Primary and Secondary Dapsone Resistance of *M. leprae* in Martinique, Guadeloupe, New Caledonia, Tahiti, Senegal, and Paris Between 1980 and 1985[1]

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The resistance of *Mycobacterium leprae* to diaminodiphenylsulfone (dapsone, DDS) was first reported by Pettit and Rees in 1964 ([8]) less than 4 years after the development by Shepard of the mouse foot pad model ([10]). Since then, there have been many subsequent reports of acquired and primary dapsone resistance from different parts of the world, of which a well-documented review has been made recently by Ji ([3]). Secondary dapsone resistance appears common among patients who relapse after long-term (5 years or more) dapsone monotherapy, and is usually of high degree ([1–7]). Conversely, primary dapsone resistance that is observed in untreated patients is usually of low degree ([3, 9]). Because *M. leprae* strains with a high degree of dapsone resistance are able to grow in the presence of a dapsone concentration that corresponds to the serum level achieved in patients treated with 100 mg dapsone per day, the resistance of these strains is highly significant from a therapeutic point of view.

Although *M. leprae* strains with low-degree dapsone resistance are definitely different from fully sensitive strains ([11]), there are doubts about the therapeutic significance of their resistance. A patient harboring such a strain is likely to respond favorably to a 100 mg daily dose of dapsone but the favorable response could well be short lived ([6, 12]).

This paper provides information on dapsone resistance observed between 1980 and 1985 in *M. leprae* strains isolated from patients of the French West Indies (Martinique and Guadeloupe), New Caledonia, Tahiti, Senegal, and also from overseas patients hospitalized in Paris. It confirms what has been observed in other parts of the world, and indicates that dapsone resistance, especially primary resistance, is a threatening worldwide problem.

MATERIALS AND METHODS

From 1 January 1980 onward it was decided that all patients with active multibacillary leprosy, either new cases or relapses, from Martinique and Guadeloupe should be biopsied and their biopsies sent by air freight in special wet-ice containers to Paris for dapsone-sensitivity testing by mouse foot pad inoculation according to Shepard's technique ([10]). Thereafter, biopsies from patients from New Caledonia and Tahiti were also received in Paris, as well as biopsies from overseas patients hospitalized in Paris. Furthermore, during the years 1983–1985 a survey of primary dapsone resistance was conducted in the Cap Vert area of Senegal.

Table 1 gives the type (new cases or relapses) and the geographical distribution of

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the patients whose biopsies were received in the Paris laboratory from 1980 to 1985. A total of 415 biopsies was received, 280 inoculated and only 234 infective. Among the latter, 133 were from new cases and 101 from relapsed cases of leprosy. A relapse case of multibacillary leprosy was defined as clinically and bacteriologically active leprosy in a patient who is on prescribed dapsone therapy for at least 5 years. Other patients, mainly totally untreated cases, were considered as new cases.

Epidemiological data are available from Guadeloupe patients. The 31 biopsies from new cases were taken from the 56 new cases of lepromatous leprosy detected between 1980 and 1985. The 33 biopsies from relapsed cases were taken from the 41 relapses that occurred from the average 663 lepromatous patients who had been treated for at least 5 years and who were still living. Some patients eligible for biopsy were not biopsied because they had been put under treatment with combined chemotherapy with rifampin before a biopsy could be taken.

To limit as much as possible the number of mouse inoculations followed by no growth, biopsies received in Paris were not inoculated when: a) $<5 \times 10^4$ acid-fast bacilli (AFB) per ml were recovered, b) the morphological index (MI) was $<10\%$, and c) the length of time elapsed between the collection of the biopsy and its receipt in Paris was more than 14 days.

