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The THELEP Controlled Clinical Drug Trials*,**

Subcommittee on Clinical Trials of the Chemotherapy of Leprosy (THELEP)***
Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

Ten years ago, when the THELEP program was conceived ([4]), it was already clear that efforts to control leprosy by treating the infectious patients in the community were failing; patients could not be maintained on treatment for the long duration of dapsone monotherapy required, and the frequency of dapsone-resistant relapse was increasing. It was clear that treatment by regimens composed of two or more drugs, each acting by a different antimicrobial mechanism, would prevent relapse with dapsone-resistant *Mycobacterium leprae*; however, unless the combined regimens led also to early "cure," employment of the regimens appeared unlikely to increase the effectiveness of programs of leprosy control based on case-finding and treatment. Only regimens that were effective if administered for a limited time, the termination of which would not be followed by a high frequency of relapse, might be expected to lead to improved case-holding. Persistence of viable, drug-susceptible *M. leprae* [persisting organisms or persisters ([14])] had already been demonstrated after many years of monotherapy with dapsone or rifampin ([15, 16]), and after combined chemotherapy with rifampin and dapsone ([2]), and it was feared that, after the therapy had been withdrawn, persisting *M. leprae* would cause relapse of a large proportion of patients.

At that time, a central issue in attempting to improve chemotherapy of leprosy was whether administration of drugs in combination could reduce either the number of patients haboring persisting organisms, or the numbers of persisting *M. leprae* in individual patients, thereby diminishing the risk of relapse following cessation of treatment. To conduct clinical trials in which chemotherapy of patients with lepromatous leprosy was deliberately stopped and relapse rates subsequently measured appeared

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** Many of the data included in this report are to be published separately in greater detail.

*** Members of the THELEP Clinical Trials Subcommittee are: Dr M. J. Colston, National Institute for Medical Research, London, U.K.; Dr G. A. Ellard, National Institute for Medical Research, London, U.K.; Dr C. A. P. Ferracci, Institut Marchoux, Bamako, Mali; Dr J. H. Grosset, Faculte de Medecine Pitie-Salpêtrière, Paris, France; Dr G. Grossetete, Institut Marchoux, Bamako, Mali; Dr C. G. S. Iyer, Central Leprosy Teaching and Research Institute, Chingleput, South India (deceased); Dr R. R. Jacobson, National Hansen's Disease Center, Carville, Louisiana, U.S.A.; Dr Ji Baohong, World Health Organization, Geneva, Switzerland; Dr Kyaw Lwin, Ministry of Health, Rangoon, Burma; Dr D. L. Leiker, Royal Tropical Institute, Amsterdam, The Netherlands; Dr L. Levy, Hebrew University–Hadassah Medical School, Jerusalem, Israel; Dr S. K. Noordeen, World Health Organization, Geneva, Switzerland; Dr S. R. Pattyn, Prince Leopold Institute for Tropical Medicine, Antwerp, Belgium; Dr J. M. H. Pearson, Dhoolpet Leprosy Research Centre, Hyderabad, India; Dr R. J. W. Rees, National Institute for Medical Research, London, U.K.; Dr H. Sansaricq, World Health Organization, Geneva, Switzerland; Dr P. S. Seshadri, Central Leprosy Teaching and Research Institute, Chingleput, South India; Dr J. K. Seydel, Borstel Research Institute, Borstel, Federal Republic of Germany; Dr C. C. Shepard, Centers for Disease Control, Atlanta, Georgia, U.S.A. (deceased); Dr M. F. R. Waters, Hospital for Tropical Diseases, London, U.K.

Also participating in this study were H. Ouologuem, Institut Marchoux, Bamako, Mali; M. N. Padma and S. Balakrishnan, Central Leprosy Teaching and Research Institute, Chingleput, South India; D. H. McRae, Centers for Disease Control, Atlanta, Georgia, U.S.A.; A. C. McDougall, Slade Hospital, Oxford, U.K.; P. Christie, I. Mondavia, H. Morgan, H. Shears and M. Silver, Laboratory for Leprosy and Mycobacterial Research, National Institute for Medical Research, London, U.K.; and R. D. McDermott and G. R. F. Hilson, Department of Medical Microbiology, St George's Hospital Medical School, London, U.K. J. L. Duppenthaler, World Health Organization, Geneva, Switzerland, provided statistical consultation throughout the trials and M. Anker, World Health Organization, performed the statistical analyses.

unethical; relapse rates were expected to be unacceptably high, as a consequence of the ubiquity of persisters. Therefore, the THELEP Planning Committee could not undertake to measure the risk to patients presented by the persisting *M. leprae*. On the other hand, controlled clinical trials could be undertaken among patients with lepromatous leprosy to examine the efficacy of various combined drug regimens in reducing the proportions of patients harboring persisters, or the numbers of persisting *M. leprae* harbored by patients.

