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# Combined regimens of one year duration in the treatment of multibacillary leprosy—I. Combined regimens with rifampicin administered during one year

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*Summary* In 1981, 1982 and 1983, 216 multibacillary patients in Anjouan (Comores) and Burundi were treated for 8 weeks with daily rifampicin (600 mg) ethionamide (500 mg) and dapsone (100 mg) or clofazimine (100 mg) followed for 44 weeks by once weekly rifampicin (600 mg) and daily ethionamide (500 mg) and dapsone (100 mg) or clofazimine (100 mg). There were 109 previously untreated patients and 107 patients who had had dapsone monotherapy, 16 of whom were infected with proven dapsone resistant *Mycobacterium leprae*. Clinical and bacteriological results were excellent but hepatotoxicity of this regimen remains a problem.

No relapses were observed during a 2 to 6 years (mean: 4·29 years) follow-up period after the end of treatment (upper 95% confidence limit of 0·40 per 100 persons years). It is concluded that multibacillary leprosy can be successfully treated with a regimen of one year duration, but less toxic regimens, more easily applicable in the field, are necessary.

## Introduction

At present, 4 drugs are known to be active against *Mycobacterium leprae*. Their characteristics have been thoroughly studied in experimental infections in mice[1–9] and in man.[10–12] Two of them, rifampicin (RMP) and the thioamides ethionamide (ETH) or prothionamide (PRO), are bactericidal, the two others, dapsone (DDS) and clofazimine (CLO), are primarily bacteriostatic and slowly bactericidal.

The optimal use of these drugs for the treatment of leprosy, particularly of multibacillary (MB) leprosy, is still unknown. The combined therapy regimen advocated by the WHO,[13] based on the most recent knowledge regarding bacteriology of *M. leprae*, immunology of the patient, and epidemiology of the disease, is one of many possibilities. In order to establish the ideal combination

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of drugs, with a minimal duration of treatment, and minimal side-effects, the organization of prospective therapeutic trials is needed.[14,15]

The results of two combined regimens of one year duration, with a follow-up period of 4 and 5 years, have been published.[16] The shortcomings of these regimens, one using 2 drugs and the other 3 drugs, were discussed. The two-drug regimen, consisting of RMP and DDS, is unacceptable in the light of the high and increasing prevalence of DDS resistance (DDS-R), which was unknown at the moment the trial was initiated.[17] In fact, a substantial number of patients, harbouring DDS-R organisms, would receive RMP in monotherapy, implying the risk of selection of RMP-R mutants of *M. leprae*, which would lead to relapses not responding to RMP.

A prospective therapeutic trial in MB leprosy patients, using a triple drug regimen of 1 year duration, was conducted in Burundi (BUR) and on the island of Anjouan (ANJ), part of the République Fédérale Islamique des Comores, from 1981 to 1984. The results of the patient cohorts of 1981, 1982 and 1983 who have been followed up for 5 to 7 years after the start of treatment are presented in this analysis.

## Patients and methods

Patients were diagnosed either after self-reporting to the leprosy service, or through referral or examination of contacts. All patients were examined clinically and neurologically by experienced paramedical workers. Disabilities were noted using the WHO scale.[18,19] Twelve (6 right and 6 left) peripheral nerves (*n. retroauricularis, n. ulnaris, n. medianus, n. radialis* (*ramus cutaneus*), *n. peroneus communis* and *n. tibialis posterior*) were routinely examined for hypertrophy, tenderness at palpation, and spontaneous tenderness. A skin smear was taken at 3 sites (one earlobe and two skin lesions), and examined locally. Only the number of bacilli was taken into consideration. The quality of the locally performed bacteriological examination was checked by regularly sending skin smear slides to Antwerp for verification. All results were recorded on specially designed files, a copy of which was sent to Antwerp.

In Burundi most patients were biopsied routinely from the start, in Anjouan after the trial had been going on for about 6 months. They were fixed in 10% formalin and sent to Antwerp. Sections were stained by the Trichrome Fite-Farracco technique.

Multibacillary (MB) leprosy was diagnosed when the bacteriological index (BI) was 2 or more (Ridley scale)[20] at any of the 3 sites examined. Patients were taken into the trial if they agreed to stay in or near the treatment centre for 12 months, or if they were capable of coming to the treatment centre daily. Thus all treatments were supervised.

