contain some bacilli that are resistant to anti-bacillary drugs. However, in resistant strains, the *proportion* [italics added] of such bacilli is considerably higher than in sensitive strains." They pointed out that sensitivity tests that do not discriminate between a predominantly sensitive strain and a predominantly resistant strain may misclassify sensitive strains as resistant. They remarked that, "Paradoxically, sensitivity testing might even result in actual harm by leading to unnecessary changes of chemotherapy from effective and acceptable regimens." (3) Smear examination "to assess the progress of therapy at intervals" was accorded priority over sensitivity tests in tuberculosis control programs (3). It might prove prudent to reconsider the interpretation of sensitivity tests in leprosy. Regular skin smear examination retains its value in monitoring the response to treatment as well as the occurrence of drug-resistant infection, in both individual leprosy patients and in epidemiological studies.

SUMMARY

At the Schieffelin Leprosy Research and Training Centre, Karigiri, India, a study of the population of Gudiyatham Taluk revealed that the prevalence of dapsone (DDS)-resistant infection among lepromatous (LL) and borderline lepromatous (BL) leprosy patients treated for a minimum of three years was 3.3% (33 per 1000), with an

average annual incidence of 0.28% per year. DDS-resistant infection was diagnosed when review of skin smear readings showed a continuing increase in the number of *Mycobacterium leprae* in successive smears despite adequate DDS treatment.

The attainment of smear negativity in an LL or BL patient was found to be a favorable prognostic sign, indicating a reduced risk of DDS-resistant infection. No association was found between the incidence of DDS-resistant infection on the one hand and either the regularity or the initial dosage of DDS treatment on the other.

Ninety-five (88.0%) out of 108 successful mouse foot pad tests on patients with a Bacterial Index (BI) $\geq 2+$ detected DDS-resistant *M. leprae*. The mouse test detected bacilli resistant to 0.01% w/w DDS in mouse diet not only among patients deteriorating despite adequate DDS monotherapy, but also among patients improving on DDS monotherapy. Since the mouse test as presently used does not measure the proportion of *M. leprae* in a sample that are resistant to DDS, the detection of DDS-resistant bacilli in the mouse test may not always indicate that the patient will fail to respond to DDS monotherapy.

RESUMEN

Un estudio sobre la infección resistente a la dapsona (DDS) entre los pacientes lepromatosos (LL) e intermedios (BL) tratados por un mínimo de 3 años reveló una prevalencia del 3.3% (33 por mil), con una incidencia anual promedio del 0.28%. El estudio se realizó en el Centro Schieffelin de Investigación y Adiestramiento de la Lepra, Karigiri, India, en la población de Gudiyatham Taluk. La infección resistente al DDS se diagnosticó cuando en la revisión de los exudados de linfa cutánea se encontró un incremento continuo en el número de *Mycobacterium leprae* en preparaciones sucesivas, no obstante el adecuado tratamiento con DDS.

La conversión de las preparaciones a negativas en un paciente LL o BL se consideró como un signo de pronóstico favorable, indicando un riesgo reducido de infección resistente al DDS. No se encontró asociación entre la incidencia de infección resistente al DDS, por un lado, y la regularidad o la dosis inicial del tratamiento con DDS, por el otro.

En noventa y cinco (88%) de 108 pruebas exitosas en el cojinete plantar del ratón con material de pacientes con un Indice Bacterial (BI) $>2+$, se encontraron *M. leprae* resistentes al DDS. La prueba en el ratón permitió descubrir bacilos resistentes a 0.01% (p/p) de DDS en la dieta del ratón, no solo entre los pacientes en deterioro a pesar de la adecuada terapia con DDS sino también entre los pacientes en mejoría por la monoterapia con DDS. Puesto que la prueba en el ratón como se usa actualmente no mide la proporción de *M. leprae* resistentes al DDS en una muestra, el hallazgo de bacilos resistentes en el ratón no siempre indicará que el paciente será incapaz de responder a la monoterapia con DDS. Esto es similar a la experiencia que se tiene con las drogas que se usan en la quimioterapia de la tuberculosis.

RÉSUMÉ

Une étude de la population du Gudiyatham Taluk, menée au Schieffelin Leprosy Research and Training Centre de Karigiri, en Inde, a montré que la prévalence d'infection résistante à la dapsone (DDS) parmi les malades de la lèpre lépromateuse (LL) et dimorphe (BL) traités pour trois ans minimum, s'élevait à 3.3% (33 pour mille). L'incidence annuelle moyenne était de 0.28% par an. Le diagnostic d'une infection résistante à la DDS a été posé lorsqu'à la revue des lectures des frottis cutanés, on a constaté une augmentation continue du nombre de *Mycobacterium leprae* dans des frottis successifs, malgré un traitement adéquat par la DDS.

Le fait qu'un malade LL ou BL présente un frottis négatif s'est révélé un signe pronostique favorable, indiquant un risque réduit d'infection résistante à la DDS. Aucune association n'a été observée entre l'incidence d'infection résistant à la DDS d'une part, et d'autre part la régularité, ou le dosage initial, de la thérapeutique par la DDS.

Parmi 108 épreuves de passage au coussinet plantaire de la souris, réussies avec succès, chez des malades présentant un Index Bacterien (BI) $\geq 2+$, nonante cinq (88.0%) ont révélé des bacilles de la lèpre résistant à la DDS. L'épreuve chez la souris a mis en évidence des bacilles résistant à 0.01% de DDS (en poids par rapport au poids de la souris) dans l'alimentation de la souris, non seulement chez les malades dont l'état empirait malgré une monothérapie adéquate par la DDS, mais aussi chez des patients qui présentaient une amélioration sous monothérapie à la DDS. Du fait que l'épreuve chez la souris, telle qu'elle est pratiquée actuellement, ne mesure pas dans un échantillon la proportion de *M. leprae* résistant à la DDS, la mise en évidence de bacilles résistant à la DDS par l'épreuve à la souris ne peut toujours prédire que le malade ne répondra pas à la monothérapie par la DDS. Ceci est semblable à ce que l'on observe avec des médicaments utilisés pour la chimiothérapie de la tuberculose.

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