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Chemotherapy of leprosy for control programmes

Report of a
WHO Study Group

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CONTROL PROGRAMMES

Geneva, 12-16 October 1981

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CHEMOTHERAPY OF LEPROSY FOR CONTROL PROGRAMMES

Report of a WHO Study Group

A WHO Study Group on Chemotherapy of Leprosy for Control Programmes met in Geneva from 12 to 16 October 1981. The objectives of the meeting were:

- (1) to review information collected since 1976 (the year when the WHO Expert Committee on Leprosy last met) on the problems related to chemotherapy and chemotherapeutic regimens of leprosy;
- (2) to recommend, for use in leprosy control programmes, appropriate multidrug regimens for multibacillary cases including new, treated, and drug-resistant cases, whether clinically suspected or proved;
- (3) to recommend regimens for paucibacillary cases; and
- (4) to identify further research needs in the clinical and operational aspects of chemotherapy of leprosy.

The meeting was opened by Dr A. Zahra, Director, Division of Communicable Diseases, on behalf of the Director-General. He noted that leprosy control programmes were at an important cross-road in the containment of leprosy, particularly in the context of attaining the objective of health for all by the year 2000. There had recently been a revival of interest in leprosy control and a definite commitment had been made by governments, through resolutions they had adopted in the World Health Assembly, to contain this ancient scourge.

While progress had been made in expanding leprosy control programmes, the twin constraints of dapsone resistance and bacterial persistence were causing serious operational problems and a feeling of uncertainty regarding the future of leprosy control programmes. There was therefore an urgent and imperative need for recommendations on globally applicable therapeutic regimens based on research efforts from all over the world and on the operational and logistic constraints in the field.

INTRODUCTION

In its fifth report the WHO Expert Committee on Leprosy that met in 1976 emphasized the need to prevent the much feared development of drug resistance, and, in view of this, recommended that all active cases of multibacillary leprosy (LL, BL and BB in the Ridley-Jopling classification), whether previously untreated or relapsed, should be treated with at least two effective antileprosy drugs (1). However, relatively few countries and individual centres have introduced multidrug therapy as a routine practice in their leprosy control programmes. Furthermore, there has been considerable uncertainty with regard to the selection of appropriate drug regimens for combined chemotherapy, on the grounds of both efficacy and operational feasibility. This is evidenced by the many and various multidrug regimens recommended since 1976.

Welcoming the steady progress made by the Scientific Working Group on the Immunology of Leprosy (IMMLEP)¹ in its long-term objective of developing a leprosy vaccine of proved effectiveness, the Study Group considered that the classical strategy of leprosy control, based on early detection and effective chemotherapy, is likely to remain unchanged for many years. The Study Group reviewed the problem of dapsone resistance (both secondary and primary) which has now become acute. It also reviewed the problem of resistance to other antileprosy drugs and the operational problems that have hindered the implementation of combined chemotherapy.

After reviewing the small number of bactericidal drugs available for the treatment of leprosy, the Study Group proposed certain multidrug regimens to treat the different groups of multibacillary patients, and a further combined regimen designed for the short-term chemotherapy of paucibacillary patients. In addition, the Study Group recommended ways of overcoming the operational problems that might impede the practical application of the proposed regimens in leprosy control programmes.

¹The activities of the Scientific Working Group on the Immunology of Leprosy are carried out in the framework of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

1. THE PROBLEM

1.1 Dapsone resistance

Resistance of *Mycobacterium leprae* to dapsone should be suspected when a patient fails to improve or deteriorates during supervised treatment with the drug. Dapsone resistance may be confirmed by inoculating mice with *M. leprae* recovered from the patient and then treating the mice with dapsone to determine whether the drug is capable of preventing multiplication of the organisms. When the drug does not prevent multiplication of *M. leprae* in the mice the inoculated strain of *M. leprae* is said to have proved resistance to dapsone.

Until the mid-1970s virtually all strains of *M. leprae* isolated in mice from previously untreated patients were inhibited from multiplying by the administration of 0.1 mg of dapsone per 100 g of food in the diet (0.0001 g%). Strains of *M. leprae* capable of multiplying in mice to which dapsone has been administered in this or a greater concentration are defined as "resistant". Strains inhibited from multiplying by the administration of 0.1 mg of dapsone per 100 g diet are said to be fully susceptible. Strains capable of multiplying in mice administered 0.1 mg per 100 g, but inhibited by 1 mg per 100 g (0.001 g%) are said to exhibit a low degree of resistance. Strains multiplying in mice administered 1 mg per 100 g, but inhibited from multiplying when given 10 mg/100 g (0.01 g%) are said to show an intermediate degree of resistance; and strains that multiply in mice administered dapsone in a concentration of 10 mg per 100 g in the diet are said to be fully resistant. Administration to mice of 10 mg of dapsone per 100 g of diet yields a dapsone concentration of about 1 μ g per ml in the plasma, roughly equal to that found in the plasma of humans administered 100 mg of dapsone.