Follow-up examinations are performed yearly, and are identical to those at intake. Most patients were biopsied 2 years after the end of treatment. Follow-up biopsies are taken annually till histopathological cure is established. Criteria for evaluation of the therapy are: absence of active clinical lesions, decrease of the BI in skin smears and biopsies, absence of solidly staining bacilli in the biopsies, decrease or even disappearance of histopathological lesions, and absence of side-effects. Evaluation of neurological complications was done in two ways. The disability score at the last folow-up examination was compared to the score at intake, and each change was noted. Likewise, the number of hypertrophied nerves at the last follow-up examination was compared to the number at intake, and each change was noted.

The drug regimen used (8-44 RED) was: RMP 600 mg, ETH 500 mg and DDS 100 mg daily (except on Sundays) for 8 weeks, followed by RMP 600 mg once a week, with ETH 500 mg and DDS 100 mg daily for 44 weeks. This regimen was given to all previously untreated patients, to Anjouan patients previously treated with DDS or DDS–CLO for less than 5 years, and to previously treated Burundi patients shown, during a previous DDS-R survey,[21] to harbour DDS-sensitive *M. leprae*. An identical regimen, but with CLO replacing DDS (regimen 8-44 REC), was given to previously treated Burundi patients shown to harbour DDS-R organisms.[21] In Anjouan, none of the patients

had a history of more than 5 years of previous treatment. Therefore no DDS resistance was suspected in those patients. Four of the 16 proven DDS-R cases, as well as 2 of the 8 previously treated DDS-sensitive Burundi patients, had received one dose of 1500 mg RMP 12 to 24 months prior to inclusion in the present study.

Every drug administration, as well as the occurrence of complications (mainly reactions and hepatitis) and their treatment, was noted on a treatment file. Upgrading reactions were treated with acetyl-salicylic acid, antiphlogistics and corticosteroids. ENL was treated with the same drugs, with the addition of thalidomide in males, and in females of unfertile age. SGOT, SGPT and serum bilirubin were determined monthly on Anjouan. Since 1982 in Burundi, serum tests were performed when hepatitis was clinically suspected.

If a patient showed an increase in liver enzymes, RMP and ETH administration was stopped till serum levels returned to normal.

Statistical analysis was done by the Student $t$-test, the $\chi^2$ test with Yates' continuity correction for $2 \times 2$ tables, and the Mantel–Haenszel $\chi^2$ test for comparing rates. Confidence limits, assuming a binomial distribution, were taken from *Tabulae Scientificae*.[22]

## Results

Five groups of patients are considered: BUR patients, previously untreated, receiving 8-44 RED, ANJ patients, previously untreated, receiving 8-44 RED, BUR patients, previously treated, receiving 8-44 RED, ANJ patients, previously treated, receiving 8-44 RED, BUR patients, previously treated, receiving 8-44 REC. One BUR patient, previously untreated, was erroneously given 8-44 REC.

Two hundred and thirty-one patients were started on the trial regimen in 1981, 1982 and 1983. Before the first year of follow-up, 2 patients died of liver complications, 6 died of unrelated causes, and 7 (3·0%) were lost to follow-up. Two patients found to have taken leprostatic drugs after the end of the study regimen were also eliminated from the analysis, which totals 214 patients: 3 were followed for 1 year, 14 for 2 years, 24 for 3 years, 81 for 4 years, 60 for 5 years and 32 for 6 years after the end of treatment (Table 1). This gives a total of 919 person years of follow-up with a mean of 4·24 years.

The bacteriological characteristics of the patients at the moment of intake are summarized in Table 2. The mean BI at intake of previously treated patients: 2·80 is significantly lower than that of previously untreated patients: 3·43 ($0{\cdot}001 < p < 0{\cdot}01$).

