

Relapses Among Leprosy Patients Treated with  
Multidrug Therapy: Experience in the Leprosy Control  
Program of the All Africa Leprosy and  
Rehabilitation Training Center (ALERT) in Ethiopia;  
Practical Difficulties with Diagnosing Relapses;  
Operational Procedures and Criteria for  
Diagnosing Relapses<sup>1</sup>

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Since the recommendation of a World Health Organization Study Group on multidrug therapy (MDT) for the treatment of leprosy patients was published in 1982 (<sup>42</sup>), the regimens have been implemented in many leprosy-endemic countries. From several parts of the world it has been reported that the regimens are well accepted and tolerated by the patients. Regularity of attendance for the treatment has been very satisfactory, and side effects of the drugs have not been a serious problem (<sup>7, 30, 36, 41, 44-47</sup>).

The ultimate test of chemotherapeutic effectiveness of the MDT regimens is the relapse rate among patients who have completed a prescribed course of the treatment, relapse being defined as the fresh multiplication (and spread) of surviving leprosy bacilli in a patient who has previously responded to therapy (<sup>39</sup>). Diagnosing a multibacillary (MB) relapse is, from the increase in the bacterial index (BI), the finding of new skin lesions, and the histological appearances, not considered difficult (<sup>38, 39, 41</sup>). Ultimate proof for a MB relapse will be the multiplication of bacilli in the foot pads of mice (<sup>38, 39</sup>). A paucibacillary (PB) relapse appears much more difficult to diagnose since the appearances, including the histological findings, are often indistinguishable

from those of a late reversal reaction (<sup>6, 26, 38, 39, 43, 45</sup>).

This paper reports on relapses which have been diagnosed among leprosy patients treated with MDT in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. Clinical, bacteriological and histopathological findings are presented and discussed. Operational procedures and criteria are proposed for making the diagnosis under conditions where facilities for back-up investigations, biopsy examinations, and mouse foot pad inoculations are not available.

#### MATERIALS AND METHODS

The ALERT leprosy control program is responsible for leprosy control in the Shoa Region, the central region of Ethiopia. An analysis of relapses after MDT was made in Addis Ababa and 4 of the 11 rural districts of the region. This area covers approximately 35,000 sq km with an estimated population of 4.45 million, of whom about 38% reside in the city of Addis Ababa (1989).

In 2 of the 4 rural districts no release of patients on dapsone was carried out before implementation of MDT. In these districts MDT was introduced in January 1981, while criteria for release of patients on dapsone monotherapy were defined at the end of 1983 (<sup>1, 5</sup>). In the other two rural districts and Addis Ababa, where MDT was introduced in March 1984, 47% of the PB patients and 40% of the MB patients who were on dap-

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sone at the end of 1983 were released from treatment.

MB patients were clinically borderline lepromatous (BL, including the few BB patients) or lepromatous (LL) patients, having a BI of 2 or more in at least one site. PB patients were clinically indeterminate, tuberculoid (TT) or borderline tuberculoid (BT) patients having a BI of not more than 1+ in any site. In January 1990 the 1988 recommendation of the WHO Expert Committee on Leprosy to classify, for the purpose of MDT, clinically PB cases showing skin-smear positivity as MB<sup>(41)</sup> was introduced.

In the field program skin smears had to be examined from four sites, one of each earlobe and two of skin lesions. If old skin lesions were not visible any more skin smears were routinely taken from two earlobes, an elbow and a knee. In the ALERT hospital skin smears from six sites were examined, either as indicated on the smear request form or routinely from two earlobes, an eyebrow, an elbow, a knee, and a buttock.

The MDT regimens were as recommended by the WHO Study Group in 1982<sup>(42)</sup>. PB patients were treated with 6 four-weekly, supervised doses of 600 mg rifampin and 100 mg dapsone daily self-administered for 24 weeks. The doses of MDT had to be completed within a maximum period of 9 months. MB patients were treated with at least 26 four-weekly supervised doses of 600 mg rifampin and 300 mg clofazimine, and 50 mg clofazimine and 100 mg dapsone daily, self-administered for 2 years. The doses of MDT had to be completed within a maximum period of 3 years. Patients with negative skin smears, including a BI of 1+ in one or more sites, in two consecutive sets of smears which had to be taken during the few months before completion of the 26 doses of MDT were released from MDT. Patients with positive skin smears had to continue the treatment until skin-smear negativity. Clinical and bacteriological examinations were done annually until the patient could be released from MDT. For patients of less than 15 years of age the dosages of MDT were adapted according to age.

At the time of release from MDT patients were instructed to attend the service at any time they observed new skin lesions and/or

a loss of sensation or muscle strength in the eyes, hands or feet. PB patients who had been treated with dapsone before MDT and all MB patients were told to attend the service annually for a period of 5 years. In order to detect late reversal reaction at an early stage, PB patients who were treated with MDT only were, in addition, given appointments for examination during the third and sixth months after release from MDT. Patients who did not attend for follow-up examinations were not traced.

From release from treatment registers and patient record cards, it was estimated that 60% to 70% of the patients attended for the follow-up examination during the first or second year after release from MDT. During the fifth year after release only 10% to 30% of the patients still attended. Because over 90% of the patients released from MDT were self-reporting when they were first diagnosed with leprosy, it was expected that they would also attend the service if they observed new signs of the disease. In a study on relapses after release from dapsone, it was confirmed that the vast majority of the patients who developed a relapse reported to a clinic. Among 2204 patients released from dapsone, 125 relapses (5.7%) had been diagnosed during the first 3½ years after stopping the treatment<sup>(14)</sup>. In a random sample of 135 patients who had not been diagnosed with a relapse and who were examined during the third year after release from treatment, only one unreported relapse was diagnosed (0.7%; 95% confidence interval 0–2.2%). Patients who attended for follow-up examinations were examined clinically. Of all former MB patients and of former PB patients who presented with new clinical activity of the disease, skin smears were examined.

During 1984, senior staff of ALERT defined the following criteria for suspected and confirmed relapse<sup>(3)</sup>: a) A MB relapse is suspected if a BI of 2+ or more is found in one or more sites, whether or not there is new clinical activity of the disease. The positive skin-smear results should be confirmed by a second set of skin smears. In the ALERT hospital the finding of leprosy bacilli in a skin or nerve biopsy was considered proof for a MB relapse, even if skin smears were negative. b) A PB relapse is suspected if a patient develops new clinical

TABLE 1. Patients released from MDT during different periods and the relapses diagnosed among these patients.

Period	Paucibacillary			Multibacillary		
	RFT <sup>a</sup>	Relapses	%	RFT	Relapses	%
	No. patients	No. patients		No. patients	No. patients	
6/83-7/83	286	3	1.0	0	0	0
7/83-7/84	1335	13	1.0	0	0	0
7/84-7/85	705	9	1.3	670 <sup>b</sup>	2	0.3
7/85-7/86	242	3	1.2	887	11	1.2
7/86-7/87	244	4	1.6	489	9	1.8
7/87-7/88	253	2	0.8	333	2	0.6
Total	3065	34	1.1	2379	24	1.0

<sup>a</sup> RFT = Released from treatment.