The presence of fully-resistant *M. leprae* may be suspected when patients relapse during treatment with dapsone in supervised daily doses of 100 mg. The presence of *M. leprae* of a low degree of resistance does not imply that dapsone therapy is of no use in these patients. On the contrary, such patients may respond well to treatment with dapsone, 100 mg daily. However, they are very likely to relapse in time with fully-resistant *M. leprae* if only dapsone monotherapy is continued.

1.2 Secondary dapsone resistance

Treatment of leprosy with sulfones was introduced in 1943. Although sulfone resistance was suspected in the 1950s, resistance to dapsone *per se* was first proved in the mouse footpad in 1964 (2). In 1966, Pettit et al. (3) estimated that the prevalence of dapsone resistance among 5000 cases at risk in Sungei Buloh Leprosarium in Malaysia was about 1 per 1000. Since in this study the authors employed only large concentrations of dapsone in the mouse diet, the prevalence rate of 1 per 1000 was probably an underestimate of the true prevalence of resistance. In a later study Pearson (4), using lower concentrations of dapsone in the mouse diet, found the prevalence rate in the same centre to be 2 per 1000, with an incidence rate of about 0.1% per year. At this rate of incidence, dapsone resistance did not appear to be an important problem.

Subsequently, in 1973, the prevalence of secondary dapsone resistance among the same patients was estimated to be about 25 per 1000, with an incidence of about 0.3% per year for patients who had received full-dosage dapsone therapy from the beginning of treatment (5). A second group of patients, who had received sola-sulfone as initial treatment in a dosage equivalent to about 10 mg of dapsone daily and were subsequently changed to dapsone, showed a prevalence of dapsone resistance of about 75 per 1000, with an incidence of about 0.8% per year, confirming that lower-dosage dapsone therapy had predisposed the patients to the subsequent development of dapsone resistance.

In 1975, the same centre reported 100 patients with proved dapsone resistance (6); by 1980, the number of footpad-proved cases at the centre had risen to 166. In 1981, it was estimated that the prevalence of dapsone resistance for all of Malaysia was as high as 10% of all surviving treated multibacillary cases.¹ Since many of the older, well-treated inpatients had by now died from natural causes, this figure must reflect an increased incidence as well as a continuing prevalence.

Pearson and his colleagues reported an even more disturbing situation in Ethiopia (7, 8). Among 1500 multibacillary patients at risk in the Addis Ababa area, 295 were known to have relapsed. Fifty-one of 53 strains of *M. leprae* tested in mice were found to be

¹Final report of the Regional Working Group on Drug Policy and Operational Research in the Leprosy Programme. Unpublished document ICP/BVM/005 issued by the WHO Regional Office for the Western Pacific, Manila, 1981.

dapsone-resistant, yielding an estimated prevalence of about 190 per 1000. During each year of the study (1973–77), about 50 new cases of relapse were seen with *prima facie* evidence of dapsone-resistant leprosy, yielding an incidence of about 3% per year. Countrywide studies yielded prevalence estimates of 100 per 1000 in Costa Rica (9), and of 37 per 1000 in Israel (10).

This was the situation at the time when the WHO Expert Committee on Leprosy met in 1976. During the five years since then secondary resistance to dapsone has been reported from many other countries. Dapsone resistance was proved in the mouse footpad in India by Taylor et al. in 1976 (11), in an area that had enjoyed well-delivered dapsone monotherapy since 1963. A well-planned survey of the prevalence of dapsone resistance in that area began in 1978, with assistance from the Scientific Working Group on the Chemotherapy of Leprosy¹ (THELEP). According to that survey, in India 1580 multibacillary patients who began dapsone monotherapy at least five years earlier were considered at risk. Balraj et al. (12), on the basis of interim data, had reported a prevalence of about 23 per 1000 in the same area. More recent data from that study indicate that the prevalence of secondary dapsone resistance in the area is much higher: probably about 70 per 1000 (M. Christian, unpublished data). In an adjacent area of South India another THELEP-supported prevalence survey is in progress, and preliminary data indicate a prevalence of about 20 per 1000 (P. N. Neelan, unpublished data).

Surveys of the prevalence of secondary dapsone resistance among smaller populations of multibacillary patients have yielded the following results: Jiangsu Province, China, 51 per 1000 (13); Shanghai, China, 35–40 per 1000 (Ji Baohong, unpublished data); Burundi, about 50 per 1000 (S. R. Pattyn, unpublished data), and Mali, also about 50 per 1000 (14). In addition, sporadic instances of secondary dapsone resistance proved in the mouse footpad have been reported from Australia,² Guadeloupe (15), Jamaica,² Malawi,² Martinique (15), Morocco (16), Nigeria,² Philippines,³ Senegal (17), Sierra Leone,² Singapore,² Thailand,² United Republic of Tanzania,² Upper Volta (18), USA (19), and Zambia.² A number of

¹ The activities of the Scientific Working Group on the Chemotherapy of Leprosy are carried out in the framework of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

² Unpublished data from R. J. W. Rees.