The mouse foot pad inoculation for dapsone-sensitivity testing was performed directly from all biopsies according to standard procedure ([7, 10]). In brief, 5×10^3 AFB were inoculated into the left hind foot pad of four groups of eight mice. The first group acted as an untreated control, being fed a drug-free diet, and the other three groups were administered diets containing dapsone in concentrations of 0.0001, 0.001, and 0.01 dapsone per 100 g, respectively. Harvests from drug-treated mice were always performed immediately after harvests from untreated control mice had yielded unmistakable evidence that the organisms had multiplied (10^5 AFB or more per foot pad). Therefore, groups of three control mice had to be harvested first at month 7 and, if there was no evidence of multiplication at the first harvest, at month 10 and, if no evidence of multiplication at the second harvest, at month 12. However, due to the increased workload in the laboratory, the first harvest was frequently done at month 10 or even later (Tables 5 and 7). The possible consequences of the late harvests will be discussed later. If there was evidence of multiplication, five mice from each treated group of mice were harvested, beginning with those treated with the lowest concentration of dapsone. If there was no multiplication in the control mice, *M. leprae* were considered to have been noninfective for the mouse. A strain of *M. leprae* was considered resistant to a given concentration of dapsone when at least one mouse fed with that concentration yielded at least 10^5 AFB per foot pad.

TABLE 1. *Number of biopsies received from 1980 to 1985 in Paris laboratory for foot pad inoculation, inoculated, and found infective.*

Place	Biopsies		
	Received	Inoculated	Infective
	New cases		
Guadeloupe	31	31	29
Martinique	32	21	20
New Caledonia	30	26	19
Senegal	50	41	39
Paris	23	18	19
Tahiti	10	6	2
Others	5	5	5
Subtotal	181	148	133
	Relapse cases		
Guadeloupe	33	29	18
Martinique	131	71	58
New Caledonia	18	14	10
Senegal	7	5	5
Paris	25	11	8
Tahiti	11	0	0
Others	9	2	2
Subtotal	234	132	101
Totals	415	280	234

RESULTS

Dapsone resistance in relapse cases. From relapsed cases of lepromatous leprosy, 101 infective strains were isolated. Table 2 shows the results of dapsone-susceptibility testing of these strains according to the patients' geographical distribution. Among them, 18 (17.8%) were fully sensitive to dapsone, sug-

TABLE 2. *Dapsone susceptibility of* M. leprae *isolated from relapse cases.*

Place	Total infective	Susceptibility to dapsone			
		Sensitive	Resistant to (g % in diet)		
			0.0001	0.001	0.01
Guadeloupe	18	1	4	5	8
Martinique	58	10	6	13	29
New Caledonia	10	2	1	2	5
Paris	8	3	2	1	2
Others	7	2	1	1	3
Total	101	18	14	22	47
	100%	17.8%	13.9%	21.8%	46.5%

gesting that in these cases the relapses were due to patient noncompliance in taking prescribed dapsone therapy. Of the remaining 83 strains, 14 (13.9% of total infective strains) were of low-degree, 22 (21.8%) were of intermediate-degree, and 47 (46.5%) were of high-degree dapsone resistance. Therefore, the majority (68.3%) of the strains isolated from relapsed cases were of intermediate- or high-degree dapsone resistance, as already pointed out by many other workers ([1–7]).

Since biopsies from New Caledonia, Paris, and other places were limited in number, only the biopsies from Guadeloupe and Martinique may be taken for analysis of the differences related to geographical origin. No significant differences were observed in dapsone susceptibility between Guadeloupe and Martinique.

Table 3 gives the distribution of the *M. leprae* strains according to their degree of dapsone resistance and the duration of dapsone therapy prescribed for the patients. Since all of the patients were treated only with dapsone monotherapy, the duration of prescribed dapsone therapy corresponds to the length of time that elapsed between the commencement of treatment and the detection of relapse. Data presented in Table 3 suggest that the longer the prescribed dapsone therapy, the more frequent the high-degree dapsone resistance. However, fully dapsone-sensitive strains were isolated from 12 out of 73 patients having had >15 years of prescribed dapsone therapy.

TABLE 3. *Dapsone susceptibility of* M. leprae *in relapse cases of multibacillary leprosy according to duration of previously prescribed dapsone therapy.*

Susceptibility to dapsone (g %)	Total	Duration of dapsone therapy	
		<15 yrs	>15 yrs
Sensitive	18	6	12
Resistant to 0.0001%	14	6	8
Resistant to 0.001%	22	8	14
Resistant to 0.01%	47	8	39[a]
Total	101	28	73

[a] $p < 0.05$.

