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# Prevalence of Secondary Dapsone Resistance in Gudiyattam Taluk, the Leprosy Control Area of the Schieffelin Leprosy Research and Training Centre, Karigiri. 1. Preliminary Report[1]

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Laboratory confirmation of resistance to diaminodiphenylsulfone (DDS or dapsone) was first reported in 1964 by Pettit and Rees ([5]). There have been many subsequent reports from different parts of the world ([1,2,3,4]). Taylor, Chacko, and Job ([7]) from Karigiri were the first to report dapsone resistance in India. Population based data on the prevalence of dapsone resistance are not available from India, and therefore the present study was undertaken to estimate the magnitude of the problem. This paper reports the results of an initial study of prevalence of dapsone resistance conducted between March 1978 and February 1979 in Gudiyattam Taluk, Tamil Nadu, India.

## MATERIALS AND METHODS

Gudiyattam Taluk of the North Arcot District in Tamil Nadu is the leprosy control area of the Schieffelin Leprosy Research and Training Centre, Karigiri. It is about 1320 square kilometers in area with a total population of 426,205 (1971 census) and is hyperendemic for leprosy. The prevalence of leprosy within the control area is 26 per 1000, and in December 1977 the control program had 6880 patients under treatment. For more than 15 years, dapsone has been extensively used in this area, and fairly accurate records of treatment schedules have been maintained. Between 1972 and February 1978, 11 cases of secondary dapsone resistance were clinically detected and confirmed by animal experiments. However, at the commencement of this study, there were only nine of them in the control area, one having migrated from the area and the other having died.

All the lepromatous and borderline lepromatous patients in the area (numbering 1580) were chosen as those at risk of developing secondary resistance. While efforts were made to clinically and bacteriologically screen all, only 1431 (90.56%) were finally examined. Signs of reactivation and relapse were looked for, and smears were taken from routine sites as well as sites where active lesions were evident.

Patients who presented with reactivation or signs of relapse with a Bacillary Index (BI) of 2.00 or more and smear BI on the increase after having had 260 weeks (5 years) or more of dapsone therapy were suspected of dapsone resistance. Following a recommendation of the WHO/THELEP Steering Committee (personal communication, 20 November 1977), skin biopsies were taken from such patients from a site with a BI of 2.00 or more for mouse foot pad study and routine histopathology. Most biopsies were performed in the patient's home or the village clinics, and the biopsy

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TABLE 1. *Patients screened.*

| Lepromatous and borderline lepromatous patients | Number of patients | Percentage examined |
|---|---|---|
| Total patients registered | 1580 | |
| Total patients screened | 1431 | 90.56 |

was transported on wet ice to the laboratory. One patient who was included in the study was found to have completed fewer than 4 years of treatment on analysis of the patient's record.

Patients who presented themselves with reactivation or relapse with a bacillary index of 2.00 or above but who had absented themselves from the clinic for 5 months or more were not biopsied even though they had received more than 260 weeks of dapsone therapy. The long-term absentees were given a trial period with dapsone in full recommended dosage (100 mg per day) before deciding on biopsy for foot pad studies.

Skin biopsies were processed within 24 hr, and the bacilli isolated from them were inoculated into the foot pads of four groups (A, B, C, and D) of CBA mice with eight mice in each group. Group A served as controls while groups B, C, and D were fed 0.01%, 0.001%, and 0.0001% respectively of DDS in their diets. Two mice were sacrificed from each group at 6 and 8 months after inoculation and their foot pads harvested ([6]). The remaining four mice were kept for harvest at 10 and 12 months if *M. leprae* were not detected at 8 months. The patients under study continued treatment with dapsone alone until the results of the experiments were known.

## RESULTS

Of the 1580 lepromatous and borderline lepromatous patients registered, 1431 were examined (Table 1). Among the 1431 patients who were screened, there were 1017 males and 414 females. The distribution of patients according to the time of registration for treatment in 5 year periods is given in Table 2.