³ Unpublished data from R. S. Guinto.

cases have also been reported from the Netherlands among immigrants from Indonesia and Suriname.¹

Wherever dapsone resistance has been sought among treated and relapsed patients with lepromatous leprosy (LL) or borderline lepromatous leprosy (BL), it has been found. The number of countries with dapsone resistance is now probably over 25, and the prevalence is steadily increasing. Therefore, urgent action must be taken to prevent the further development of dapsone resistance, otherwise leprosy control methods developed over the last 30 years may be rendered completely ineffectual.

Low-dosage dapsone therapy and irregular treatment appear to predispose leprosy patients to the subsequent development of dapsone resistance. (Dapsone resistance also occurs in patients receiving regular treatment, but probably with a much lower prevalence.) The full effect of a decade and a half of low-dosage dapsone therapy given in a number of countries up to 1976 has still to be seen. Since the regularity of treatment appears to influence the prevalence, it would follow that patients in poorly managed leprosy control programmes are more likely to develop dapsone resistance than those in well managed programmes. Furthermore, the personnel of the former will be the least well trained and the least able to diagnose dapsone resistance.

1.3 Primary dapsone resistance

When LL and BL patients relapse with secondary dapsone resistance, they can infect their contacts with dapsone-resistant *M. leprae*, and those who subsequently develop clinical leprosy will suffer from primary dapsone resistance. It follows that primary dapsone resistance can occur in any type of leprosy. Among nonlepromatous patients there is no immediate clinical or bacteriological way of differentiating dapsone-resistant leprosy from previously untreated dapsone-sensitive leprosy. However, in lepromatous leprosy primary resistance may be recognized by mouse inoculation.

At the time of the meeting of the Expert Committee on Leprosy in 1976, proved primary dapsone resistance had not yet been reported, although *prima facie* cases had been detected in Colombia and in the Pacific island of Ponape (20, 21). However, the Expert Committee did warn of its probable emergence (1).

¹ Unpublished data from D. L. Leiker.

Shortly afterwards, Pearson et al. (22) reported that 5 of 8 randomly selected, newly diagnosed cases of lepromatous leprosy in Ethiopia were found to be infected with dapsone-resistant strains of *M. leprae*. Subsequently, it was found that 5 of 14 patients from the Addis Ababa area and 11 of 15 from other parts of Ethiopia were suffering from primary resistance (8). The high proportion of primary resistant cases found in this study initially came as a surprise. However, since only about half the active infectious cases of lepromatous leprosy in Addis Ababa at the time of the study were untreated (and were presumably transmitting susceptible *M. leprae*), the other half, comprising those who had relapsed after dapsone therapy and now probably had dapsone-resistant leprosy, it might have been predicted that about half the new cases would show primary dapsone resistance.

Primary dapsone resistance has also been reported from the USA (18 of 93 patients admitted to the National Hansen's Disease Center at Carville, LA, with multibacillary leprosy between 1971 and 1979),¹ India (1 of 3 patients tested) (23), the Philippines (2 of 55 patients tested) (24), and Malaysia (6 of 22 patients tested) (A. B. G. Laing, unpublished data). In most of the above countries the majority of strains of *M. leprae* showed a low degree of dapsone resistance, whereas among those from Malaysia the majority were fully resistant, probably reflecting the fact that most secondary dapsone-resistant strains in that country were fully resistant.

In a THELEP controlled clinical drug trial in South India, 6 of 40 previously untreated lepromatous patients serially admitted to the trial were found to have dapsone-resistant *M. leprae*; 5 strains showed a low degree of resistance and 1 an intermediate degree.

In another THELEP trial in Mali, strains of *M. leprae* isolated from 11 of 30 serially admitted patients were found to be dapsone-resistant: 7 showed a low degree of resistance, 3 showed intermediate resistance, and 1 was fully resistant. It should be noted that the first proved case of secondary dapsone resistance was detected in Mali in 1978 (25), the year in which the trial began. Therefore, if in a leprosy control programme secondary dapsone resistance has not been detected, or has been detected only recently, it should not automatically be assumed that primary resistance has not yet arisen.

¹Final report of the Regional Working Group on Drug Policy and Operational Research in the Leprosy Programme. Unpublished document ICP/BVM/005 issued by the WHO Regional Office for the Western Pacific. Manila, 1981.

It must be assumed that primary dapsone resistance occurs in at least as high a proportion of tuberculoid as of lepromatous patients, although tuberculoid patients cannot be surveyed using the mouse-footpad technique because they do not harbour a bacterial population sufficient to infect the mouse. Indeed, since the prevalence of secondary dapsone resistance is steadily rising and the incubation period of tuberculoid leprosy is believed to be shorter by several years than that of lepromatous leprosy, it is possible that primary dapsone resistance is currently occurring in a higher proportion of new tuberculoid than of new lepromatous patients. Unless the possibility of primary dapsone resistance is kept constantly in mind when diagnosing and treating tuberculoid patients and their source of infection is checked whenever possible, those suffering from primary resistance may undergo serious deterioration with new skin lesions and increasing nerve damage, or they may even downgrade to lepromatous leprosy before such a diagnosis is considered (26).