At its first meeting, in April 1977, the THELEP Scientific Working Group decided to mount controlled clinical trials among previously untreated patients with lepromatous leprosy at Bamako and Chingleput, in order to compare the proportions of patients treated by each regimen in whose skin biopsy specimens viable *M. leprae* could be detected at intervals after beginning treatment ([9]). Six regimens were selected for study: In Bamako, A_2: rifampin, prothionamide and dapsone, in daily doses of 600, 500, and 100 mg, respectively, for two years; C: rifampin, in a single initial dose of 1500 mg, and dapsone, 100 mg daily for two years; E_2: rifampin, 900 mg once weekly, and prothionamide, 500 mg daily for the first three months, together with dapsone, 100 mg daily for two years; and in Chingleput, A_1: rifampin, clofazimine and dapsone, in daily doses of 600, 100, and 100 mg, respectively, for two years; C: as for Bamako; D_1: rifampin, in a single initial dose of 1500 mg, clofazimine, in a daily dose of 100 mg for the first three months, and dapsone, 100 mg daily for two years ([9]).

Admission of patients was begun during the latter half of 1978, and the last patients were recruited during the latter half of 1983; by this time, 116 patients had been admitted to the trial in Chingleput and 99 into that at Bamako. Intensive study of the 215 patients with previously untreated lepromatous leprosy has yielded considerable information with respect to the characteristics of the patients observed before treatment was instituted, the prevalence of primary resistance to dapsone, and the frequency with which persisting *M. leprae* have been detected.

The patients recruited into the two trials and the methods employed in the trials are the following ([9]): In brief, patients with LL, LI or BL leprosy were recruited who denied prior treatment, and in whose urine dapsone and its metabolites were not detectable. The patients' disease was classified clinically, multiple smears of slit-skin scrapings were examined for measurement of the bacterial index (BI) ([5]), and skin-biopsy specimens were obtained and air-shipped on wet ice to the U.K. In the Department of Medical Microbiology, St. George's Hospital Medical School, London, the fresh specimens were weighed, the numbers of *M. leprae* counted, and the susceptibility of the organisms to dapsone measured. Histopathological examination, including Ridley-Jopling classification ([7]) and measurement of the logarithmic biopsy index (LIB) ([6]), was performed on a fixed specimen in the Department of Dermatology, The Slade Hospital, Oxford.

Periodically during treatment, patients were examined and interviewed for evidence of ENL and adverse reactions to the drugs. At much the same intervals, specimens of urine and blood were obtained for laboratory investigation. Smears of slit-skin scrapings were prepared and examined every three months. At intervals of 3, 12 and 24 months after beginning treatment by one of the three regimens under study at each treatment center, biopsy specimens were obtained from the same skin lesions and shipped fresh on wet ice to the National Institute for Medical Research (NIMR), London, where the largest possible number of organisms, to a maximum of 10^5 per foot pad, was inoculated into each hind foot pad of thymectomized and irradiated (TR) mice, usually eight per specimen, in the search for persisting *M. leprae*.

Characteristics of the patients recorded before treatment ([11]). As shown in Table 1, no significant difference of patient-age was found among regimens or between centers. Only male patients had been recruited in Bamako; in Chingleput, where only a few female patients were recruited, the proportion of female patients did not differ significantly among the three regimens.