On smear examination, 336 patients were positive and 1095 were negative (Table 3a). One hundred eight patients in the positive group showed clinical evidence of reactivation and/or relapse of the disease. The remaining 228 patients showed no evidence of relapse even though they were smear positive. Of these, 160 patients had a BI of less than 2.00 and 68 more than 2.00 (Table 3b). These patients are to be kept under surveillance during the coming year.

The smear status of 114 patients who showed reactivation or relapse is shown in Table 3c. Six were smear negative, and 62 showed a BI less than 2.00. These patients

TABLE 2. *Distribution of the patients screened according to year of registration for treatment.*

| Years of registration | Males | Females | Total |
|---|---|---|---|
| 1962 and before | 59 | 18 | 77 |
| 1963–1967 | 502 | 183 | 685 |
| 1968–1972 | 254 | 126 | 380 |
| 1973–1977 | 199 | 86 | 285 |
| Data incomplete | 3 | 1 | 4 |
| Total | 1017 | 414 | 1431 |

TABLE 3a. *Smear status of the patients screened.*

| Patients screened | Smear positive | Smear negative | Total |
|---|---|---|---|
| Patients with reactivation and/or relapse | 108 | 6 | 114 |
| Patients without reactivation or relapse | 228 | 1089 | 1317 |
| Total | 336 | 1095 | 1431 |

TABLE 3b. *Smear status of 228 smear positive patients without reactivation or relapse.*

| | BI less than 2.00 | BI more than 2.00 | Total |
|---|---|---|---|
| Number of patients | 160 | 68 | 228 |

TABLE 3c. *Smear status of 114 patients with reactivation and/or relapse.*

| | Smear negative | BI less than 2.00 | BI more than 2.00 | Total |
|---|---|---|---|---|
| Number of patients | 6 | 62 | 46 | 114 |

TABLE 4a. *Data regarding 46 patients with reactivation, relapse, and BI more than 2.00.*

| Total | Patients absent from clinics for 5 months or longer | Patients autopsied for foot pad study on suspicion of resistance |
|---|---|---|
| 46 | 20 | 26 |

TABLE 4b. *Period of absence from treatment at time of screening among 20 patients with reactivation, relapse, and BI more than 2.00.*

| Period of absence | Number of patients |
|---|---|
| 5 months | 1 |
| 1 year | 1 |
| 2 years | 5 |
| 5 years | 10 |
| 10 years | 3 |
| Total | 20 |

TABLE 4c. *Results of foot pad studies.*

| | Patients biopsied | Dapsone resistant | Dapsone sensitive |
|---|---|---|---|
| Present study | 26 | 24 | 2 |
| Resistant cases before[a] | | 9 | |
| Total | | 33 | |

[a] Patients with dapsone resistance detected before commencement of this study.

are also to be followed up during the next year of study.

Forty-six patients had a smear of 2.00 or above. Of these patients 20 had been absent from clinics for 5 months or longer (Tables 4a and 4b), and the reactivation or relapse could be attributed to discontinuation of treatment. These patients were therefore given a trial period of full doses of dapsone (100 mg per day for a minimum of 6 months) before deciding on biopsy for foot pad studies.

At the end of the year 24 patients were found to be resistant to dapsone, and two were sensitive (Table 4c). There were nine previously identified from the control area,

TABLE 5. *Growth and sensitivity of the 33 resistant and two sensitive cases in foot pads of mice.*

| Number of patients | Growth of *M. leprae* in mice fed on | | | Sensitivity to DDS |
|---|---|---|---|---|
| | 0.01% DDS in diet | 0.001% DDS in diet | 0.0001% DDS in diet | |
| 31 | + | + | + | resistant |
| 2 | 0 | + | + | partially resistant |
| 2 | 0 | 0 | 0 | sensitive |

giving a total of 33 dapsone resistant patients in Gudiyattam Taluk. Table 5 shows that 31 of the strains isolated were fully resistant to dapsone at the three concentrations, 0.01%, 0.001%, and 0.0001%, used in the diet. Organisms isolated from the remaining two patients were suppressed at the highest dosage used in the diet, 0.01%, but grew in animals receiving lower concentrations of dapsone in the diet (0.001% and 0.0001%) and are therefore considered partially resistant.*

Analysis of the charts of these 33 patients revealed that only two had more than 75% attendance and hence could be considered regular (Table 6). In 28 patients, DDS resistant bacilli were isolated 5 to 15 years after dapsone therapy (The Figure). One patient treated for fewer than 4 years was found to have developed resistance.