1.4 Secondary resistance to other bactericidal antileprosy drugs

1.4.1 Rifampicin

In general, rifampicin has been used for limited periods in the initial intensive phase of multidrug treatment of newly-diagnosed cases of multibacillary leprosy. It is, however, being increasingly used in the long-term treatment of proved dapsone-resistant lepromatous patients, since it was first employed for this purpose in Malaysia and the USA (Carville, LA) more than a decade ago. In both centres, the initial patients received rifampicin monotherapy. None of the Malaysian patients has so far developed resistance. However, in Carville, 1 of 8 patients who were treated with 600 mg rifampicin daily relapsed clinically after 43 months, and 1 of 8 who were treated with 300 mg rifampicin daily relapsed after 45 months of treatment. In both cases *M. leprae* strains were subsequently shown to be rifampicin-resistant in the mouse footpad (16, 27).

1.4.2 Clofazimine

Despite the widespread use of clofazimine, both to treat erythema nodosum leprosum (ENL) and to treat dapsone-resistant patients, no proved case of clofazimine resistance has as yet been reported. This suggests that the pattern of clofazimine resistance may be found to resemble that of resistance to high-dose, regularly taken dapsone.

1.4.3 Ethionamide and protionamide

Prima facie ethionamide resistance was suspected by Rollier & Rollier (28), who noted relapse in 7 of 102 patients treated with 500 mg ethionamide daily as monotherapy. Strains of *M. leprae* were isolated from 6 of those 7 patients, and 5 of 6 strains were found to be ethionamide-resistant in the mouse footpad (29). Four of the resistant strains were from patients who had relapsed after more than 5 years of treatment. Two strains were tested for cross-resistance to protionamide, thioacetazone, and thiambutosine, and were found to be resistant (30).

1.5 Persistence of *M. leprae*

Although approximately 99.9% of leprosy bacilli are killed in about 3–4 months by dapsone (in the dosage of 50–100 mg daily) and clofazimine, and within 3–7 days by rifampicin administered in single doses of 600–1500 mg, it has been known from the earliest days of the chemotherapy of leprosy that multibacillary patients can relapse if they stop the treatment.

In 1974, small numbers of persisting viable leprosy bacilli were detected in 7 of 12 patients treated for 10–12 years with dapsone (31). The three strains of *M. leprae* which were successfully passaged were all fully susceptible to dapsone. Subsequently, small numbers of viable, drug-susceptible *M. leprae* have been isolated from patients treated with rifampicin (as monotherapy, or combined with thiambutosine) for 5 years (32), and with clofazimine as monotherapy for 10 years (R. J. W. Rees, unpublished data). These viable, fully drug-susceptible *M. leprae* that are able to survive for many years in the patient, despite the presence of bactericidal concentrations of an antileprosy drug, are called “persisters”. It is postulated that persisters are physiologically dormant bacilli and can thus escape the action of antileprosy drugs.

It is not yet known for certain how long persisters may survive in patients remaining on regular monotherapy. In a study of 362 lepromatous and borderline (LL and BL) inpatients treated for 18.5–22 years up to 1970 with supervised dapsone monotherapy in Malaysia,¹

¹Third annual report of the Special Programme for Research and Training in Tropical Diseases. Geneva, World Health Organization, 1979 (unpublished WHO document TDR/AR(3)/79.7).

it was found that 25 patients (8.8%) relapsed over the next 8–9 years, giving an annual relapse rate of about 1%. This study shows that in a small proportion of patients well treated with dapsone monotherapy, persisters may survive for as long as 20 years.

Experience in the treatment of tuberculosis indicates the importance of using drugs with specific sterilizing activity if the time required for cure is to be significantly shortened. Unfortunately, so far no drug alone appears to be capable of eliminating persisting *M. leprae*. The possibility that combinations of anti-leprosy drugs may be able to eliminate such persisting organisms and thus significantly reduce the required duration of treatment is currently under investigation in THELEP controlled clinical trials.

In a trial in Malta combined chemotherapy with rifampicin, dapsone, prothionamide and isoniazid was administered for a period of 18–24 months to a group of more than 200 patients (33); more than 80 of the lepromatous patients were assessed by Leiker (unpublished data) after 4½ years of follow-up subsequent to cessation of therapy. Only one had possibly relapsed.

1.6 Difficulties in implementing the therapy recommended in the fifth report of the WHO Expert Committee on Leprosy

The Study Group believed that there were several reasons that contributed to the failure of leprosy control programmes to implement the regimens recommended by the WHO Expert Committee on Leprosy in its fifth report (1). These are discussed in the sections below.