The reason for the strains having kept full sensitivity or having a low degree of resistance to dapsone despite long-term prescribed dapsone therapy is unclear, although very irregular treatment is the most probable explanation. However, the changes in dapsone resistance of two strains successively isolated from two different patients, summarized in Table 4, deserve careful attention. Patient no. 1, who was prescribed dapsone for >32 years before the occurrence of relapse, had at the time of relapse in March 1982 a strain with low-degree dapsone resistance. Because he refused initial hospitalization and multidrug therapy, he was again given daily 100 mg dapsone alone. Three years later, his condition deteriorated and a *M. leprae* strain with high-degree dapsone resistance was isolated. Patient no. 2 was also prescribed >30 years of dapsone alone before he relapsed in January 1984 with a fully dapsone-sensitive strain. Because he, too, refused initial hospitalization and multidrug therapy, he was given dapsone alone. One year later, in April 1985, his condition had not improved and a strain of low-degree dapsone resistance was isolated. In both of these patients, one wonders whether the increase in dapsone resistance between the first and second biopsies is due to the selection of more resistant organisms

TABLE 4. *Detailed results of susceptibility testing of* M. leprae *isolated from two successive biopsies of two different patients.*

Patient no.	Date of biopsy	AFB/mg (MI)	No. AFB inoculated	No. AFB harvested/foot pad				
				Date	Controls	DDS		
						0.0001%	0.001%	0.01%
1	Mar. 1982	7×10^3 (25%)	4×10^2	Feb. 1983	1×10^5	$<2 \times 10^4$	$<2 \times 10^4$	$<2 \times 10^4$
					2×10^5	8×10^4	$<2 \times 10^4$	$<2 \times 10^4$
					3×10^5	2×10^5	$<2 \times 10^4$	$<2 \times 10^4$
						5×10^5	$<2 \times 10^4$	$<2 \times 10^4$
						9×10^5	$<2 \times 10^4$	$<2 \times 10^4$
	June 1985	9×10^5 (23%)	5×10^3	Apr. 1986	5×10^5	ND[a]	2×10^5	$<2 \times 10^4$
					7×10^5		3×10^5	8×10^4
					9×10^5		6×10^5	2×10^5
							7×10^5	3×10^5
							7×10^5	4×10^5
2	Jan. 1984	8×10^5 (26%)	5×10^2	Nov. 1984	2×10^5	$<2 \times 10^4$	ND	ND
					5×10^5	$<2 \times 10^4$		
					6×10^5	$<2 \times 10^4$		
						$<2 \times 10^4$		
						$<2 \times 10^4$		
	Apr. 1985	3×10^6 (59%)	5×10^2	Mar. 1986	5×10^5	1×10^5	$<2 \times 10^4$	ND
					1×10^6	2×10^5	$<2 \times 10^4$	
					2×10^6	2×10^5	$<2 \times 10^4$	
						2×10^5	$<2 \times 10^4$	
						7×10^5	$<2 \times 10^4$	

[a] ND = not done.

or to a better adaptation of the strain to grow in the presence of dapsone in the sensitivity testing. If the latter hypothesis is correct, the strain kept the same dapsone susceptibility but the results of the sensitivity test were different because of a better multiplication of *M. leprae* in dapsone-treated mice or a later harvest. To assess the possible role of a later harvest, the results of all dapsone-sensitivity tests performed on *M. leprae* from previously treated patients were examined in relation to the time of harvests. As shown in Table 5, the dapsone-susceptibility results obtained when harvests were performed earlier than 11 months after inoculation were not significantly different from those obtained when harvests were performed on month 11 or later from the strains classified as dapsone sensitive or for those strains of low-, intermediate, or high-degree dapsone resistance (χ^2 test used).

Available epidemiological data provide the yearly incidence of secondary dapsone resistance in Guadeloupe. Of the 41 relapses diagnosed between 1980 and 1985 among the mean number of 663 lepromatous patients on prescribed dapsone therapy for >5 years, 33 were biopsied. Four biopsies contained $<5 \times 10^4$ bacilli and were not inoculated into the mouse foot pad. Eleven that contained enough bacilli were not infective. The 18 biopsies that were infective yielded 1 dapsone-sensitive strain and 17 dapsone-resistant strains. The 15 biopsies that failed to yield growth in the mouse foot pad or that were not inoculated because of too low a number of AFB may be assumed to contain fully dapsone-sensitive *M. leprae*. Therefore, from the 33 biopsies we can estimate that 17 (52%) contained dapsone-resistant and 16 (48%) dapsone-sensitive *M. leprae*. If the proportion of dapsone-resistant and dapsone-sensitive strains was similar among the remaining 8 relapse cases that were not biopsied, 5 additional strains of dapsone-resistant *M. leprae* should be added to the 17 that were isolated, giving a total of 22 dapsone-resistant strains in 6 years (1980–1985) from a mean number of 663 lepromatous patients. Therefore, the yearly incidence of secondary dapsone resistance in Guadeloupe can be estimated to be