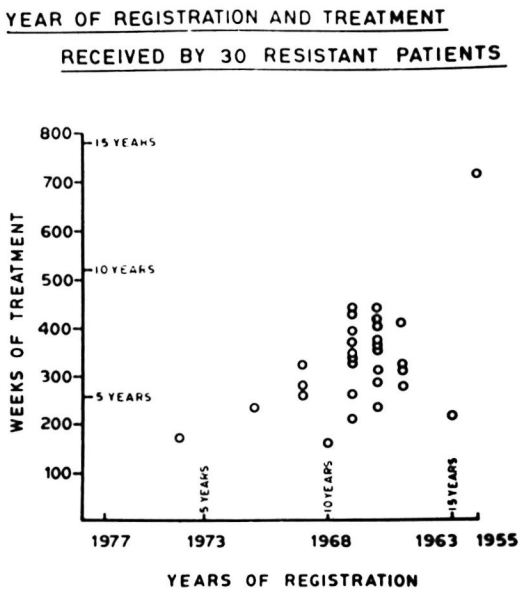
## DISCUSSION

In a study conducted in Malaysia ([2]), there was no discrepancy between clinical-

* Editor's Note: Other workers would, by their conventional usage, term this "intermediate resistance" and would use "partial resistance" to refer to strains multiplying in mice fed 0.0001% w/w dietary dapsone but inhibited by 0.01% and 0.001% w/w dapsone in the diets.—RCH

TABLE 6. *Regularity of attendance of the 33 resistant patients.*

| Regularity | Male | Female | Total |
|---|---|---|---|
| 75% and more | — | 2 | 2 |
| 50%–74% | 15 | 5 | 20 |
| 49% and below | 4 | 4 | 8 |
| Data incomplete | 3 | — | 3 |
| Total | 22 | 11 | 33 |




THE FIGURE. Chart showing relationship between year of registration and weeks of treatment received (clinic attendance) of 30 dapsone resistant patients.

ly detected and experimentally confirmed sulfone resistance. It was confined to the lepromatous form of the disease 5 to 24 years after the institution of sulfone treatment. Of the 100 resistant cases, 25 had histoid leprosy.

In the present study, confirmation by mouse foot pad studies of clinically suspected dapsone resistance was obtained in 24 of 26 patients from whom biopsies were taken (Table 4c). A high correlation between clinical diagnosis and experimental proof was obtained. All were clinically lepromatous leprosy, and there were none with histoid leprosy in this group of patients. Resistance to dapsone in these 28 patients occurred from 4 to 15 years from the initiation of dapsone therapy (The Figure). Among the 1431 patients, there are 33 dapsone resistant patients, giving a crude prevalence rate of 2.3%.

Before the commencement of this study, nine cases of secondary resistance included in the study had been detected in the control area during the period 1972 to February 1978. These were patients referred by the medical officers from time to time during the routine course of work, on clinical suspicion. However, when a carefully planned search was made, 24 cases were detected in one year. Further, there is a very close relationship between the DDS resistant patients clinically suspected and those confirmed by laboratory studies. Thus the criteria used in this study may form useful guidelines in control areas where laboratory facilities for mouse foot pad work are not available.

One patient was found to harbor dapsone resistant organisms within 4 years of starting therapy. After initial clinical and bacteriological improvement with dapsone, this patient later had reactivation of old lesions and a high bacillary index.

A greater awareness of the problem of secondary resistance on the part of medical officers, constant vigilance to detect the emergence of relapse or reactivation of the disease, and the adoption of strict criteria for evaluating and monitoring lepromatous and borderline lepromatous patients should help in early detection of dapsone resistance among them.