Once treatment was started, clinical improvement in all patients was rapid. The BI's were by no means negative at the end of treatment, but they continued to decrease steadily afterwards, although the decrease differed considerably from patient to patient. Of the 212 patients followed-up

**Table 1.** Follow-up of the multibacillary patients taken into the study in Birundi and Anjouan in 1981, 1982, 1983

| | 1981 | 1982 | 1983 | 1984 | 1985 | 1986 | 1987 | 1988 |
|---|---|---|---|---|---|---|---|---|
| Patients taken in | 52 | 96 | 66 | — | — | — | — | — |
| Patients | | | | | | | | |
| died | — | — | — | — | 4 | 1 | 1 | — |
| lost | — | — | — | — | — | 7 | 22 | — |
| Patients seen | — | — | 52 | 148 | 210 | 202 | 179 | 128 |
| Patients not yet seen | | | | | | | | 51 |

**Table 2.** Bacteriological characteristics of patients at intake

| Regimen | 8-44 RED (BUR + ANJ) | | 8-44 REC (BUR) | |
|---|---|---|---|---|
| Treatment history | Untreated | Treated | Treated* | Total |
| *n* of patients | 106 | 91 | 17 | 214 |
| BI at intake† | | | | |
| Mean | 3·43 | 2·74 | 3·18 | 3·13 |
| SD | 1·06 | 1·19 | 1·24 | 1·18 |
| Median | 3·5 | 2·5 | 3·5 | 3·5 |
| Range | 1–6 | 0·5–5 | 0·5–5 | 0·5–6 |

8-44 RED/8-44 REC, see Patients and methods.

BUR, Burundi; ANJ, Anjouan; *n*, number; SD, standard deviation.

*1 previously untreated patient, who erroneously received this regimen, had a BI at intake of 3·5.

† Calculations are based on mean BI per patient rounded to the nearest 0·5. Thus a skin smear result of 4-2-2 becomes 2·5, while a result of 2-0-0 becomes 0·5.

until recently, 186 (87·7%) have a negative BI (Table 3). All 26 patients with a positive BI at the last follow-up examination show a satisfactory clinical and bacteriological evolution, except for one patient, whose initial BI was 4 and still is 3·5 at 5 years. However all bacilli are granular and the skin lesions have all but disappeared.

During follow-up none of the patients showed any sign of relapse as defined clinically by the appearance of new lesions or aggravation of existing lesions, and bacteriologically by a BI becoming positive again after negativation or increasing with at least 2 units at any site. The 95% confidence intervals for 0 relapses according to the person years per year of follow-up, are given in Table 4.

There were 12 cases of hepatitis (5·1%) 2 of whom died. No differences between any of the groups could be demonstrated. Upgrading reactions were observed in 16·1% of the patients. They occurred more frequently in previously untreated (21·7%) than in previously treated (9·1%) patients, but the difference is not significant ($0{\cdot}1 < p < 0{\cdot}05$). Five of the upgrading reactions (= 20·8%) started after stopping treatment, at 4, 8, 20, 25 and 28 months after the end of therapy. These are late reversal reactions, with a mean incubation time of 17 months, and a median of 20

**Table 3.** Evolution of the bacterial index after stopping treatment

| Number of patients | | 214 |
|---|---|---|
| Annual decrease of BI in units | *n* | % |
| 0 | | 0 |
| 0·01–0·49 | 11 | 5·1 |
| 0·50–0·99 | 86 | 40·2 |
| 1·00–1·49 | 66 | 30·8 |
| 1·50+ | 51 | 23·8 |
| Negative at moment of analysis | 186 | 86·9 |
| Mean annual decrease | | 1·12 |

**Table 4.** Ninety-five per cent confidence intervals for 0 relapses, according to the person years of follow-up, and assuming a binomial distribution of the occurrence of relapses

| Years of follow-up | Number of patients seen | Person years of follow-up (cumulative) | Confidence interval for 0 relapses per 100 person years |
|---|---|---|---|
| 1 | 214 | 214 | 0–1·73 |
| 2 | 211 | 425 | 0–0·87 |
| 3 | 197 | 622 | 0–0·59 |
| 4 | 173 | 795 | 0–0·46 |
| 5 | 92 | 877 | 0–0·42 |
| 6 | 32 | 919 | 0–0·40 |

months. ENL reactions occurred in 16·8% of the patients. They were more frequent in Anjouan (20·8%) than in Burundi (7·0%), but the difference is not significant ($0{\cdot}1 < p < 0{\cdot}05$). Although only 1 upgrading reaction and no ENL were observed in the 17 patients receiving 8-44 REC, this was not significantly different from the observations in the 8-44 RED patients ($0{\cdot}8 < p < 0{\cdot}7$ for upgrading reaction; $0{\cdot}2 < p < 0{\cdot}1$ for ENL).