<sup>b</sup> All of these patients were released from MDT during the period 1/85-7/85.

activity of the disease more than 1 year after release from MDT, while skin smears are negative. The results of detailed clinical examination and histological finds in skin and/or nerve biopsy(ies) should confirm whether or not the patient suffers from a relapse.

Patients suspected of a relapse by the leprosy control field staff were referred to the ALERT hospital for clinical, bacteriological, and histological examination. Of patients suspected of a MB relapse, a relapse lesion had to be biopsied, part for histology and part for inoculation of bacilli into mice. However, due to problems with re-establishing the mouse foot pad laboratory, mouse inoculation was not possible during most of the period in which the relapses presented in this paper were diagnosed.

Estimated annual relapse rates per 1000 patient-years after release from MDT were calculated. Patients released during different periods were considered to have been released in the middle of that period. In the calculation of the estimated number of patient-years, all patients released from MDT were included, while an annual reduction for death and leaving the control area of 3%

for PB patients and 4% for MB patients was made. These percentages were, as averages, observed during the period 1983 to 1991 for patients on MDT in the districts under study.

## RESULTS

The numbers of patients released from MDT during different periods and the numbers and percentages of relapses diagnosed among them are given in Table 1. Approximately 30% of the 3065 PB patients and 20% of the 2379 MB patients had not been treated with dapsone before MDT. The average periods after stopping MDT were 6.1 years (range 2½-7½ years) for the PB patients and 4.7 years (range 2½-6 years) for the MB patients. Table 2 gives the original classification versus the relapse classification of the 58 patients who were diagnosed with a relapse.

### Relapses among paucibacillary patients

The clinical and bacteriological findings of the relapses which were diagnosed in PB patients are presented in Table 3. Past records of two of the patients who, based on

TABLE 2. Original classification vs relapse classification of the patients diagnosed with a relapse after MDT.

Original classification	Relapse classification				Total no. patients	%
	PB		MB			
	No. patients	%	No. patients	%		
PB	18	52.9	16	47.1	34	58.6
MB	6	25.0	18	75.0	24	41.4
Total	24	41.4	34	58.6	58	

active skin lesions and positive skin smears, were diagnosed with a MB relapse strongly suggested MB classification. These patients had multiple, symmetrically distributed, ill-

defined skin lesions, and enlargement of several nerves, although skin smears were negative. In the patient who presented with new nerve function loss, a MB relapse was

TABLE 3. Clinical and bacteriological findings of relapses diagnosed among paucibacillary patients.

Findings	Relapse classification			
	PB		MB	
	No. patients	%	No. patients	%
Active skin lesions	8	44.4		
New lesions	3			
Old lesions	1			
New + old lesions	1			
Not specified	3			
Active skin lesions and new nerve function loss	8	44.4		
New lesions	2			
Old lesions	3			
Not specified	3			
New nerve function loss	2	11.1	1	6.3
Active skin lesions and positive skin smears			14	87.5
New nerve function loss and bacilli in nerve			1	6.3
Total	18		16	

TABLE 4. Period of dapsone before MDT, period between release from MDT to diagnosis of relapse, clinical findings, and biopsy results for PB relapses diagnosed among PB patients.

Patient no.	Dapsone before MDT (yr)	Period RFT <sup>a</sup> to relapse (mo.)	Clinical findings	Biopsy results
25	None	22	Activity in old skin lesions; new nerve function loss	Granuloma skin
26	4	71	Activity in old skin lesions; new nerve function loss	ND <sup>b</sup>
27	None	35	New active skin lesions	Granuloma skin
28	None	48	Active skin lesions; new nerve function loss	ND
29	¼	55	New active skin lesions	ND
30	None	23	New nerve function loss	ND
31	1	19	Active skin lesions	Granuloma skin
32	None	31	Active skin lesions; new nerve function loss	Granuloma skin; lympho-hist. nerve <sup>c</sup>
33	8	48	Activity old skin lesions; new nerve function loss	Granuloma skin; lympho-hist. nerve
34	1	24	Active skin lesions; new nerve function loss	Granuloma skin
35	None	38	New active skin lesions	Granuloma skin
36	2	24	Activity in old lesions	Granuloma skin
37	None	13	New active skin lesions; activity in old skin lesions	ND
38	4	76	New nerve function loss	Lympho-hist. nerve
39	5	76	New active skin lesions	Granuloma skin
40	None	37	Active skin lesions	Granuloma skin
41	1	59	New active skin lesions; new nerve function loss	ND
42	None	62	Active skin lesions; new nerve function loss	ND

<sup>a</sup> RFT = Release from treatment.

<sup>b</sup> ND = Not done.

<sup>c</sup> Lympho-hist. nerve = Lympho-histiocytic infiltrate in the nerve.

TABLE 5. *Period of dapsone before MDT, period between release from MDT and diagnosis of relapse, skin-smear results, clinical findings, and biopsy results for MB relapses diagnosed among PB patients.*

Patient no.	Dapsone before MDT (yr)	Period RFT <sup>a</sup> to relapse (mo.)	Bacterial index	Clinical findings	Biopsy results
43	None	11	0000 <sup>b</sup> /ND <sup>c</sup>	New nerve function loss	Neuritis; some AFB
44	9½	39	4334/3222	Active skin lesions	ND
45	3	50	2003/3100	Active skin lesions	ND
46	4½	54	3324/ND	Active skin lesions	ND
47	8½	62	2433/2322	Active skin lesions	ND
48	3½	54	2445/4564	Active skin lesions	ND
49	None	36	0000/2100	Active skin lesions	ND
50	6	40	2210/ND	Active skin lesions	ND
51	4	44	0000/ND	New nerve function loss	ND
52	2½	82	4233/3242	Active skin lesions	ND
53	None	26	002000/32100	Active skin lesions	ND
54	RLO <sup>d</sup>	31	221141/20112	Active skin lesions	"I" skin <sup>e</sup>
55	6	73	4312/4422	Active skin lesions	ND
56	2	80	4434/ND	Active skin lesions	ND
57	1½	52	2211/2211	Active skin lesions	ND
58	RLO	40	2110/1100	Active skin lesions	ND

<sup>a</sup> RFT = Release from treatment.

<sup>b</sup> 0000 = Smears from 4 sites, all 0 BI; 4334/3222 = smears from 4 sites on 2 occasions with BIs = 4+, 3+, 3+, 4+ and 3+, 2+, 2+, 2+, etc.

<sup>c</sup> ND = Not done.

<sup>d</sup> RLO = Relapse after release from dapsone monotherapy.

<sup>e</sup> "I" skin = Indeterminate leprosy in skin biopsy.

diagnosed because past clinical records were considered in favor of MB leprosy.

The period of dapsone before MDT, the period between release from MDT and diagnosis of the relapse, clinical findings, and biopsy results for PB relapses in PB patients are given in Table 4. The information for MB relapses and the skin-smear results are given in Table 5. Solid-staining bacilli were not found in any of the positive skin smears. The average period between release from MDT and the time of diagnosis of the relapse was 44.4 months; median period, 42 months.