In Table 1 are also shown median initial values of the BI, LIB and logarithm_{10} of the number of AFB per g of biopsy specimen

TABLE 1. *Distribution of patient characteristics by center and regimen.**

Center regimen	Bamako				Chingleput			
	A_2	C	E_2	All	A_1	C	D_1	All
				Age and sex				
Median age	26	26	25	25	29	30	26	29
No. patients	12	44	43	99	39	39	38	116
No. males	12	44	43	99	36	36	33	105
				BI, LIB and LAFBPG				
Median BI	4.8	4.5	4.5	4.7	4.3	4.2	4.4	4.3
No. patients	12	41	38	91	39	39	38	116
Median LIB	5.5	5.3	5.0	5.3	5.6	5.5	5.5	5.5
No. patients	12	44	43	99	39	39	38	116
Median LAFBPG	8.3	8.5	8.4	8.4	8.5	8.3	8.4	8.4
No. patients	12	42	41	95	39	37	35	111
				CLINCLAS (no. patients)				
LL	0	7	7	14	11	8	8	27
LI	12	32	30	74	25	26	29	80
BL	0	5	6	11	3	5	1	9
				HISTCLAS (no. patients)				
LL	1	1	0	2	0	1	0	1
LI	11	37	31	79	38	37	36	111
BL	0	5	9	14	0	1	2	3
Other	0	1	3	4	1	0	0	1

* Patient age did not differ significantly between centers or among regimens within centers. The proportions of male and female patients did not differ significantly among Chingleput regimens. The BIs of Bamako patients were significantly larger than those of Chingleput patients ($p = 0.003$), but no significant differences of the BI among regimens within centers were discerned. The LIB was significantly larger among Chingleput than among Bamako patients, but no significant differences were observed among regimens within centers. No significant differences of LAFBPG were found between centers or among regimens within centers. The proportion of patients with CLINCLAS LL did not differ significantly between centers nor among regimens. The proportion of patients with HISTCLAS BL or "other" was significantly higher among Bamako than among Chingleput patients ($p < 0.01$). No significant difference of the proportion classified BL or "other" was found among regimens within centers.

(LAFBPG). The BI was significantly larger among Bamako than among Chingleput patients, and the LIB was significantly larger among the latter. No significant difference of the LAFBPG was found between the centers, nor of the pretreatment values for BI, LIB and LAFBPG among regimens. As expected, the individual initial values for BI, LIB, and LAFBPG were closely interrelated.

TABLE 2. *Distribution of dapsone-resistant patients and degree of resistance between centers.**

Patient category	No. of patients	
	Bamako	Chingleput
Total	99	116
Susceptible	37	45
Resistant	27	22
0.0001 g %	21	18
0.001 g %	6	4
0.01 g %	0	0
Non-infective	35	49

* The frequency of patients harboring drug-resistant organisms did not differ significantly between centers.

The distribution of patients between treatment centers and among regimens according to clinical classification (CLINCLAS) and histopathological classification (HISTCLAS) is also shown in Table 1. In both centers, the majority of patients were classified LI, and the proportions of patients classified LL, LI or BL did not differ significantly between centers or among regimens within each center. The majority of patients in both centers were also LI by HISTCLAS. Although the proportions of patients classified BL or "other" did not vary significantly among regimens within each center, the proportion of patients with HISTCLAS BL or other was significantly larger in Bamako than in Chingleput.

TABLE 3. *Relationship of dapsone resistance to pretreatment patient characteristics.**

Pretreatment characteristic	Bamako		Chingleput	
	Resistant	Susceptible	Resistant	Susceptible
Median age (years)	26	25	30	25
Median BI	4.7	4.7	4.3	4.3
Median LIB	5.6	5.3	5.4	5.5
Median LAFBPG	8.5	8.4	8.7	8.3
Proportion with CLINCLAS LI	0.74	0.78	0.64	0.73
Proportion with HISTCLAS LI	0.81	0.83	0.95	0.93

* No significant difference of any pretreatment characteristic was found between patients with dapsone-resistant and those with susceptible organisms in either center.

Thus, although some differences among regimens or between centers were observed with respect to the patient characteristics recorded upon admission to the trials, no important differences were recognized, and the various characteristics appear to have been rather uniformly distributed among regimens and between centers by the method of random assignment to regimen employed.

Primary resistance to dapsone ([10, 12]). As shown in Table 2, the susceptibility to dapsone could not be assessed of the strains of *M. leprae* obtained from the pretreatment biopsy specimens of 35 of 99 (35%) Bamako patients and 49 of 116 (42%) Chingleput patients. Organisms recovered from these 84 specimens either failed to multiply to a level $\geq 10^5$ in untreated control mice, or multiplied to a level $\geq 10^5$ in at least one mouse, but failed to multiply in a proportion of control mice significantly greater than 0, so that the failure of these organisms to multiply in dapsone-treated mice could not be taken as evidence of susceptibility to the drug. Although the inocula prepared from these specimens contained viable *M. leprae*, the viable organisms must have represented only a small proportion of the total, so that multiplication occurred in some mice but not in others.