Table 5 shows the changes in neurological observations. The number of hypertrophied nerves at intake is compared to the number hypertrophied at the last follow-up examination. Table 5 gives the number of patients in whom the number of hypertrophied nerves remained unchanged, increased (by 1 to 4 nerves), and decreased (by 1 to 10 nerves). Overall, 8·9% of the patients show an increase

**Table 5.** Neurological evolution of the patients: change between last follow-up examination and examination at intake

| | 8-44 RED | | | | 8-44 REC | |
|---|---|---|---|---|---|---|
| Regimen | Untreated | | Treated | | Treated | Total |
| Treatment history | | | | | | |
| Country (*n*) | BUR (19) | ANJ (87) | BUR (8) | ANJ (83) | BUR (17) | (214) |
| Nerve hypertrophy | | | | | | |
| Unchanged: *n* (%} | 2(10) | 21(24·1) | 2(25) | 26(31·3) | 4(23·5) | 55(25·7) |
| Increased: *n* (%) | | | | | | |
| By 1 to 2 nerves | 1(5·2) | 5(5·7) | 3(37·5) | 5(6) | 2(11·7) | 16(7·5) |
| By 3 to 4 nerves | 1(5·2) | 1(1·1) | 1(12·5) | — | 0 | 3(1·4) |
| Decreased: *n* (%) | | | | | | |
| By 1 to 3 nerves | 9 | 38 | 1 | 37 | 3 | 88 |
| By 4 to 6 nerves | 4 | 19 | — | 13 | 8 | 44 |
| By 7 to 10 nerves | 2 | 3 | 1 | 2 | — | 8 |
| Total | 15(80) | 60(69) | 3(37·5) | 52(62·7) | 11(64·7) | 140(65·4) |
| Disability scores | | | | | | |
| Unchanged | 81(71) | 482(92·3) | 41(85) | 421(84·5) | 66(65) | 1091(85) |
| Worsened 1–2 units | 30(26·3) | 36(6·9) | 3(6·2) | 58(11·6) | 25(24·5) | 152(12) |
| Worsened 3 units | | | | | 3(2·9) | 3(·2) |
| Improved 1–2 units | 3(2·6) | 4(·7) | 2(4·2) | 19(3·8) | 8(7·8) | 36(2·8) |
| Improved 3 units | | | 2(4·2) | | | 2(·1) |

8-44 RED/8-44 REC *see* Patients and Methods.
BUR, Burundi; ANJ, Anjouan; *n* number.

in hypertrophied nerves: 84% of these have 1 or 2 additional hypertrophied nerves, and 16% have 3 or 4. There is no significant difference between previously treated and previously untreated patients nor between REC and RED groups nor between Anjouan and Burundi patients. An often dramatic decrease in hypertrophied nerves was seen in 65·4% of patients. No differences are manifest between Anjouan and Burundi patients, nor between previously treated and untreated patients, nor between REC and RED patients.

Table 5 also shows the changes in disability scores (WHO scoring system, 6 scores per patient) between the examination at intake and the last follow-up examination. At the last follow-up 2·9% of all scores were improved, while 12·2% of the scores were worse. Increase in disability score was significantly worse in REC (35·3%) than in RED (7·0%) patients ($0{\cdot}001 < p < 0{\cdot}005$). It was also significantly worse in Burundi (28·3%) than in Anjouan (4·1%) patients ($p < 0{\cdot}001$). It should be noted that all REC patients are Burundi patients.

## Discussion

The necessity for combined chemotherapy in MB leprosy has been recognized for about 15 years,[19] but how to apply such a combined therapy was entirely unknown, particularly with respect to the drugs to be given, the frequency of their administration and the duration of therapy.