Of the 34 relapses, 14 (41.2%; 5 PB and 9 MB) were diagnosed in the field. Most of these patients resided in very remote areas. Because of the practical problems of referral, refusal by some patients to go the hospital and admission problems, these patients were diagnosed by supervisors in the field. Of the 13 PB and 7 MB patients who were diagnosed in the hospital, results of skin and/or nerve biopsies were available for 11 PB and 2 MB patients. In Table 6 the estimated annual relapse rates and the mean relapse rate, per 1000 patient-years after release from MDT, are given. The rate

of relapse did not vary significantly from year to year ( $\chi^2 = 9.0$ ,  $p = 0.25$ ).

#### Relapses among MB patients

In Table 7 the clinical and bacteriological findings in the relapses which were diagnosed among MB patients are given.

TABLE 6. *Estimated annual relapse rates among PB patients per 1000 patient-years after release from MDT.*

Yr after release	No. relapses	Estimated no. patient-years after release	Estimated no. relapses/1000 patient-years
1	1 (0) <sup>a</sup>	2,950	0.3 (0) <sup>a</sup>
2	6 (0)	2,850	2.1 (0)
3	5 (1)	2,775	1.8 (0.4)
4	8 (4)	2,450	3.3 (1.6)
5	6 (4)	2,175	2.8 (1.8)
6	3 (3)	1,900	1.6 (1.6)
7	5 (4)	1,300	3.9 (3.1)
8	0 (0)	100	0 (0)
Total	34 (16)	16,500	2.1 (1.0)

<sup>a</sup> Numbers in parentheses relate to relapses for which there was strong positive evidence for the diagnosis.

Table 8 presents the period of dapsone before MDT, the period between release from MDT and the diagnosis of relapse, bacteriological findings, clinical signs, and biopsy results in patients diagnosed with a MB relapse. Except in one set of skin smears (patient number 14), solid-staining bacilli

were not observed in the skin smears. A biopsy was taken for mouse foot pad inoculation from patients numbers 13 and 14. In the suspension of the biopsy of patient number 13 some solid-staining bacilli were found. Whether the bacilli were actually inoculated in mouse foot pads could not be

TABLE 7. Clinical and bacteriological findings of relapses diagnosed among MB patients.

Findings	Relapse classification			
	MB		PB	
	No. patients	%	No. patients	%
Active skin lesions			2	33.3
New nerve function loss	1	5.6		
Active skin lesions and new nerve function loss			4	66.7
Active skin lesions and positive skin smears	5	27.8		
Positive skin smears	10	55.6		
New nerve function and bacilli in nerve biopsy	1	5.6		
Active skin lesions and bacilli in skin biopsy	1	5.6		
Total	18		6	

TABLE 8. Period of dapsone before MDT, period between release from MDT and diagnosis of relapse, skin-smear results during MDT and at the time of diagnosis of relapse, clinical findings, and biopsy results of MB relapses diagnosed with MB patients.

Patient no.	Dapsone before MDT (yr)	Period RFT-RL <sup>b</sup> (mo.)	BI during MDT <sup>c</sup>			BI at relapse <sup>d</sup>	Clinical signs <sup>e</sup>	Biopsy results <sup>f</sup>
1	> 10	16	1	0	00	2000/ND	None	Lymph-his.
2	6	7	4	3	2 00	1320/001121	None	Scarring
3	2½	27	3	4	2 10	0002/421221	None	Scarring
4	None	8	5	5	4 00	3221/3222	None	ND
5	10	12	5	5	00	4000/4000	None	ND
6	> 10	5	5	2	0 10	020210/010011	None	Scarring
7	RLO <sup>a</sup>	8	3	0	00	2131/213100	None	Lymph-his.
8	2	14	5	1	00	1110/ND	NFL	Scarring
9	> 10	13	6	4	4 00	1200/1200	None	Scarring
10	5	11	4	3	2 01	100102/202000	None	Lymph-his.
11	1	7	0	2	00	230111/120010	ASL	Granuloma
12	RLO	20	4	4	0 11	1111/2100	ASL	"I" lepr.
13	> 10	12	4	0	00	0300/003100	ASL	Scarring
14	RLO	15	5	1	00	3200/440012 (MI 2%, 1%)	ASL	Regr.MB No AFB
15	RLO	44	2	0	00	000000/000000	NFL	Some AFB in nerve
16	½	19	0	0	00	000000/ND	ASL	Granuloma; some AFB
17	6	18	1	0	00	2011/1112	None	ND
18	8	17	4	2	00	3210/ND	ASL	ND

<sup>a</sup> RLO = Relapse after release from dapsone monotherapy. (In patients numbers 1, 5, 6, 9, 13 and 14 dapsone resistance was confirmed or suspected.)

<sup>b</sup> RFT-RL = Released from treatment to relapse.

<sup>c</sup> Last skin-smear results are the highest BIs of the two sets of skin smears which were examined prior to release from MDT.

<sup>d</sup> 2000 = Smears from 4 sites, BIs = 2+,0,0,0, etc.

<sup>e</sup> ND = Not done; NFL = new nerve function loss; ASL = active skin lesions.

<sup>f</sup> If there were no clinical signs, results are those of the nerve biopsy: "I" lepr. = indeterminate leprosy; Regr.MB = regressive MB lesion.

TABLE 9. *Period of dapsone before MDT, period between release from MDT and diagnosis of relapse, clinical findings, and biopsy results for PB relapses diagnosed among MB patients.*

Patient no.	Dapsone before MDT (yr)	Period RFT <sup>a</sup> to relapse (mo.)	Clinical findings	Biopsy results <sup>b</sup>
19	2	28	Active BT skin lesions; new nerve function loss	Granuloma skin
20	None	25	Active BT skin lesions	Granuloma skin
21	1½	15	Active BT skin lesions; new nerve function loss	Granuloma skin; lympho-hist. nerve
22	4	32	Active BT skin lesions; new nerve function loss	No leprosy-skin; no signs react.
23	½	48	Active BT skin lesions; new nerve function loss	Granuloma skin; lympho-hist. nerve
24	RLO <sup>c</sup>	42	Active TT skin lesions	Granuloma skin

<sup>a</sup> RFT = Release from treatment.

<sup>b</sup> Lympho-hist. nerve = Lympho-histiocytic infiltrate in the nerve; no leprosy-skin = findings in skin not suggestive for leprosy; no signs react. = no signs of reversal reaction in nerve biopsy.

<sup>c</sup> RLO = Relapse after release from dapsone monotherapy.

traced. In patient number 14 the suspension was negative for acid-fast bacilli. The records of this patient indicated that the biopsy had been taken from the wrong site.

The information for the six PB relapses is given in Table 9. These patients were all classified as BL leprosy in the past. The average period between release from MDT and the time of diagnosis of the relapse was 18.0 months; median period, 15.5 months. All except two MB relapses were diagnosed in the hospital. Of 12 of the 14 MB and all of the 6 PB relapses which were diagnosed in the hospital, a skin and/or nerve biopsy was examined.

The estimated annual relapse rates and the mean relapse rate, per 1000 patient-years after stopping MDT, are given in Table 10. The rate of relapse did not vary significantly from year to year ( $\chi^2 = 7.9$ ,  $p = 0.16$ ).