$$\frac{22 \times 100}{6 \times 663} = 0.55\%.$$

TABLE 5. *Dapsone susceptibility of* M. leprae *harvested from previously treated patients in relation to time of harvest.*

Harvest time (mos.)	Total strains		Susceptibility to dapsone			
	No.	%	Sensitive	Resistant to (g % in diet)		
				0.0001	0.001	0.01
7	2	2	1	1	—	—
8	2	2	1	—	—	1
9	7	7	1	—	1	5
10	40	39	7	7	9	17
11	15	15	3	2	5	5
12	29	29	4	3	4	18
13	6	6	1	1	3	1
Total	101	100	18	14	22	47
Mean (mos.) = 10.7 ± 0.3						

Primary dapsone resistance. From new cases of leprosy, 133 infective strains were isolated. Table 6 shows the results of dapsone-susceptibility testing of these strains according to the patients' geographical distribution. Among them, 81 (61%) were fully susceptible and 52 (39%) harbored some degree of dapsone resistance; 37 (28%) being of low-, 8 (6%) of intermediate-, and 7 (5%) of high-degree dapsone resistance. Dapsone resistance of *M. leprae* isolated from patients considered as previously untreated was evenly distributed at a similar rate, and a low degree of dapsone resistance was prominent in all of the places. None of the strains isolated from untreated patients from Guadeloupe and Martinique were of high-degree dapsone resistance; whereas some strains with such high resistance were isolated from all other places. Since the patients from Guadeloupe and Martinique were those with the most precise clinical history, one may suppose that some so-called "untreated" patients from places other than Guadeloupe and Martinique had, in fact, received prior dapsone treatment. This could have occurred, in particular, for several patients in Paris who came from overseas. Despite that possibility, the proportion of resistant cases among new cases of leprosy was significantly lower than among the relapsed cases, and the grade of resistance was also quite lower. The survey on primary dapsone resistance conducted during 1983–1985 in the Cap Vert area of Senegal yielded a prevalence rate of primary dapsone resistance at least as high as in other places, emphasizing the worldwide problem of primary dapsone resistance, whatever the prevailing network of leprosy control.

Finally, the results of primary dapsone resistance were examined in relation to the time when harvests were performed. As shown in Table 7, when harvests were performed before 11 months, the results were significantly different from those obtained when harvests were performed on month 11 or later. The differences are significant

TABLE 6. *Dapsone susceptibility of* M. leprae *strains isolated from new cases.*

Place	Total infective	Susceptibility to dapsone			
		Sensitive	Resistant to (g % in diet)		
			0.0001	0.001	0.01
Guadeloupe	29	19	10	0	0
Martinique	20	8	10	2	0
New Caledonia	19	14	2	1	2
Senegal	39	27	7	3	2
Paris	19	9	5	2	3
Others	7	4	3	0	0
Total	133	81	37	8	7
	100%	61%	28%	6%	5%

TABLE 7. *Dapsone susceptibility of* M. leprae *harvested from untreated patients in relation to time of harvest.*

Harvest time (mos.)	Total strains		Susceptibility to dapsone			
	No.	%	Sensitive	Resistant to (g % in diet)		
				0.0001	0.001	0.01
8	7	5	5	2	—	—
9	10	8	8	2	—	—
10	51	38	39	7	2	3
11	35	26	20	8	3	4
12	25	19	8	14	3	—
13	5	4	1	4	—	—
Total	133	100	81	37	8	7
Mean (mos.) = 10.6 ± 0.2						

for the distribution of the strains as dapsone sensitive or resistant as well as for the distribution of the dapsone-resistant strains as of low or of higher degrees of resistance (χ^2 test used). They tend to indicate either that primary dapsone-resistant *M. leprae* strains multiplied more slowly in mice fed with a diet containing dapsone than a dapsone-free diet, or that they contained a mixture of dapsone-sensitive and dapsone-resistant organisms.