1.6.1 Failure to perceive the urgency of the situation

The shortcomings of dapsone monotherapy do not appear to have been fully understood, particularly with respect to the threat posed by dapsone resistance. It appears to have been assumed that, provided dapsone was administered in full dosage (1–2 mg/kg body weight) and efforts were made to ensure regularity of treatment, the threat of dapsone resistance would be contained, or at least its emergence very significantly delayed, in both paucibacillary and multibacillary patients. Such a view naturally precludes the possibility of the early emergence of primary resistance.

Furthermore, there appears to have been insufficient recognition of the fact that unsupervised, self-administered chemotherapy simply

could not be enforced for the long periods of time commonly advocated for the treatment of leprosy. Many control programmes continued to have high drop-out rates. A number of investigations have indicated that even the patients who collect the drugs regularly from leprosy clinics do not necessarily ingest them.

It has remained the practice in some control programmes to interrupt dapsone therapy during lepra reactions, because of the belief that dapsone exacerbates the reactions. This practice increases the risk of the subsequent emergence of dapsone resistance.

Another factor operating against good patient compliance with the prescribed treatment was that treatment was often continued indefinitely because of the fear of relapse, even in cases meeting the criteria for stopping the treatment. The very large number of patients remaining under treatment put unnecessary pressure on leprosy clinics and consequently acted to the detriment of the quality of treatment. This situation further contributed to poor compliance.

1.6.2 *Need for revision of control programmes*

In addition to the failure to sense the urgency of the situation with regard to dapsone resistance, there was frequently reluctance in control programmes to undertake the basic revisions needed to carry out fully the recommendations of the WHO Expert Committee on Leprosy (1).

Combined chemotherapy with more potent, somewhat more toxic, and more expensive drugs requires much closer supervision than does dapsone monotherapy. The potential burden of supervision of combined chemotherapy, even for limited periods, appears frequently to have presented insurmountable problems to many control programmes. Moreover, the additional activities could not readily be incorporated into the existing control programmes, which were already stretched to the limit in terms of finance and manpower. The major policy changes that were delayed concern:

- (1) the retraining of personnel for the management of patients on combined chemotherapy;
- (2) the reassignment of tasks and priorities of treatment activities, including educating patients on their disease and its treatment; and
- (3) the comparison of the cost-effectiveness of effective combined chemotherapy for a limited period with expensive drugs, on the one hand, with the much less effective monotherapy for a long period of time with inexpensive drugs, on the other.

1.6.3 Uncertainty with regard to the combined chemotherapy regimens recommended in the fifth report of the WHO Expert Committee on Leprosy (1)

Although the recommendation of combined chemotherapy regimens was based on sound scientific knowledge, clinical experience of combined therapy with rifampicin and clofazimine in combination with dapsone was too limited to allow of decisions on optimum regimens for different forms of leprosy. Furthermore, there was fear of toxicity and other complications associated with such therapy, which are particularly difficult to deal with under field conditions.

1.7 The present situation

During the five years that have elapsed since the publication of the fifth report of the WHO Expert Committee on Leprosy, the need to adopt combined chemotherapy has become even more urgent. When the Expert Committee met in 1976, primary resistance had not yet been demonstrated; hence, combined chemotherapy for paucibacillary cases was not considered at that time. Now, however, primary dapsone resistance is threatening to undermine the efforts being made to control leprosy. The widespread prevalence of dapsone resistance (both primary and secondary) now precludes the recommendation of dapsone plus *one* additional drug for multibacillary patients, since this is likely to give rise to multiple drug resistance.

Further delays in implementing well-planned and well-executed programmes of combined chemotherapy could result in a catastrophic situation, with a further increase in the prevalence of dapsone resistance and the development of multidrug resistance.

2. DRUGS FOR MULTIDRUG REGIMENS

The important properties of the drugs available for chemotherapy of leprosy are listed in Table 1. (Isoniazid is not listed, because it has been shown to be ineffective against *M. leprae* in mice (34).) The table shows, for each drug, its minimal inhibitory concentration (MIC) for *M. leprae*, the usually recommended dosage, and the ratio of the peak serum concentration of the drug in man, following a single dose, to its MIC. It also shows the length of time, following a

Table 1. Drugs available for chemotherapy of leprosy

Drug	Minimal inhibitory concentration (MIC) ($\mu\text{g/ml}$)	Dosage (mg)	Ratio of peak serum concentration to MIC ^a	Number of days during which peak serum concentration exceeds MIC ^b	Bactericidal activity
Rifampicin	0.3	600	30	1	high
Dapsone	0.003	100	500	10	low
Acedapsona	0.003 ^c	225	15	200	none
Ethionamide	0.05	375	60	1	intermediate
Protionamide	0.05	375	40	1	intermediate
Clofazimine ^d		50–100			low
Thioacetazone	0.2	150	8	2	none
Sulfamethoxy-pyridazine ^e	30	1000	3	3	none
Thiambutosine ^f	0.5	1500	1	<1	none

^a Ratio of peak serum concentration in man, after a single dose, to MIC determined in the mouse.

^b Serum concentrations in man after a single dose.