## DISCUSSION

### Assessment of Findings

#### Relapses among PB patients

**PB relapses.** At present there are three criteria on which the diagnosis of PB relapse has to be based: a) clinical findings, b) histological findings, c) the period between release from treatment and the development of new clinical signs of the disease.

**Clinical findings.** Some investigators have listed signs of relapse, namely, the development of erythema, infiltration of skin lesions, new skin lesions, pain/tenderness in

nerves, new muscle paralysis, and extension of existing lesions (<sup>21</sup>). Others have reported that these signs can also be observed in reversal reactions (<sup>39</sup>). Some consider the increase in size of existing skin lesions as proof of a relapse (<sup>39</sup>). However, even when, at the time the patient is released from MDT, a record of the lesions is made by experienced staff, it is often difficult to ascertain whether the skin lesions have increased in size. Others differentiate relapses from late reversal reactions based on the onset of the clinical signs (<sup>22</sup>). While a relapse usually has a slow and insidious onset, a reversal reaction develops more rapidly. However,

TABLE 10. *Estimated annual relapse rates among MB patients per 1000 patient-years after release from MDT.*

Yr after release	No. relapses <sup>a</sup>	Estimated no. patient-years after release	Estimated no. relapses/1000 patient-years <sup>a</sup>
1st	8 (0)	2,275	3.5 (0)
2nd	9 (0)	2,200	4.1 (0)
3rd	4 (0)	2,100	1.9 (0)
4th	3 (0)	1,725	1.7 (0)
5th	0 (0)	1,250	0 (0)
6th	0 (0)	300	0 (0)
Total	24 (0)	9,850	2.4 (0)

<sup>a</sup> Numbers in parentheses indicate only relapses for which there was strong positive evidence for the diagnosis.

patients often cannot tell whether or not the signs developed gradually. Some define a relapse as the reappearance of active disease (18, 24, 29, 31, 36). While the same definition is also applicable to a reversal reaction, it is only of practical use if it can be ascertained that the patient had attained clinical inactivity earlier.

**Histological findings.** The finding of a granuloma in skin lesions during the first few years after stopping MDT appears to be no proof for a relapse. Pattyn, *et al.* reported that in PB patients treated with the MDT regimen recommended by the World Health Organization (WHO), granulomas were still present 24 months after the start of MDT in 40% of the patients, at 36 months in 28%, at 48 months in 10%, and at 60 months in none of the patients (23). Further, the finding of lymphocytic infiltrate in a nerve biopsy is unrelated to whether or not living bacilli are present in the nerve, because persisting antigen of dead bacilli may also maintain the infiltrate (M. F. R. Waters, personal communication). Therefore, this can be observed in a relapse as well as in a late reversal reaction.

**Period after release from treatment.** THELEP has suggested that signs which develop within 6 months after stopping MDT are almost certainly due to a reversal reaction; whereas signs which develop more than 1 year after release from MDT are more likely to be due to a relapse (48). Although most reversal reactions in PB patients occur within 1 year after starting antileprosy treatment, late reversal reactions can undoubtedly occur 2 or more years after commencing MDT (6, 8, 39). Reversal reactions, although few, were even observed during the fourth year after stopping MDT (6). It is not known when late reversal reactions can no longer be expected.

From the above it can be concluded that neither clinical signs nor histological findings are conclusive for the diagnosis of relapse. The time factor appears an important criterion. The longer the period after release from MDT, the higher the chance that signs of clinical activity are due to a relapse. A relapse appears very likely if signs of clinical activity or histopathological findings are observed 4 years or more after stopping MDT.

Persisting granuloma could well account for the histological finding in some of the

patients, notably patients numbers 25, 27, 31, 32, 34, 35, 36 and 40 (Table 4). These patients, and also numbers 30 and 37, most probably suffered from a reversal reaction, rather than from a relapse. Only patients numbers 26, 28, 29, 33, 38, 39, 41 and 42 should be considered positively as having a PB relapse. Unfortunately, only in patients numbers 33, 38, and 39 had back-up histological examinations been done.

**MB relapses.** Of the patients who were diagnosed with a MB relapse, the diagnosis in patient number 43 was based on the finding of bacilli in the nerve, while skin smears were negative. Several investigators have demonstrated that the bacterial indices in skin and nerve biopsies taken from patients at the same time are discrepant in many, possibly 50%, of the cases (20, 32, 33). The nerves may contain a bacterial density of up to 1000 times that of the skin. Therefore, the finding of some bacilli in a nerve should not be considered evidence for a MB relapse. This patient most probably suffered from a late reversal reaction. Patient number 51 may have suffered from a PB relapse but there is no evidence for a MB relapse.

In patients numbers 46, 50 and 56 skin smears were examined only once, and in patients numbers 49 and 58 a BI of 2+ was found only once. Although these patients may have suffered from a MB relapse, the information on which the diagnosis was based is inadequate. In patients numbers 44, 45, 47, 48, 52, 53, 54, 55 and 57, there is certainly evidence for MB relapse. In only one patient (number 54) was a skin lesion biopsied. The histological finding of indeterminate leprosy, however (Table 5), does not support the diagnosis of MB relapse.

MB relapse in patients originally classified as PB patients has been reported (9, 15, 21, 37). However, the possibility of wrong classification and, hence, inadequate antileprosy treatment in the past should also be considered. This was most probably the case in patients numbers 48 and 54, whose past clinical records strongly suggested MB leprosy.

In conclusion, the diagnosis of PB relapse is likely in nine patients, and there is strong evidence for a MB relapse in seven patients. Ultimate proof for the MB relapses would have been the growth and multiplication of the bacilli in mouse foot pads.



### Relapses among MB patients

**MB relapses.** With respect to the MB relapses (Table 8), a number of points emerge:

In several of the patients the skin-smear results during MDT are inconsistent. One would not expect a BI of 4+ or 5+ to become 0 in 1 or 2 years. These inconsistencies are, in particular, observed among patients with confirmed or suspected dapsone resistance and among those diagnosed with a relapse after release from dapsone monotherapy, notably patients numbers 5, 6, 7, 9, 12, 13 and 14. The long-term follow up of these patients is difficult, because unless the relapse lesions are smeared, skin smears may be negative. Observations from the records of these patients showed that, while skin smears with a high BI had been taken from new or subsiding lesions, those with a BI of 0 were taken from routine sites. Also, in patients numbers 4 and 8 the skin-smear results are inconsistent. The observed increase in the BI in the skin smears after release from MDT was most probably not a genuine increase, but one due to the selection of different smear sites at different times.

In 10 of the 18 patients the diagnosis was based solely on the finding of positive skin smears. In patient number 1 the information is inadequate because skin smears were examined only once. In patients numbers 2, 4, 6 and 7 positive skin smears were observed within 8 months after release from MDT. Certainly, if the diagnosis of relapse is exclusively based on the finding of positive skin smears, a critical approach in the interpretation of skin-smear results (including those during MDT) is required. In none of the skin smears of these 10 patients were solid-staining bacilli found.