DISCUSSION

The most important findings reported in this paper are that 82% of patients who relapsed when on prescribed long-term dapsone monotherapy harbored dapsone-resistant *M. leprae* which were mainly of high degree, and that 39% of patients with newly discovered lepromatous leprosy also harbored dapsone-resistant *M. leprae* which were, in contrast, mainly of low degree. The high frequency of dapsone resistance did not result from a bias in the selection of patients because all eligible cases, at least in Guadeloupe and Martinique, were biopsied with the only exception of those who were, by error, put on combined treatment with rifampin before a biopsy could be taken. Since the results observed in Guadeloupe and Martinique were similar to those from Senegal, New Caledonia, Tahiti, and Paris, where a bias in the selection of patients cannot be excluded, the high frequency of dapsone resistance is likely to reflect the actual situation. The fact that our data were consistent with all data from other places in the world ([3]) is also indirect evidence of their value.

One possibility of error in our results could be the concentration of dapsone in the mouse diet. If the actual concentration of dapsone was lower than indicated, some sensitive strains could have grown in the mice fed a dapsone-containing diet and be considered as resistant. In fact, all batches of the dapsone-containing diets were not systematically controlled for their dapsone content but the dapsone levels in the blood of mice were always, when measured, in the normal range ([2]). Thus, our data on dapsone resistance can be considered as accurately reflecting the actual situation in those places where the study was conducted.

A point of concern is the precise meaning of reported data on secondary dapsone resistance. Secondary dapsone resistance was being studied yearly in Guadeloupe among all patients who had clinical and bacteriological relapse. In studies conducted by other workers ([1, 6]), secondary dapsone resistance was mainly studied for a limited duration of time among all, or a sample of, smear-positive patients with and without clinically active disease. Comparison is, therefore, difficult between data from Guadeloupe and data from other parts of the world, with the exception of data giving the annual incidence of secondary resistance, the range of which being 0.1% to 3% ([3]). With the relatively low incidence of 0.55%, Guadeloupe can be considered in an intermediate position. An interesting finding is the positive relationship between the degree of dapsone resistance and the length of prescribed dapsone therapy, a finding that indirectly supports the commonly accepted view ([3]) of step-wise dapsone resistance. It

also indirectly supports the commonly accepted view concerning primary dapsone resistance, which would result from the infection of naive subjects by *M. leprae* from patients who have relapsed 10–15 years ago. Because those who relapsed first were those who had acquired low-degree dapsone resistance, in relation to low-dosage dapsone treatment and poor compliance ([3]), the first dapsone-resistant *M. leprae* to be transmitted should have been those with low-degree dapsone resistance. If that is actually the case, an increase in the degree of primary dapsone resistance could occur in the future, unless standard combined chemotherapy is applied as recommended by international organizations ([13]).

All of the data we have collected in the 6 years of this study do not give an answer to the question of the clinical and biological meaning of primary dapsone resistance. Because of the usual low degree of primary dapsone resistance, it is likely that the majority of strains of primary resistance as well as totally sensitive strains will respond to dapsone given at full dosage. But it is also possible that some strains that appear to have low-degree dapsone resistance do not respond well to dapsone treatment because they are not as sensitive as they seem to be. That possibility is not fully hypothetical when we consider the strains isolated from our two patients who relapsed after more than 30 years of prescribed dapsone therapy. These strains appeared much less resistant at first isolation than at second isolation a few months later. Between both isolations, the patients were given dapsone alone which could have been responsible for a rapid increase of the degree of resistance. Of course, these strains were isolated from already treated patients and not from newly diagnosed ones, and it may not be possible to compare strains with primary resistance to strains with secondary strains.

Our findings that the later the harvest the more frequent the dapsone resistance among *M. leprae* strains isolated from untreated patients raises a number of questions. Is that phenomenon due to a slower growth of primary dapsone-resistant strains in the presence of dapsone because these strains have not yet recovered their full capacity to express their resistance, or because they contained a mixture of dapsone-sensitive and dapsone-resistant organisms? It is not possible to decide whether one of the two or both explanations are correct. That the proportion of sensitivity tests with partial resistance (only some of the five mice harvested were positive) has been similar among strains from previously treated patients and untreated patients, and because there was no relation between time of harvest and frequency of resistance with strains isolated from previously treated patients, tend to indicate that the right explanation may not be a mixture of sensitive and resistant organisms.