The regimen investigated was conceived in 1980 well before the regimen for chemotherapy of leprosy for control programmes by the World Health Organization was conceived and published. By analogy with what is known about the therapy of tuberculosis we suggested that in leprosy an association of two, preferably three bactericidal drugs (but only 2, RMP and ETH, are available in leprosy) have to be given with the addition of one bacteriostatic drug.[15]

In this interpretation the use of a second bacteriostatic drug would be unnecessary. Therefore we used DDS in new patients never treated before and replaced it by CLO in patients with proven DDS-R leprosy and in those treated for 5 years or more with DDS monotherapy, because these patients are at risk of harbouring DDS-R *M. leprae*. Since that time it has been made clear[23] that the multibacillary patient harbours three populations of leprosy bacilli: 1, an overwhelming number of drug sensitive organisms; 2, several small populations of naturally occurring mutants resistant to individual drugs; and 3, a small population of drug sensitive nonmultiplying bacilli known as persisters, which by definition, are untouched by any drug or drug combination. The great majority of the population, being RMP-S is killed by RMP, while the RMP-R fraction has to be eliminated by the other drugs administered, in this case either ETH and DDS or ETH and CLO.

It was also thought that treatment could consist of two phases: an intensive introductory phase of 2 months during which RMP is given daily, followed by a second less intensive phase during which RMP is given only once a week. From experiments in mice and studies in man it is known that RMP in contrast to ETH is still active against *M. leprae* when administered only once a week.[1,3,4,11] This would allow RMP to be administered under supervision in field conditions once a week during the second phase of treatment.

The opinion prevails that MB leprosy has to be treated until bacteria are completely cleared from the skin, and even longer. This was probably true as long as only monotherapy with the mainly bacteriostatic drug dapsone was available. However this opinion has to be revised when powerful bactericidal drugs are administered, leading to a dissociation between rapid bacterial killing and slow elimination of the dead bacilli from the skin. The more so since Shepard[24] showed that in mice, drug combinations, particularly ETH–DDS and ETH–CLO with or without RMP are additive in bacterial killing. It may therefore be justified in these circumstances to stop antibacterial treatment in MB leprosy before bacterial negativity in the skin is reached. On a purely empirical basis it was hoped that the different actively metabolizing subpopulations of *M. leprae* would be killed by the three drugs within one year and therefore this duration of treatment was chosen. The judgement of the efficacy of treatment regimens in MB leprosy has to be based on clinical, bacteriological, and

histopathological evaluation of the disease process and above all on the absence of relapse. Relapse is defined clinically as appearance of new lesions or aggravation of existing ones, and bacteriologically (BI increasing by at least 2 units at any site examined, compared with a previous examination) confirmed by histopathology (increase of the BI by at least 2 units and increase of the morphological index as well).

In the present study, no relapses were observed after a mean follow-up period of 4·29 years after the end of treatment and a total of 919 person years of follow-up. It is expected that for 95% of the time, the regimen under study will give rise to less than 0·40 early relapses per 100 person-years of follow-up. This absence of relapses should be compared to the relapse rate after DDS monotherapy. The literature was searched for studies looking at clearly defined MB patients whose treatment was stopped and mentioning the person-years of follow-up. Three studies mention relapses after stopping short-course (mean: 3·5 years) DDS monotherapy: Erickson[25] observed 5 relapses in 11 patients, with a total of 22 person-years of follow-up; Price[26] found 6 relapses among 24 patients with a total of 20·2 person-years of follow-up; Lowe[27] found 15 relapses among 139 patients with a total of 255 person years of follow-up. The comparison of each of these relapse rates with the O relapse rate found in the present study, gives highly significant results ($p < 0{\cdot}0005$).

One study[28] covered relapses after prolonged (19–22 years) DDS monotherapy. The patients were followed up to 8 and 9 years. During the first 4 years of follow-up, 11 relapses were observed for a total of 1297 person years of follow-up. Compared with the present study in which treatment was stopped after 12 months, regardless of the BI at that moment, this difference is highly significant ($p = 0{\cdot}007$). The regimen studied did not only kill the RMP sensitive *M. leprae* population, but the daily ETH–DDS combination for one year also eliminated the RMP resistant mutants. The BI continues to decrease after therapy is stopped, illustrating once more that it is not necessary to continue treatment until the BI is negative. The mean annual decrease (1·12) is near the theoretically expected decrease of 1·00. However, 65·5% of the patients are slow decreasers ( $< 0{\cdot}5$ units per year), while 23·8% are rapid decreasers ( $> 1{\cdot}5$ units per year). It is possible that these rapid decreasers were originally BT patients who downgraded to BL or LLs but who, aided by the therapy, return towards the tuberculoid pole of the spectrum. The slow decreasers could be originally lepromatous patients who remain at the lepromatous end of the spectrum throughout their evolution. The data assembled in the present study do not permit us to check this assumption. A considerable number of patients (87%) have become bacteriologically negative at the moment of the present analysis. In view of the continuing decrease in BI, it is expected that all those patients will eventually become negative.