The *M. leprae* recovered from 82 pretreatment specimens, obtained from 37 of 63 (59%) Bamako patients and 45 of 67 (67%) Chingleput patients, multiplied to a level $\geq 10^5$ in a significant number of control mice, and in no mouse administered dapsone in the smallest concentration (0.0001 g dapsone per 100 g mouse diet). The organisms recovered from 39 specimens multiplied to a level $\geq 10^5$ *M. leprae* per foot pad in at least one mouse administered dapsone in the smallest concentration, but in no mouse administered dapsone in the concentration of 0.001 g per 100 g diet. Organisms obtained from 10 specimens demonstrated an intermediate degree of resistance to dapsone, multiplying to a level $\geq 10^5$ per foot pad of at least one mouse administered dapsone in the smallest concentration, and in mice administered the drug in the intermediate concentration, but not in the mice administered dapsone in the largest concentration (0.01 g dapsone per 100 g diet). No

TABLE 4. *Proportions of specimens in which persisting* M. leprae *were detected.*

Duration of treatment (mo)	Bamako regimens			Chingleput regimens			Total	%
	A_2	C	E_2	A_1	C	D_1		
	Number "positive" specimens/total number							
3	0/11	4/42*	4/34	2/37°	4/38⁺	4/35ˣ	18/197	9.1
12	3/9	2/32	3/27	4/32°	2/30	3/32ˣ	17/162	10.5
24	1/7	2/20*	1/17	0/23	3/20⁺	1/22	8/109	7.3
Total (3 + 12 + 24)	4/27 (14.8%)	8/94 (8.5%)	8/78 (10.3%)	6/92 (6.5%)	9/88 (10.2%)	8/89 (9.0%)	43/468	9.2**

*,°,⁺,ˣ One patient is represented in both categories; only 4 of 162 patients represented by more than one specimen were found to harbor persisters on more than one occasion.

** 95% confidence interval (6.59–11.79).

TABLE 5. *Relationships between persistence of* M. leprae *and dapsone resistance, with the data for regimens and centers pooled.*

Duration of treatment (mo)	Degree of resistance to dapsone				Total
	Susceptible	Low	Intermediate	"Non-infective"	
3	3	5	1	9	18
12	7	2	2	6	17
24	5	0	0	3	8
All persisters	15	7	3	18	43
(%)	(34.9)	(16.3)	(7.0)	(41.9)	
All specimens	82	39	10	84	215
(%)	(38.1)	(18.1)	(4.6)	(39.1)	

specimen yielded *M. leprae* capable of multiplying in mice administered dapsone in the largest concentration (the definition of strains demonstrating a high degree of resistance to dapsone). The proportion of patients harboring dapsone-resistant *M. leprae* did not differ significantly among the regimens.

Although it is not possible absolutely to exclude the possibility that some of the patients determined to represent instances of primary resistance to dapsone may actually have concealed previous treatment, such patients, having been treated, responded and subsequently relapsed, might be expected to be older on the average than those patients who had not been previously treated. However, as shown in Table 3, the ages of dapsone-resistant patients did not differ significantly from those of the dapsone-susceptible patients at either center. Moreover, no relationships could be demonstrated between admission order, on the one hand, and age or resistance to dapsone on the other, nor could significant differences be discerned between those patients of either center harboring susceptible *M. leprae* and those harboring strains resistant to dapsone, with respect to BI, LIB, LAFBPG, and the proportions of patients classified clinically or histopathologically as LI.

Persistence of *M. leprae* ([13]). By 31 December 1984, the results of study of 468 biopsy specimens—about 75% of results expected from each treatment center—had been obtained. These results were derived from the study of skin biopsy specimens from 199 patients, of whom 107 were represented by three specimens, and an additional 55 by two specimens. The data of Table 4 show that persisting *M. leprae* were detected in about 9% of all specimens; the proportions of specimens in which persisting organisms were detected did not differ significantly between centers, among regimens, or at the three time intervals. Also striking is that persisters were detected in two biopsy specimens from only four of the 39 patients; assuming persisting *M. leprae* to be uniformly distributed among the biopsy specimens, the number of such patients expected by chance is three.