^c Acedapsona is inactive against *M. leprae* but is converted to dapsone – the figures for MIC and peak serum concentration refer to the values for dapsone.

^d Because of uneven tissue distribution, estimate of the MIC is not possible.

^e Cross-resistant with dapsone.

^f Manufacture discontinued.

single dose, during which the serum concentration exceeds the MIC; this time is a function of both the ratio of peak serum concentration to MIC and the rate at which the drug disappears from the blood. Finally, the table presents an estimate of the degree of bactericidal activity of each drug.

Using figures in Table 1 as an example, after a single 100-mg dose of dapsone, which disappears from the blood very slowly (half-life = 27 hours) and which yields a peak serum concentration 500 times the MIC, the serum concentration of the drug will remain higher than its MIC for 10 days. Such a drug will inhibit the multiplication of fully susceptible *M. leprae*, even when it is administered at long intervals. In contrast to dapsone, thiambutosine (a bacteriostatic drug) has a very short half-life and its peak serum concentration does not exceed its MIC. (For a bacteriostatic drug to inhibit continuously the multiplication of *M. leprae*, it is necessary to administer the drug in a dosage that will maintain its concentration in the blood above its MIC.) Thiambutosine, therefore, is not suitable for multidrug therapy. Acedapsona, thioacetazone and sulfamethoxypyridazine (together with other long-acting sulfonamides) are also only bacteriostatic—i.e., they only inhibit the multiplication of the organisms, but do not kill them. Such drugs might be considered if life-long treatment of leprosy patients could be contemplated. Since this is not ad-

visible, only bactericidal drugs should be considered as candidates for multidrug regimens which are to be administered only for limited periods of time. The remaining four bactericidal drugs (ethionamide and prothionamide are considered together) are discussed in more detail below.

2.1 Dapsone

Dapsone is cheap, and virtually without toxicity in the dosages used. Employed in a dosage of 100 mg daily or its equivalent, the drug has been shown to be weakly bactericidal against *M. leprae*, both in the mouse and in man. Such a dosage results in peak serum levels that exceed the MIC of dapsone against *M. leprae* by a factor of about 500. So large a therapeutic margin is quite exceptional and is of great importance; such high levels of the drug will inhibit the multiplication of mutants of *M. leprae* with low or even moderate degrees of dapsone resistance. The maximum dosage of the drug should be used from the start and should not be reduced during lepra reactions.

2.2 Rifampicin

Rifampicin is an expensive drug. It is relatively nontoxic when administered daily. When it is administered intermittently, however, toxic syndromes may be encountered. The toxicity of intermittently-administered rifampicin depends both on dosage (toxic effects being more frequent with large doses) and on the interval between doses (toxic effects being more frequent at weekly than at shorter intervals). No toxic effects have been reported in the case of monthly administration (35).

Single doses of 20 mg per kg of body weight or more in mice, and doses of 10 mg/kg or greater in man are rapidly bactericidal for *M. leprae*, although prolonged treatment with a daily dose of 600 mg has been shown not to eradicate the large bacterial populations in lepromatous patients (32). It has been shown that daily administration of 600 mg rifampicin is no more effective than monthly administration of 600 mg on each of two consecutive days. Because of its expense and the risks of toxicity accompanying intermittent administration at certain intervals, administration of rifampicin should be *fully supervised*. Rifampicin-resistant strains of *M. leprae* have been isolated from two patients whose lepromatous leprosy relapsed after approximately 4 years of treatment with rifampicin as monotherapy (16, 27).

2.3 Clofazimine

Clofazimine is also an expensive drug. It is virtually free of toxicity when administered in dosages not greater than 100 mg daily, but its use is accompanied by side-effects including red-purple coloration of skin lesions and darkening of areas of skin exposed to sunlight, which some patients find objectionable. The drug is weakly bactericidal against *M. leprae*, both in the mouse and in man. Clofazimine is most active when administered thrice-weekly or daily, but can be administered at monthly intervals also, thus permitting supervision of dosage. No instances of clofazimine resistance have yet been proved by mouse inoculation.

2.4 Ethionamide and protionamide

Ethionamide and protionamide are virtually interchangeable and give cross-resistance with each other. These drugs are both more expensive and more toxic than dapson. In mice, the drugs are bactericidal for *M. leprae*. In man, their rate of killing of *M. leprae* has only been studied in a few lepromatous patients; the drugs probably kill *M. leprae* faster than full-dosage dapson, but more slowly than rifampicin. Experimental studies in mice suggest that the bactericidal activity of ethionamide/protionamide would be severely compromised if the drugs were taken intermittently. However, these two drugs remain the only alternatives to clofazimine in patients requiring triple drug therapy who will not accept clofazimine.

3. RECOMMENDED CHEMOTHERAPEUTIC REGIMENS

3.1 Treatment of multibacillary leprosy

Multibacillary leprosy includes both lepromatous (L) and borderline (B) leprosy in the Madrid classification (36) and LL, BL, and BB leprosy in the Ridley & Jopling classification (36, 37).