## SUMMARY

A preliminary study of the prevalence rate of secondary dapsone resistance among leprosy patients in Gudiyattam Taluk, Tamil Nadu, was undertaken. During the period March 1978 to February 1979, there were 1580 lepromatous and borderline lepromatous patients considered to be at risk of developing secondary resistance. Of them, 1431 were examined clinically, and reactivation and/or relapse was found in 114 patients. Of these, 46 had a bacteriological index of 2.00 and more. Skin biopsies were taken from 26 patients for mouse foot pad studies. Resistance to dapsone at the highest drug concentration was found in 22 and partial resistance in two patients. The organisms from two patients were sensitive to dapsone. Twenty patients were not biopsied because they had been absent from treatment for significant periods of time. These patients are now under observation.

Prior to this study, nine patients had been confirmed to have dapsone resistance in the control area, and during the present study 24 additional patients with secondary resistance have so far been detected. Thus 33 patients with dapsone resistance among the 1431 patients examined yields a crude prevalence rate of 2.3% in Gudiyattam Taluk.

## RESUMEN

Se efectuó un estudio, preliminar, sobre la prevalencia de resistencia secundaria a la dapsona entre los pacientes con lepra de Gudiyattam Taluk, Tamil Nadu. Durante el periodo de Marzo de 1978 y Febrero de 1979, hubieron 1580 pacientes lepromatosos y lepromatosos limítrofes (''borderline lepromatous'') considerados en riesgo de desarrollar resistencia secundaria a la dapsona. De ellos, 1431 fueron examinados clínicamente encontrándose reactivación o recurrencia en 114 pacientes. De éstos, 46 tuvieron un índice bacteriológico de 2.0 o mayor. De 26 pacientes se tomaron biopsias para estudios en los cojinetes plantares del ratón. En 22 casos se encontró resistencia a la dosis más alta de dapsona y en dos pacientes, una resistencia parcial. Los microorganismos aislados de dos pacientes fueron sensibles a la dapsona. En 20 casos no se tomaron biopsias porque los pacientes habían estado sin tratamiento por periodos prolongados de tiempo. Estos pacientes se encuentran actualmente en observación.

Antes de este estudio, se había confirmado que 9 pacientes tenían resistencia a la dapsona en el área geográfica arriba mencionada. Durante el presente estudio se han detectado, hasta ahora, 24 pacientes más con resistencia secundaria a la dapsona. De esta manera, 33 pacientes con resistencia a la dapsona entre los 1431 pacientes examinados, dan una prevalencia aproximada del 2.3% en Gudiyattam Taluk.

## RÉSUMÉ

On a entrepris une étude préliminaire du taux de prévalence de résistance secondaire à la dapsone chez des malades de la lèpre du Gudiyattam Taluk, dans le Tamil Nadu. Au cours de la période s'étendant de mars 1978 à février 1979, on a considéré que 1580 malades atteints de lèpre lépromateuse ou lépromateuse borderline étaient exposés au risque de développer une résistance secondaire. Parmi ces malades, 1431 ont été examinés cliniquement, et on a observé chez 114 d'entre eux une réactivation, une récidive, ou ces deux phénomènes à la fois. Parmi ces malades, 46 présentaient un index bactériologique de 2.00 et plus. Des biopsies cutanées ont été prélevées chez 26 individus malades, en vue de procéder à des inoculations dans le coussinet plantaire de la souris. Chez 22 malades, on a conclu à une résistance à la dapsone à la concentration la plus élevée du médicament, alors qu'une résistance partielle a été découverte chez deux autres malades. Les organismes provenant de deux derniers malades étaient sensibles à la dapsone. Les biopsies n'ont pu être pratiquées chez 20 malades, par suite de leur absence au traitement pendant des périodes de temps prolongées. Ces malades ont maintenant été repris en observation.

Avant cette étude, une résistance à la dapsone avait été confirmée chez 9 malades de cette zone de traitement, alors qu'au cours de la présente étude, 24 malades supplémentaires présentant une résistance secondaire ont été jusqu'à présent découverts. Dès lors, 33 malades avec résistance à la dapsone ayant été dépistés parmi 1431 malades examinés, on conclut que le taux de prévalence brut est de 2,3% en Gudiyattam Taluk.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