Because patient populations of *M. leprae* diminish substantially during treatment, the proportions of specimens obtained at the later intervals in which persisters were detected may underestimate the true frequency of this phenomenon. In fact, 90% of the specimens provided inocula of at least 10^4 *M. leprae* for TR mice, and 73% of the specimens provided inocula of 10^5 organisms per foot pad, whereas only two specimens contained so few organisms that none could be counted. Thus, efforts to detect persisting *M. leprae* were not limited by the number of organisms available for inoculation.

One of the characteristics that might be associated with persistence of *M. leprae* is primary resistance to dapsone, which had been identified in approximately 37% of these patients. As shown in Table 5, however, the distribution of the 43 specimens in which persisting *M. leprae* were detected with respect to susceptibility to dapsone determined on the pretreatment isolate does not differ significantly from that of all 215 pretreatment isolates.

The distributions of a number of patient characteristics, observed at the time of admission into the clinical trials in Bamako and Chingleput, among the patients in whose specimens persisting *M. leprae* were detect-

TABLE 6. *Relationship between persisters and pretreatment patient characteristics.*

Pretreatment characteristic	Bamako		Chingleput	
	Persisters	No persisters	Persisters	No persisters
No. patients*	19	80	20	96
Mean age (years)	27.1	28.2	28.0	30.6
Mean LIB	5.4	4.9	5.2	5.3
Mean BI	4.8	4.4	4.3	4.3
Mean LAFBPG	8.5	8.3	8.4	8.4
No. patients with:				
CLINCLAS LL	2	12	7	20
CLINCLAS LI	16	58	10	70
CLINCLAS BL	1	10	3	6
HISTCLAS LL	0	2	0	1
HISTCLAS LI	16	63	19	92
HISTCLAS BL	3	14	1	3

* Complete information was not available for all patients.

ed, are compared in Table 6 with the distributions of these characteristics among those in whose specimens no persisters were detected. No significant associations could be demonstrated between the detection of persisting organisms and patient age, pretreatment values for BI, LIB, and LAFBPG, and initial clinical and histopathological classifications.

Detection of persisting *M. leprae* in approximately 9% of all specimens, without regard to dapsone susceptibility or to duration of treatment between three and 24 months, with a frequency no greater than that predicted by chance in a second specimen, and the lack of association of the detection of persisters with any other recorded characteristic of the patients suggest that persisting *M. leprae* may be distributed rather uniformly among the patients, and that their detection may be a chance event. If this assumption is valid, then one may estimate the absolute numbers of organisms persisting at each interval. Presented in Table 7 are the data describing the 43 specimens in which persisting *M. leprae* were detected. In each case, the number of organisms inoculated and the proportion of inoculated mouse feet demonstrating multiplication of *M. leprae* have been employed to calculate the most probable number (MPN) of viable organisms, expressed here as the MPN of viable organisms per 10^6 *M. leprae*. Taking as an example the first entry in this table, and assuming that multiplication would have occurred in none of 10 foot pads inoculated each with 10^4 organisms, and in all of 10 foot pads inoculated with 10^6 organisms, the MPN of viable *M. leprae* in the inoculum may be calculated by the equation of Halvorson and Ziegler [3] to be $4.93/10^6$. Assuming the total (viable plus dead) bacterial population of a patient with BI = 4.0 is 10^{11} (i.e., 10^{BI+7}) [1, 8], this patient appears to harbor MPN $\times$ 10^{BI+7} = 4.93×10^5 viable organisms.

After treatment for three months, the mean BI calculated from the values observed for the 197 patients examined, was 4.42 (unpublished data). Thus, the total population of *M. leprae* of these patients was $197 \times 10^{11.42} = 5.18 \times 10^{13}$. Considering the 18 patients found to harbor persisting *M. leprae* at this interval, one may calculate from the data of Table 7 that they harbored a total of 1.32×10^7 viable *M. leprae*. Assuming that these were all of the viable *M. leprae* in the total population of 5.18×10^{13}, the proportion of persisters at this interval is seen to be 2.55 per 10^7 organisms, and the average number of persisters per patient to be 6.70×10^4.