There are two objectives of chemotherapy of multibacillary leprosy: (1) to interrupt the transmission of the infection in the community; and (2) to cure the patient. Combined chemotherapy has the additional objective of preventing the emergence of drug-resistant

strains of *M. leprae* and thereby preventing the spread of such strains in the community.

Up to now the chemotherapy of leprosy has relied almost entirely on dapsone monotherapy. This has led to a dangerous epidemiological situation with increasing numbers of patients relapsing with dapsone-resistant leprosy, and the spread of the resistant strains among their contacts. This jeopardizes the whole strategy of leprosy control.

The only way to prevent the spread of dapsone-resistant leprosy is to use multiple drug therapy. It is well known that the simultaneous administration of several different antibacterial drugs may prevent the selection of drug-resistant mutants. The patients most at risk of developing drug resistance are multibacillary patients. The proposed multidrug regimen is designed for the treatment of all categories of multibacillary patients including:

- freshly diagnosed, previously untreated patients;
- patients who have responded satisfactorily to previous dapsone monotherapy;
- patients who have not responded satisfactorily to previous dapsone monotherapy;
- patients who have relapsed while on dapsone monotherapy or after its cessation.

Since combined therapy can prevent or cure drug resistance in all patients, whether or not they are infected with dapsone-resistant *M. leprae*, there is no justification whatever for attempting to diagnose dapsone-resistant leprosy by means of a period of supervised dapsone monotherapy. Even in situations in which mouse-footpad testing can be accomplished, treatment with combined therapy should be started immediately after biopsy, without waiting for the result of mouse-footpad inoculation.

3.1.1 Drugs

A review of the efficacies of the available antileprosy drugs indicates that only 4 drugs can be recommended for combined chemotherapy—namely, rifampicin, dapsone, clofazimine, and ethionamide/protionamide¹. Since new lepromatous leprosy patients may have primary dapsone resistance, and patients previously treated with

¹ Either drug (ethionamide or protionamide) may be used.

dapsone monotherapy who have previously responded well to treatment may harbour dapsone-resistant *M. leprae*, and since dapsone plus only one additional drug can increase the risk of multiple resistance, it is recommended that at least two additional drugs should be combined with dapsone. Also, one of the two additional drugs should always be rifampicin because of its great potency.

3.1.2 *Dosages*

Rifampicin can be given at a dosage of 600 mg daily or monthly (but see below) for patients weighing over 35 kg and 450 mg for those weighing less. Dapsone should be given at a dose of 1–2 mg/kg body weight. It *must* be given daily. Clofazimine should be given at a dose of 50 or 100 mg daily; larger doses may be given at longer intervals. Ethionamide or protionamide should be given at a dose of 5–10 mg/kg body weight regardless of the dosage interval.

3.1.3 *Duration of treatment*

Combined treatment should be given until the size of the bacillary population has been reduced to such an extent that resistant mutants are no longer present. Since the exact time required to achieve this is not known, it is recommended that combined therapy be given for at least two years and be continued, wherever possible, up to smear negativity.

3.1.4 *Rhythm*

In order to facilitate supervision and to maximize the duration of combined chemotherapy with a given supply of drugs, it is most advantageous to give rifampicin intermittently. Since there is no evidence to indicate that the efficacy of monthly treatment with rifampicin is inferior to that of daily treatment with the drug, and because of the dangers of unsupervised use of this very costly, much sought-after, and potentially toxic drug, it is recommended that a single supervised dose of rifampicin be given once every month. Although it may be useful, there is no evidence that an initial period of daily rifampicin treatment is necessary. Evidence indicates that clofazimine may also be effective when given on a monthly basis. However, significant added benefit may be anticipated by supple-

menting supervised monthly doses of clofazimine with daily self-administered treatment with the same drug, particularly for patients with dapsone-resistant leprosy; the dangers of unsupervised clofazimine treatment are very much smaller than those of unsupervised treatment with rifampicin.

3.1.5 Recommended standard regimen for multibacillary leprosy¹

Rifampicin	600 mg once-monthly, supervised
Dapsone	100 mg daily, self-administered
Clofazimine	300 mg once-monthly, supervised, and 50 mg daily, self-administered

The standard regimen may be supplemented by the addition of monthly supervised doses of 500 mg ethionamide/prothionamide, but studies are required to assess the potential contribution of such an addition to the efficacy of the regimen. Every effort should be made to persuade patients to agree to treatment with clofazimine, since the acceptability of the only alternative drugs available, ethionamide and prothionamide, has yet to be established. Where clofazimine is totally unacceptable owing to the coloration of skin lesions that it causes, its replacement by 250–375 mg self-administered daily doses of ethionamide/prothionamide should be considered.

If a multibacillary leprosy patient also has active pulmonary tuberculosis, this regimen alone will not be sufficient because of the risk of the patient developing rifampicin-resistant *Mycobacterium tuberculosis*. It is recommended that such patients should be given appropriate chemotherapy for active pulmonary tuberculosis in addition to this regimen.