Of the six patients with active skin lesions and positive skin smears or some bacilli in the skin biopsy, the skin smears were examined only once in patients numbers 16 and 18. In one set of skin smears (patient number 14) some solid bacilli were found. The skin biopsy results of this patient—regressive MB leprosy lesions and no acid-fast bacilli (AFB)—however, do not support MB relapse. The same applies to the histological findings in the skin biopsies of patients numbers 11 and 12. Patients numbers

11 and 16 most probably suffered from a reversal reaction.

In the two patients with new nerve function loss, the findings in patient number 8 give evidence for neither a relapse nor a reversal reaction. The nerve function loss in this patient may be caused by ongoing scarring in the nerve. Negesse and Miko have reported this as a possible mechanism in the alteration of nerve function (<sup>19</sup>). Patient number 15 may have had a reversal reaction, but there is no evidence for MB relapse.

**PB relapses.** As regards the PB relapses which were diagnosed among MB patients, they probably underwent reversal reactions to BT. This has been reported in BL patients several years after commencing effective chemotherapy (<sup>30</sup>, and M. F. R. Waters, personal communication). In conclusion, for none of the relapses which were diagnosed in MB patients was there strong positive evidence for the diagnosis.

### Conclusions

If the relapse rates are calculated for the patients for whom there was strong positive evidence for the diagnosis, the percentage of relapses among the 3065 PB patients will be 0.5 and the average estimated relapse rate 1.0 per 1000 patient-years after release from MDT (Table 6). The estimated annual relapse rates are then significantly higher during the fourth and following years after stopping MDT, compared with the first 3 years ( $\chi^2 = 16.6$ ,  $p = 0.01$ ). For the 2379 MB patients the rates will be 0 (Table 10).

This study shows that diagnosing a PB as well as a MB relapse after MDT is certainly not easy and that, unless strict criteria for the diagnosis are defined and applied, overdiagnosis of relapses is likely. The main causes for overdiagnosis of MB relapses observed in this study are that too much reliance had been put on the skin-smear results without a careful comparison of the results from before, during, and at completion of MDT with those observed at the time a relapse was suspected. Further, the diagnosis was based on the finding of positive skin smears in one set of smears only, insufficient attention was given to the importance of finding solid-staining bacilli, and findings in biopsies, if they were examined, did not confirm the diagnosis. As regards

TABLE 11. Summary of published data on relapses in patients treated with MDT.

Authors	Population	Relapse site	Definition of relapse
		Relapses in PB patients	
Boerrigter, <i>et al.</i> <sup>(8)</sup>	499 new patients	6.5/1000 patient-yrs of follow up during 4 yrs	Appearance of new skin lesions or increase in size pre-existing skin lesions
Ekambaram and Rao <sup>(10)</sup>	14,227 patients	0.34% one year after stopping MDT	Not specified
Grugni, <i>et al.</i> <sup>(13)</sup>	1,509 patients	5.6% or 17.5/1000 patient-yrs of follow up during 0.5–5 yrs	New lesions; extension, thickening, erythema in existing lesions; thickened nerves; new paralysis
Katoch, <i>et al.</i> <sup>(18)</sup>	70 new patients	12.9% during 3–3.5 yrs of follow up	Gradual re-appearance of activity
Pattyn, <i>et al.</i> <sup>(23)</sup>	60 patients	0.5% per yr during 5.5 yrs	Return of histological lesions
Pavithran <sup>(24)</sup>	25 new patients	12.0% within 1 yr of follow up	Gradual reappearance of skin lesions; histological findings
Rangaraj and Rangaraj <sup>(28)</sup>	237 patients	5.9% during 0.5–2.5 yrs after release from MDT	Not specified
Reddy and Mohinuddin <sup>(29)</sup>	92 patients	4.3% during 0.5–4.5 yrs after release from MDT	Reappearance of the disease
Revankar, <i>et al.</i> <sup>(31)</sup>	408 patients	0.5% during 3 yrs of follow up	New skin lesions after attaining clinical inactivity
van Brakel, <i>et al.</i> <sup>(36)</sup>	555 patients	2.9% during max. period of 4.5 yrs	Return of active disease
		Relapses in MB patients	
THELEP trials, India <sup>(45)</sup>	2,241 patients	No relapses during mean follow-up of 4 yrs	
van Brakel, <i>et al.</i> <sup>(36)</sup>	372 patients	1.6% during max. period of 4.5 yrs	Return of active disease

PB relapses, too much reliance was put on histological findings while these are known to be inconclusive for differentiating between a relapse and late reversal reaction.

Even if all of the patients who were diagnosed with a relapse did, in fact, suffer from it, the relapse rates should definitely be considered low. The relapses were observed among self-reporting patients. Not all patients who developed new activity of the disease may have reported at a clinic. However, the study on relapses after release from dapsone monotherapy suggested that the vast majority of patients who develop new signs of the disease do report to a clinic.

So far, most published data on relapses after MDT concern relapses in PB patients. There are only very few reports on relapses in MB patients. A summary of the published data on relapses after MDT is given in Table 11. Because it takes into account the period after stopping MDT and those patients who were lost from observation, the relapse rate per 1000 patient-years is a much more valid measure than the per-

centage of relapses. In only a few studies was the relapse rate per 1000 patient-years calculated.

In some studies on relapses in PB patients only new patients were included; in others, new patients and patients who had been treated with dapsone before MDT. In some studies the period of MDT was extended, either to 12 months in patients with four or more skin lesions<sup>(10)</sup>, or until clinical inactivity<sup>(13)</sup>. Because of these differences, different periods and methods of follow up after stopping MDT and different diagnostic criteria for relapse, the observed relapse rates are not comparable. Several investigators reported the difficulty of differentiating between a PB relapse and a late reversal reaction<sup>(7, 17, 22, 24, 38, 39)</sup>.

Concern has been expressed about the recommended duration of MDT for PB patients, particularly from India<sup>(12, 14, 17–19, 22, 25, 26, 28, 30, 36, 40)</sup>. A common opinion is that the treatment should not be stopped if the leprosy lesions are still clinically active. It has been reported that a re-

lapse might be prevented if dapsone is continued for 1 year after the 6 months of MDT (17, 18). However, it has not been established that the risk of relapse is higher in patients who are clinically active after the 6 months of MDT than in patients who are clinically inactive. Because the definition for relapse used by several investigators may as well be applicable to a reversal reaction, several of the relapses (particularly in the studies where follow up of patients was limited to less than 3 years) may, in fact, have been reversal reactions.

In another paper from the ALERT leprosy control program it has been reported that most reversal reactions in PB patients (58/67; 87%) after stopping MDT were observed within the first 2 years (6). In contrast to this, in the present study even if all registered relapses would be genuine relapses, most of them (27/34; 79%) were observed more than 2 years after stopping MDT. A similar observation has been made by others (8).

The observation that there were no relapses for which there was strong positive evidence among the MB patients is similar to what was found in the THELEP studies carried out in South India. Also in these studies new patients and patients who were treated with dapsone before MDT were included, and MDT was continued until skin-smear negativity, while the mean period of follow up was similar to that in the present material. These findings are quite different from those observed in patients who were released from dapsone monotherapy.

Waters, *et al.*, in a follow-up study on MB relapses after dapsone monotherapy, reported that relapses occurred during each year of follow up. They observed that the risk of relapse did not vary significantly from year to year during the 8 to 9 years of observation (40).