If primary dapsone-resistant strains grow at first isolation, less well in the presence of dapsone than in the absence of dapsone, one may fear that the prevalence and the degree of primary dapsone resistance are still higher than those observed when dapsone-susceptibility testing is done according to the official rules, which indicate that the harvest should be made as soon as control mice are positive. That hypothesis could be easily tested by repeating the dapsone-sensitivity testing of *M. leprae* isolated from untreated patients and harvested from mice with the highest dapsone concentration that permits growth.

In practice, it should be emphasized that the time of harvests should be strictly standardized, as already pointed out by specialists ([3]), in order to compare data from different laboratories. As far as we are concerned, we are now working to have the first harvest done on month 7 and in case of no growth, the second on month 10.

SUMMARY

Primary and secondary dapsone resistance were studied among lepromatous patients living in Martinique, Guadeloupe, New Caledonia, Tahiti, Senegal, and Paris. Four hundred fifteen biopsies were taken from clinically active and bacteriologically positive (bacterial index > 2) patients in the 6-year period of 1980–1985. Among these, 280 biopsies that contained 5×10^4 acid-fast bacilli per ml with a morphological index of at least 0.10 were inoculated into the mouse foot pad, and 229 harbored infective *Mycobacterium leprae*. Among the 129 infective *M. leprae* isolated from new cases, 54% had some degree of dapsone resistance, a low degree being prominent in

all cases. Among the 100 infective *M. leprae* isolated from relapsed cases, 79% had a high or an intermediate degree of dapsone resistance. The annual incidence of secondary dapsone resistance was estimated to be about 0.55% in Guadeloupe.

RESUMEN

Se estudió la resistencia primaria y secundaria a la dapsona entre los pacientes de la Martinica, Guadalupe, Nueva Caledonia, Taiti, Senegal y Paris. Durante el periodo de 6 años comprendido entre 1980 y 1985, se tomaron 415 biopsias de pacientes clinicamente activos y bacteriológicamente positivos (indice bacteriológico > 2). Entre éstas, 280 biopsias que contenían 5×10^4 bacilos por ml y un índice morfológico de cuando menos 0.1, fueron inoculados en la almohadilla plantar del ratón. Doscientos veintinueve casos tuvieron *Mycobacterium leprae* infectivos. Entre las 129 muestras con *M. leprae* infectivos, aislados de casos nuevos, el 54% mostró algún grado de resistencia a la dapsona, predominando un bajo grado de resistencia en todos los casos. Entre las 100 muestras infectivas de *M. leprae* aisladas de casos de recaídas, el 79% mostró un grado alto o intermedio de resistencia a la dapsona. En la Isla de Guadalupe, la incidencia anual de resistencia secundaria a la dapsona se estimó cercana al 0.05%.

RÉSUMÉ

On a étudié la résistance primaire et la résistance secondaire à la dapsone chez des malades lépromateux vivant en Martinique, à la Guadeloupe, en Nouvelle-Calédonie, à Tahiti, au Sénégal et à Paris. On a prélevé 415 biopsies chez des malades cliniquement actifs et bactériologiquement positifs (index bactérien > 2), pendant une période de 6 ans s'étendant de 1980 à 1985. Parmi ces biopsies, on en a choisi 280 qui contenaient 5×10^4 bacilles acido-résistants par ml, avec un index morphologique d'au moins 0,10. Ces biopsies ont été alors inoculées dans le coussinet plantaire de la souris. On a constaté que 229 de ces biopsies contenaient des *Mycobacterium leprae* infectifs. Parmi les 129 souches de *M. leprae* isolées à partir de nouveaux cas, 54% présentaient un certain degré de résistance faible à la dapsone. Parmi 100 souches infectieuses de *M. leprae*, isolées de récidives, 79% présentaient un degré élevé ou intermédiaire de résistance à la dapsone. L'incidence annuelle de résistance secondaire à la dapsone a été estimée à 0,55% en Guadeloupe.

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