At 12 months, the 17 patients in whose biopsy specimens persisting *M. leprae* were detected may be seen to have harbored a total of 3.99×10^7 viable organisms. Assuming these to be the only viable organisms among the total bacterial population of 162 patients, whose mean BI was 3.98, the proportion of viable *M. leprae* may be calculated to be $(3.99 \times 10^7)/(162 \times 10^{10.98}) = 2.58$ per 10^6 organisms; thus, the

TABLE 7. *Calculation of the numbers of persisting* M. leprae.

Patient no.	Inoculum ($\times 10^5$)	Proportion of feet showing multiplication	MPN (per 10^6)	BI	$10^{BI+7} \times$ MPN ($\times 10^5$)
		3 months			
01024	1.0	4/10	4.93	4.00	4.93
01043	1.0	1/10	2.75	4.33	5.84
01049	0.30	1/8	9.57	4.00	9.57
01050	1.0	1/12	2.67	4.33	5.71
01051	1.0	1/12	2.67	4.33	5.71
01059	1.0	1/12	2.67	3.50	0.84
01073	1.0	1/8	2.87	4.33	6.14
01078	0.31	1/8	9.26	2.33	0.20
01093	1.0	3/14	3.38	3.83	2.29
01116	1.0	1/8	2.87	4.33	6.14
02033	1.0	2/8	3.62	4.33	7.74
02038	1.0	1/2	6.21	4.33	13.3
02044	1.0	2/16	2.87	4.33	6.14
02045	1.0	1/10	2.75	4.33	5.88
02048	1.0	1/8	2.87	4.00	2.87
02051	1.0	3/14	3.38	4.83	22.8
02067	1.0	1/10	2.75	4.67	12.9
02083	1.0	1/10	2.75	4.67	12.9
		12 months			
01037	0.07	1/14	37.3	3.17	5.52
01042	1.0	1/8	2.87	4.33	6.14
01043	0.18	1/6	17.2	4.33	36.8
01052	0.79	1/8	3.63	4.17	5.37
01069	1.0	1/6	3.10	4.17	4.58
01074	1.0	1/10	2.75	3.50	0.87
01079	1.0	2/12	3.10	3.87	2.30
01093	1.0	1/10	2.75	3.50	0.87
01103	1.0	6/14	5.26	3.67	2.46
02001	1.0	1/14	2.61	4.17	3.86
02011	1.0	1/16	2.57	4.00	2.57
02018	1.0	1/10	2.75	4.00	2.75
02019	1.0	1/8	2.87	4.17	4.24
02072	0.55	1/14	4.75	4.00	4.75
02073	1.0	4/14	3.88	3.91	3.15
02074	0.006	1/8	486	3.74	267
02080	0.002	1/8	144	3.50	45.5
		24 months			
01022	1.0	1/8	2.87	3.67	1.34
01047	0.70	1/10	3.93	4.00	3.93
01048	1.0	1/12	2.67	3.17	0.39
01051	1.0	1/8	2.67	3.17	0.42
02003	0.35	1/12	7.63	4.00	7.63
02015	0.05	1/12	56.8	3.24	9.87
02044	0.06	1/8	48.6	2.17	0.72
02053	0.03	1/12	92.1	3.50	29.1

average patient harbored 2.46×10^5 viable organisms. The corresponding calculation at 24 months is the following: the eight patients in whose specimens persisters were detected harbored a total of 5.34×10^6 viable *M. leprae*. The 109 patients biopsied at this interval, with a mean BI of 3.60, harbored a total of $109 \times 10^{10.33}$ organisms. Thus, the proportion of persisting *M. leprae* at this interval was 2.29 per 10^6 organisms, and the average patient may be seen to have harbored 4.90×10^4 viable organisms.

In summary, persisting *M. leprae* were detected in 43 skin-biopsy specimens obtained from 39 patients, among a total of 468 specimens obtained at intervals of 3, 12 and 24 months from 199 patients during treatment with five combined drug regi-

mens. The proportion of specimens in which persisting organisms were discovered did not vary with regimen or duration of treatment, although, because of the small number of specimens in which persisting *M. leprae* were detected, a decrease of the proportion with time cannot be excluded. The regimen consisting of a single initial dose of rifampin plus daily dapsone appeared to be as effective as regimens consisting of rifampin, dapsone and clofazimine or prothionamide, each drug administered daily. The average number of persisting *M. leprae* per patient was calculated to be no greater than 50,000–250,000 at each of the intervals.

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