In the ALERT leprosy control program 11.4% of 1123 MB patients who were released from dapsone monotherapy were diagnosed with a relapse within the first 4½ years after stopping treatment (5). If this percentage is applied to the 2379 patients who were treated with MDT, there would have been about 270 relapses among them.

Relapse after dapsone monotherapy is frequently due to the development of dapsone resistance. Multiplication of persisting,

drug-sensitive, physiologically dormant bacilli is considered the major cause for relapse after MDT. The results of clinical trials suggest that persisters are present in all MB patients and that they do not respond to any rifampin-containing MDT regimen (12, 34). Whether and under which conditions persisting bacilli will start multiplying are not known.

The recommendation for surveillance after stopping MDT is that PB patients should be examined clinically and bacteriologically once per year for a minimum period of 2 years, and MB patients should be examined clinically and bacteriologically once per year for a minimum period of 5 years (41, 43). The findings presented in this paper show that this is of little, if any, value for diagnosing relapses. Because 30% of the 3065 PB patients and 20% of the 2379 MB patients were newly detected cases, this is also applicable to patients who had not been treated with dapsone before MDT. Therefore, there is no need for routine annual examinations during the first years after stopping MDT. For drawing final conclusions on relapse rates after MDT, a period of follow up of 10 years or more may be required. Because only 10% to 30% of the patients still attended for examination during the fifth year after stopping MDT, such a long period of follow up is certainly unrealistic. Instead of periodic examination, patients should be encouraged to report as soon as they notice new signs of the disease.

### Recommendations

All patients suspected of a relapse require careful and thorough examination. In many leprosy-endemic countries this will mean thorough clinical examination, skin-smear examinations, and careful assessment of past records. Criteria for the confirmation of a relapse should be defined. To ensure that the relapses are diagnosed according to these criteria, the responsibility for diagnosing relapses should be restricted to one or a few selected centers.

Possible overdiagnosis of relapses can be limited by: a) restricting the examination of skin smears to patients who present with suspect new skin lesions and/or extension of previously existing lesions; b) repeating skin-smear examination for confirmation of positive results; c) thorough examination of

positive skin smears for the presence of solid-staining bacilli; d) critical comparison of skin-smear results from before, during, and at completion of MDT with those observed when a relapse was suspected; e) review of past clinical and bacteriological findings in patients initially classified as PB and found with positive skin smears; and f) differentiation between a PB relapse and a late reversal reaction by the response to corticosteroids (a reversal reaction will respond within a few days to weeks to prednisolone).

Centers which have (or have access to) facilities for biopsy examination and/or mouse foot pad inoculation should make optimal use of these opportunities for confirmation of the diagnosis. Suspect MB relapses require inoculation of the patient's strain of *Mycobacterium leprae* into mouse foot pads, for confirmation of the relapses as well as for drug-sensitivity testing, to assess whether the emergence of further drug resistance has been prevented by MDT.

Studies aimed at the identification of possible criteria for differentiation between a relapse and a reversal reaction, including the importance of histological examinations, should be carried out. The ALERT MDT Field Evaluation Study (AMFES) is, e.g., expected to identify possible criteria for differentiation (\*). However, the results of this study which was implemented during 1988 will, most probably, not be available before the late 1990s. Before the results of this and other studies become available and because the recommendations of such studies will probably not be applicable in all leprosy-endemic countries, there is an urgent and definite need for operational criteria for establishing the diagnosis of relapse.

The problem of distinguishing between a PB relapse and a late reversal reaction was recognized soon after introduction of MDT. It is very unfortunate that 10 years after the recommendation of MDT there are still no guidelines for differentiation under field conditions. The following operational procedures and criteria are recommended:

Patients who, at any time after release from MDT, present with new nerve function loss which, according to history or previous records, developed less than 6 months earlier should immediately be given a course

of prednisolone. What matters most to the patients is the prompt diagnosis and management of new nerve function loss in order to prevent (increase of) irreversible nerve function loss.

Patients who present with new clinical activity of the disease should, besides a thorough clinical examination, have their skin smears examined. In case of new skin lesions or any extension of previously existing lesions, the skin smears should be taken from these lesions. a) If an increase in the BI of at least 2 points is found in one or more sites in two sets of skin smears, the patient should be diagnosed with a MB relapse. b) If new clinical activity developed 4 years or more after release from MDT, while two sets of skin smears are negative, the patient should be diagnosed as suffering from a PB relapse. c) If new clinical activity developed less than 4 years after release from MDT, while two sets of skin smears are negative, the patient should be given a course of prednisolone. If there is quick response to this treatment, the patient should be diagnosed as suffering from a late reversal reaction. If there is no response to this treatment within a few weeks, a relapse should be diagnosed.

All of the above assessments should be done under close observation of the patients.

#### SUMMARY

Multidrug therapy (MDT), according to the recommendations of a WHO Study Group of 1982, was introduced in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT), Ethiopia, in January 1983. Paucibacillary (PB) patients are treated with 6 months of MDT. Multibacillary (MB) patients are treated with at least 2 years of MDT and until skin-smear negativity. An analysis was made of the relapses which had been diagnosed among self-reporting patients in four rural districts and Addis Ababa. Among 3065 PB patients, 34 relapses (1.1%) were diagnosed during an average period of 6.1 years after stopping MDT (range 2½ to 7½ years). Among 2379 MB patients, 24 relapses (1.0%) were diagnosed during an average period of 4.7 years after stopping MDT (range 2½ to 6 years). The estimated relapse rate per 1000 patient-years

after release from MDT was 2.1 for PB patients and 2.4 for MB patients.

From the analysis of the clinical, bacteriological, and histopathological findings, it was concluded that there was strong positive evidence for the diagnosis for 16 of the 34 relapses in the PB patients and for 0 of the 24 relapses in the MB patients. The main cause for overdiagnosis of MB relapses was that too much reliance had been put on skin-smear results, without a careful comparison of the results with those from before, during, and at completion of MDT; the diagnosis was based on the finding of positive smears in one set of smears only; insufficient attention was given to finding solid-staining bacilli; and findings in biopsies, if these were examined, did not confirm the diagnosis. The main cause of overdiagnosis of PB relapses was that too much reliance was put on histological findings, while these are often inconclusive for differentiating between a relapse and late reversal reaction.

Recommendations are made on how to limit overdiagnosis of relapses. Operational procedures and criteria for making the diagnosis under conditions where facilities for back-up histological and mouse foot pad investigations are not available are proposed.

### RESUMEN

En 1983 se introdujo la terapia con múltiples drogas (MDT) recomendada por la OMS, en el programa de control de la lepra del All Africa Leprosy and Rehabilitation Training Center (ALERT) de Etiopía. En este programa, en tanto que los pacientes paucibacilares (PB) se tratan durante 6 meses con la MDT, los pacientes multibacilares (MB) reciben la MDT hasta que alcanzan la negatividad bacilar, cuando menos durante 2 años. El análisis de los casos que recayeron y que se auto-reportaron en 4 distritos rurales de Addis Ababa, indicó que mientras que entre los 3065 pacientes PB se diagnosticaron 34 recaídas (1.1%) en un periodo promedio de 6.1 años después de haber suspendido la MDT (rango de 2.5 a 7.5 años), entre los 2379 pacientes MB, se diagnosticaron 24 recaídas (1.0%) en un periodo promedio de 4.7 años (rango de 2.5 a 6 años). El grado estimado de recaída por 1000 pacientes/año después de suspender el tratamiento fue de 2.1 para los pacientes PB y de 2.4 para los pacientes MB.