Hepatotoxicity is the most serious complication.[29] There were 11 cases of icterus, incidence 4–7%, two patients died (one in Burundi and one in Anjouan). The incubation time for the appearance of hepatitis varied between 25 and 364 days, with a mean of 104 days and a median of 150 days. In three sera from Burundi obtained during the acute phase of the disease, hepatitis B, anti-HBs and anti-HBc antibodies were present, indicating an infection with hepatitis B virus in the past. Hepatitis, in the absence of therapy is sometimes seen in leprosy patients, but its incidence in Central Africa can be estimated at about 1%. Although RMP and the tioamides are hepatotoxic to a certain degree, their association however is more so.[29,30] Fear of possible greater nerve damage due to the use of rapidly bactericidal drugs was not confirmed. Upgrading reactions occurred in 16·1% of the patients. This is comparable to the 17% observed after WHO therapy,[31] but less than the 50·2% observed after a regimen consisting of 182 administrations of RMP.[30] The regimen under study consists of 92 RMP administrations. The higher frequency in previously untreated patients is in agreement with observations made in other areas.[30] The overall ENL frequency of 16·8% is also comparable to the 13·2% observed previously.[31]

The reactions did not lead to increased nerve deterioration. In fact, many more patients showed neurological improvement than aggravation. The Burundi patients performed worse than the Anjouan patients in terms of neurological complications. This is probably due to the small surface of Anjouan, which makes the well-staffed leprosy service easily and immediately accessible at the onset of neurological complications.

The observations in this study do not make any assumptions about the protective action of CLO against upgrading reactions,[31] although they point in this direction.

The present study shows that MB leprosy can be successfully treated with a regimen of 1 year duration, in terms of clinical improvement, bacteriological decrease and absence of relapses. However, the hepatotoxicity of the combination RMP–ETH constitutes a serious drawback to its generalized use in the field, where close monitoring of the hepatic function is difficult. Moreover the amount of RMP used, as well as the necessity for close supervision of the patient often necessitating hospitalization, may prove to be too much of a financial and logistic burden for many leprosy control programmes. After this study was initiated, it has been shown that no difference in the killing effect against *M. leprae* can be demonstrated between daily and monthly RMP treatment.[32] The search for alternative regimens, less toxic, and more easily applicable in difficult field situations, needs to be continued.