Del análisis de los datos clínicos, bacteriológicos, e histopatológicos, se concluyó que hubieron evidencias positivas para el diagnóstico en 16 de las 34 recaídas en los pacientes PB y en 0 de las 24 recaídas en los pacientes MB. La causa principal del sobrediagnóstico de recaídas en los pacientes MB fue la demasiada con-

fianza puesta en los resultados de los extendidos de linfa cutánea, sin una cuidadosa comparación de los resultados con aquellos obtenidos antes, durante, y al completar la MDT; el diagnóstico estuvo basado en el hallazgo de extendidos cutáneos positivos sólo en una serie de extendidos; se dió insuficiente atención al hallazgo de bacilos con tinción sólida, y los hallazgos en las biopsias, si estas fueron examinadas, no confirmaron el diagnóstico. La causa principal del sobrediagnóstico de las recaídas PB, fue que se le dió mucha importancia a los hallazgos histológicos, aún cuando estos no son concluyentes para diferenciar entre una recaída y una reacción reversa.

Se hacen recomendaciones para limitar el sobrediagnóstico de las recaídas y se proponen procedimientos operacionales y criterios, para hacer el diagnóstico bajo condiciones donde no hay facilidades para hacer investigaciones histológicas de apoyo o para realizar pruebas en la almohadilla plantar del ratón.

### RÉSUMÉ

La polychimiothérapie (PCT), selon les recommandations d'un groupe d'études de l'OMS en 1982, a été introduite dans le programme de lutte contre la lèpre du "All Africa Leprosy and Rehabilitation Training Center" (ALERT) en Ethiopie, en janvier 1983. Les patients paucibacillaires (PB) sont traités avec 6 mois de PCT. Les patients multibacillaires (MB) sont traités pendant au moins deux ans de PCT et jusqu'à négativation des frottis cutanés. Une analyse a été faite des rechutes qui ont été diagnostiquées parmi les patients se présentant spontanément dans 4 districts ruraux et à Addis Abeba. Parmi 3065 patients PB, 34 rechutes (1.1%) ont été diagnostiquées durant une période moyenne de 6.1 année après l'arrêt de la polychimiothérapie (extrêmes 2,5 ans à 7,5 ans). Parmi 2379 patients MB, 24 rechutes (1.0%) ont été diagnostiquées durant une période moyenne de 4,7 ans après l'arrêt de la PCT (extrême 2,5 ans à 6 ans). Le taux de rechute estimé pour 1000 patients-années après l'arrêt de la PCT était 2.1 pour les patients PB et 2.4 pour les MB.

A partir de l'analyse des observations cliniques, bactériologiques et histopathologiques, on a conclu qu'il y avait des signes cliniques évidents pour le diagnostic de 16 des 34 rechutes chez les patients PB et pour 0 des 24 rechutes des patients MB. La cause principale du surdiagnostic des rechutes MB était la trop grande confiance placée dans les résultats des frottis cutanés, sans une comparaison soigneuse des résultats avec ceux observés avant, durant et à la fin de la PCT; le diagnostic était basé sur la découverte de frottis positifs dans un prélèvement seulement. Une attention insuffisante était donnée à la recherche de bacilles colorés uniformément; et les observations faites au niveau des biopsies, si celles-ci étaient examinées, ne confirmaient pas le diagnostic. La cause principale du surdiagnostic des rechutes PB était que trop de confiance avait été placée dans les observations histologiques alors que celles-ci n'apportent souvent pas de conclusion défi-

nitive quant à la différenciation entre une rechute et une réaction réverse tardive. Des recommandations sont faites pour limiter le surdiagnostic des rechutes.

Des procédés opérationnels et des critères pour le diagnostic, dans des conditions où les facilités d'examen histologique et sur coussinet plantaire de souris ne sont pas disponibles, sont proposés.

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### REFERENCES

1. ALL AFRICA LEPROSY AND REHABILITATION TRAINING CENTRE. Manual for implementation of multidrug therapy. 2nd rev. Addis Ababa: ALERT, 1987.
2. ALL AFRICA LEPROSY AND REHABILITATION TRAINING CENTRE. Treatment manual. 3rd rev. Addis Ababa: ALERT, 1989.
3. ALL AFRICA LEPROSY AND REHABILITATION TRAINING CENTRE. Standardization of hospital medical records and procedures. Addis Ababa: ALERT, 1984.
4. ALL AFRICA LEPROSY AND REHABILITATION TRAINING CENTRE. ALERT's Field Evaluation Studies (AMFES). Research Protocol. Addis Ababa: ALERT, 1988.
5. BECX-BLEUMINK, M. Relapses in leprosy patients after release from dapsone monotherapy; experience in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. *Int. J. Lepr.* **60** (1992) 161-172.
6. BECX-BLEUMINK, M. and BERHE, D. Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy; experience in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. *Int. J. Lepr.* **60** (1992) 173-184.
7. BOERRIGTER, G., PONNIGHAUS, J. M. and FINE, P. E. M. Preliminary appraisal of WHO-recommended multiple drug regimen in paucibacillary leprosy patients in Malawi. *Int. J. Lepr.* **56** (1988) 408-417.
8. BOERRIGTER, G., PONNIGHAUS, J. M., FINE, P. E. M. and WILSON, R. J. Four-year follow-up results of a WHO-recommended multiple drug regimen in paucibacillary leprosy patients in Malawi. *Int. J. Lepr.* **59** (1991) 255-261.
9. EKAMBARAM, V. Duration of treatment for disease arrest in nonlepromatous cases and relapse rate in these patients. *Lepr. Rev.* **50** (1979) 297-302.
10. EKAMBARAM, V. and RAO, M. K. Relapse rate in paucibacillary leprosy patients after multidrug therapy in North Arcot District. *Indian J. Lepr.* **63** (1991) 34-42.
11. GIRDHAR, B. K. Multi-drug therapy in leprosy. *Indian J. Lepr.* **59** (1987) 145-151.
12. GROSSET, J. H. and JI, B. Recent advances in the chemotherapy of leprosy. *Lepr. Rev.* **61** (1990) 313-329.
13. GRUGNI, A., NADKARNI, N. J., KINI, M. S. and MEHTA, V. R. Relapses in paucibacillary leprosy after MDT—a clinical study. *Int. J. Lepr.* **58** (1990) 19-24.
14. HANSEN, B. H. Relapse in leprosy; an epidemiological study in a population of leprosy patients released from dapsone monotherapy, 1988.
15. JESUDASAN, K. and CHRISTIAN, M. Risk of paucibacillary leprosy patients released from control relapsing with multibacillary leprosy. *Int. J. Lepr.* **53** (1985) 19-21.
16. KAR, P. K., JHA, P. K., PANAYACH, J. S. and SNEHI, P. S. A clinico-pathological study of multidrug regimen in paucibacillary leprosy. *Indian J. Lepr.* **60** (1988) 235-241.
17. KATOCH, K. Recent trends in chemotherapy of paucibacillary leprosy. *ICMR Bull.* **20** (1990).
18. KATOCH, K., RAMANATHAN, U., NATARAJAN, M., BAGGA, A. K., BHATIA, A. S., SAXENA, R. K. and RAMU, G. Relapses in paucibacillary patients after treatment with three short term regimens containing rifampin. *Int. J. Lepr.* **57** (1989) 458-464.
19. NEGESSE, Y. and MIKO, T. L. Remarks on criterion of nerve function alteration as a sign of relapse in leprosy patients during surveillance or postsurveillance periods. (Letter) *Int. J. Lepr.* **58** (1990) 722.
20. NILSEN, R., MSHANA, R. N., NEGESSE, Y. and KANA, B. Immunohistochemical studies of leprosy neuritis. *Lepr. Rev.* **57** Suppl. 2 (1986) 177-187.
21. PANDIAN, T. D., SITHAMBARAM, M., BHARATHI, R. and RAMU, G. A study on relapses in non-lepromatous and intermediate groups of leprosy. *Indian J. Lepr.* **57** (1985) 149-158.
22. PANNIKAR, V., JESUDASAN, K., VIJAYAKUMARAN, P. and CHRISTIAN, M. Relapse or late reversal reaction. *Int. J. Lepr.* **57** (1989) 526-628.
23. PATTYN, S. R., HUSSER, J. A., BAQUILLON, G., MAIGA, M. and JAMET, P. Evaluation of five treatment regimens, using either dapsone monotherapy or several doses of rifampicin in the treatment of paucibacillary leprosy. *Lepr. Rev.* **61** (1990) 151-156.
24. PAVITHRAN, K. Relapse of paucibacillary leprosy after short course multidrug therapy. *Indian J. Lepr.* **60** (1988) 225-229.
25. PAVITHRAN, K. Multidrug therapy for pauciba-

- cillary patients: WHO regimen inadequate? *Lepr. Rev.* **58** (1987) 306–308.
26. RAMACHANDRAN, A. and SESHADRI, P. S. Relapse or reversal reaction: the case for a therapeutic trial of steroids. *Lepr. Rev.* **59** (1988) 271–272.
  27. RAMANAN, R., MANGIANI, P. R., GHORPADE, A. and BHAGOLIWAL, S. K. Follow-up study of paucibacillary leprosy on multidrug regimen. *Indian J. Lepr.* **59** (1987) 50–53.
  28. RANGARAJ, M. and RANGARAJ, J. Experience with MDT in Sierra Leone; clinical, operational and managerial analysis. *Lepr. Rev.* **57** Suppl. 3 (1986) 77–91.
  29. REDDY, P. K. and MOHINUDDIN, S. K. Pattern of relapses in paucibacillary leprosy patients treated with M.D.T. (W.H.O. 1982). *Indian J. Lepr.* **60** (1988) 581–588.
  30. REPORT OF A PRE-CONGRESS WORKSHOP COMMITTEE. Workshop 4. Leprosy control, evaluation and integration. *Int. J. Lepr.* **57** (1989) 282–283.
  31. REVANKAR, C. R., KARJIVKAR, V. G., GURAV, V. J. and GANAPATI, R. Clinical assessment of paucibacillary leprosy under multidrug therapy—three years followup study. *Indian J. Lepr.* **61** (1989) 344–349.
  32. RIDLEY, D. S. and LUCAS, S. B. The use of histopathology in leprosy diagnosis and research. *Lepr. Rev.* **60** (1989) 257–262.
  33. RIDLEY, D. S. and RIDLEY, M. J. Classification of nerves is modified by the delayed recognition of *Mycobacterium leprae*. *Int. J. Lepr.* **54** (1986) 596–606.
  34. 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. Persisting *Mycobacterium leprae* among THELEP trial patients in Bamako and Chingleput. *Lepr. Rev.* **58** (1987) 325–337.
  35. TIWARI, V. D., TUTAKNE, M. A., SINGH, G. and DUTTA, R. K. Multidrug therapy in hospitalised leprosy cases. *Indian J. Lepr.* **60** (1988) 71–76.
  36. VAN BRAKEL, W., KIST, P., NOBLE, S. and O'TOOLE, L. Relapses after multidrug therapy for leprosy: a preliminary report of 22 cases in West Nepal. *Lepr. Rev.* **60** (1989) 45–50.
  37. VELLUT, C., LECHAT, M. F. and MISSON, C. B. Tuberculoid relapses. *Leprosy; Proceedings of the XI International Congress of Leprosy, 1978, Mexico City*. Amsterdam: Excerpta Medica, 1980, pp. 293–298.
  38. WATERS, M. F. R. The chemotherapy of leprosy. In: *The Biology of the Mycobacteria; Volume 3. Clinical Aspects of Mycobacterial Disease*. Ratledge, C., Stanford, J. and Grange, J. M., eds. London: Academic Press, 1989, pp. 406–474.
  39. WATERS, M. F. R., REES, R. J. W., LAING, A. B. G., KHOO KAH FAH, MEADE, T. W., PARIKSHAK, M. and NORTH, W. R. S. The rate of relapse in lepromatous leprosy following completion of twenty years of supervised sulphone therapy. *Lepr. Rev.* **57** (1986) 101–109.
  40. WATERS, M. F. R., RIDLEY, D. S. and RIDLEY, M. J. Clinical problems in the initiation of multidrug therapy. *Lepr. Rev.* **57** Suppl. 3 (1986) 92–100.
  41. WHO EXPERT COMMITTEE ON LEPROSY. Sixth report. Geneva: World Health Organization, 1988. Tech. Rep. Ser. 768.
  42. WHO STUDY GROUP. Chemotherapy of leprosy for control programmes. Geneva: World Health Organization, 1982. Tech. Rep. Ser. 675.
  43. WORLD HEALTH ORGANIZATION. A Guide to Leprosy Control. 2nd edn. Geneva: World Health Organization, 1988.
  44. WORLD HEALTH ORGANIZATION. Report of a consultation on implementation of multidrug therapy for leprosy control. Geneva: World Health Organization, 1985. WHO/LEP/85.1.
  45. WORLD HEALTH ORGANIZATION. Report of the consultation on technical and operational aspects of leprosy, Male, Maldives. Geneva: World Health Organization, 1990. WHO/CTD/LEP/90.3.
  46. WORLD HEALTH ORGANIZATION. Report of the interregional conference on leprosy control in Africa, Brazzaville. Geneva: World Health Organization, 1989. WHO/CDS/LEP/89.1.
  47. WORLD HEALTH ORGANIZATION. Report of the second coordinating meeting on implementation of multidrug therapy in leprosy control programmes, Geneva, 1986. Geneva: World Health Organization, 1987. WHO/CDS/LEP/87.2.
  48. WORLD HEALTH ORGANIZATION. Standard protocol for chemotherapy trials in non-lepromatous leprosy. Geneva: World Health Organization, 1982. TDR/THELEP/PROTOCOL/82.1.