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**References**

[1] Colston MJ, Ellard GA, Gammon PT. Drugs for combined therapy: experimental studies on the antileprosy activity of ethionamide and prothionamide and general review. *Lepr Rev*, 1978; **49:** 115–26.
[2] Ellard GA. Growing points in leprosy research. Recent Advances in the chemotherapy of leprosy. *Lepr. Rev*, 1974; **45:** 31–40.
[3] Pattyn SR, Saerens EJ. Results of intermittent treatment with dapsone and rifampicin in mice inoculated with *Mycobacterium leprae. Ann Soc Belge Med Trop*, 1974; **54:** 35–41.
[4] Pattyn SR. Further data on the effect of ethionamide and prothionamide in experimental leprosy. *Lep. Rev*, 1978; **49:** 199–202.
[5] Pattyn SR, Van Loo G. Combined chemotherapy against *Mycobacterium leprae* in the mouse. *Ann Soc Belge Med Trop*, 1980; **60:** 291–5.
[6] Pattyn SR, Portaels F, Van Loo G, Van den Breen L. Activity of the combination of isoniazed, prothionamide and dapsone against *Mycobacterium leprae* and some other mycobacteria. *Drug Res*, 1981; **31:** 2155–7.
[7] Shepard CC. Minimal effective dosages in mice of clofazimine and of ehtionamide against *Mycobacterium leprae. Proc Soc Exp Biol Med*, 1969; **132:** 120–4.
[8] Shepard CC. Combination of drugs against *Mycobacterium leprae*, studied in mice. *Int J Lepr*, 1972; **40:** 33–9.
[9] Shepard CC. Experimental chemotherapy in leprosy, then and now. *Int J Lepr*, 1973; **41:** 307–19.
[10] Gelber RH, Waters MR, Pearson JMH, Rees RJW, McDougall AC. Dapsone alone compared with dapsone plus rifampicin in short-term therapy of lepromatous leprosy. *Lepr Rev*, 1977; **48:** 223–9.
[11] Shepard CC, Levy L, Fasal P. Rapid bactericidal effect of rifampin on *Mycobacterium leprae. Am J Trop Med Hyg*, 1972; **21:** 446–9.
[12] Shepard CC, Levy L, Fasal P. Further experience with the rapid bactericidal effect of rifampin on *Mycobacterium leprae. Am J Trop Med Hyg*, 1974; **23:** 1120–4.
[13] WHO Study Group. Technical Report Series No. 675. *Chemotherapy of leprosy for control programmes.* Geneva 1982.
[14] Pattyn SR. Comments on the chemotherapy of leprosy as influenced by the present knowledge on *Mycobacterium leprae. Lepr Rev*, 1972; **43:** 126–6.
[15] Pattyn SR. The strategy of leprosy treatment: a personal view. *Ann Soc Belge Med Trop*, 1980; **60:** 253–62.
[16] Pattyn SR, Saint André P, Ferracci C, Baquillon G. Comparative study of two regimens of combined therapy of one year duration in multibacillary leprosy. *Int J Lepr*, 1984; **52:** 297–303.
[17] Bacquillon G, Ferracci C, Van Loo G, Pattyn SR. Further results on dapsone resistant leprosy in Bamako (Mali). *Lepr Rev*, 1983; **54:** 19–21.
[18] WHO Study Group Expert Committee on Leprosy. Third Report. Technical Report Series No. 319. WHO: Geneva, 1966.

[19] WHO Study Group Expert Committee on Leprosy. Fourth Report. Technical Report Series No. 459. WHO: Geneva, 1970.
[20] Ridley S. The histopathology of leprosy. *Documenta Geigy*, Basel. Switzerland.
[21] Bourland J, Van Loo G, Pattyn SR. Dapsone resistant leprosy in Burundi. *Lepr Rev*, 1983; **54:** 239–42.
[22] Tabulae Scientificae. Documenta Geigy. 7th Ed. 1978—Ciba-Geigy. Basel, Switzerland.
[23] Ellard GA. Chemotherapy of leprosy. *Brit Med Bull*, 1988; **44:** 775–90.
[24] Shepard CC. Combinations involving dapsone, rifampin, clofazimine, and ethionamide in the treatment of *M. leprae* infections in mice. *Int J Lepr*, 1976; **44:** 135–9.
[25] Erickson PT. Relapse following apparent arrest of leprosy by sulfone therapy. *Pub Hlth Rep*, 1950; **65:** 1147–57. Reprinted in *Int J Lepr.* 1952; **20:** 229–38.
[26] Price RB. Relapse of leprosy in American Samoa. *Amer J Trop Med Hyg*, 1959; **8:** 358–63.
[27] Lowe J. The late results of sulphone treatment of leprosy in East Nigeria. *Lepr Rev*, 1954; **25:** 113–24.
[28] Waters MFR, Rees RJW, Laing ABG, Khoo Kah Fah, Meade TW, Parikshak N, North WRS. The rate of relapse in lepromatous leprosy following completion of twenty years of supervised sulphone therapy. *Lepr Rev*, 1986; **57:** 101–9.
[29] Pattyn SR, Janssens L, Bourland J, Saylan T, Davies E, Grillone S, Ferracci C. Hepatotoxicity of the combination of rifampicin-ethionamide in the treatment of multibacillary leprosy. *Int J Lepr*, 1984; **52:** 1–6.
[30] Cartel JL, Millan J, Guelpa Lauras CC, Grosset JH. Hepatitis in leprosy patients treated by a daily combination of dapsone rifampicin and a thioamide. *Int J Lepr*, 1983; **51:** 461–5.
[31] Groenen G, Janssens L, Kayembe T, Nollet E, Coussens L, Pattyn SR. A prospective study on the relationship between intensive bactericidal therapy and leprosy reactions. *Int J Lepr*, 1986; **54:** 236–44.
[32] 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*, 1987; **58:** 325–37.