3.2 Treatment of paucibacillary leprosy

Paucibacillary leprosy includes indeterminate (I) and tuberculoid (T) leprosy in the Madrid classification (36), and I, TT, and BT leprosy in the Ridley & Jopling classification (36, 37), whether diagnosed clinically or histopathologically, with bacteriological index of < 2 according to the Ridley scale at any site.

¹ Dosages should be adjusted to the weight of the patient, as described on p. 23.

A large number of paucibacillary patients with single lesions heal spontaneously. Nevertheless, all paucibacillary patients should be treated because it is impossible to distinguish those who will heal spontaneously from those who will not. Furthermore, unless properly treated, those who do not heal spontaneously will develop nerve lesions, and some may even progress to multibacillary forms of the disease.

3.2.1 *Rationale*

Since in paucibacillary leprosy the maximum bacterial load is about 10^6 organisms—much lower than that in multibacillary leprosy—the problem of drug-resistant mutants arising as a result of treatment is insignificant. Any persisters remaining are likely to be contained by the adequate cell-mediated immunity this type of patient possesses. Hence, as has already been shown, short-course chemotherapy of paucibacillary patients is feasible with the potent and rapidly bactericidal drug, rifampicin (38, 39).¹

Other reasons for recommending short-course chemotherapy with rifampicin for paucibacillary patients are:

- the ineffectiveness of dapsone monotherapy in the face of increasing incidence of primary dapsone resistance;
- the need for providing short-course effective treatment to a majority of patients in view of the fact that many patients do not come for regular treatment when it is of long duration;
- the need for increasing the cost-effectiveness of the treatment and for simultaneously easing the burden of the disease on the individual patient; and
- the need for saving working time of the personnel, thereby enabling them to devote more time to the treatment of multibacillary patients and to other activities in the control programme.

Since patients with paucibacillary leprosy are usually not expected to harbour rifampicin-resistant *M. leprae*, monotherapy with rifampicin should theoretically be satisfactory. However, in order to avoid the risk of rifampicin resistance in patients who are wrongly diagnosed as paucibacillary, the Study Group recommended combined chemotherapy with rifampicin and dapsone for all paucibacillary patients.

¹ Report of the third meeting of the Scientific Working Group on the Chemotherapy of Leprosy, Geneva, 20–22 October 1980 (unpublished WHO document TDR/THELEP-SWG(3)/80.3).

3.2.2 Recommended standard regimen for paucibacillary leprosy

The following standard regimen is recommended:¹

Rifampicin 600 mg once a month for 6 months plus dapsone 100 mg (1–2 mg/kg body weight) daily for 6 months.

The administration of rifampicin should invariably be fully supervised. Dapsone may be given unsupervised. If treatment is interrupted the regimen should be recommenced where it was left off to complete the full course.

The regimen has still to be fully evaluated in terms of relapse rates on large numbers of patients. If relapse is diagnosed, the treatment regimen should be restarted. Should reversal reactions occur during the course of chemotherapy, the regimen should not be interrupted.

It is frequently difficult to distinguish between relapses and reversal reactions. Reversal reactions usually occur in tuberculoid leprosy within a few weeks or months of commencing effective antileprosy treatment. They may, however, rarely be seen 6–24 months after starting treatment in BT leprosy. Relapses normally occur at least several months and usually one or more years after stopping effective treatment. Histological examination is often, but not invariably, of help in the differential diagnosis between relapse and reversal reactions.

If a paucibacillary leprosy patient also has active pulmonary tuberculosis, this regimen alone will not be sufficient because of the risk of the patient developing rifampicin-resistant *M. tuberculosis*. It is recommended that such patients should be given appropriate chemotherapy for active pulmonary tuberculosis in addition to this regimen.

3.2.3 Priorities

Short-course chemotherapy of paucibacillary leprosy should be introduced in the following order of priority:

- (1) to all newly diagnosed paucibacillary patients;
- (2) to all dapsone-treated paucibacillary patients who relapse; and, finally,
- (3) to paucibacillary patients who are currently on treatment with dapsone monotherapy and who have not yet completed two years of treatment.

¹ Dosages should be adjusted to the weight of the patient, as described on p. 23.

4. OPERATIONAL ASPECTS

The present strategy for the control of leprosy, based on early detection and effective chemotherapy in order to interrupt the chain of transmission of the disease in the community and to avoid permanent disabilities, remains unchanged. With the introduction of more potent drug combinations for the treatment of both multi-bacillary and paucibacillary patients, case detection, treatment delivery, and case holding become more critical for the success of leprosy control programmes.

4.1 Case detection

Case-detection activities will have to be intensified in all areas in which treatment facilities are available. The Study Group recommended that appropriate and cost-effective methods should be employed in case detection.

4.2 Laboratory facilities

4.2.1 *Bacteriological examination*

With the introduction of multidrug regimens the organization of an efficient service for bacteriological examination of skin smears becomes very important. The bacteriological index (BI) remains the most practical bacteriological examination for use in the field. Nevertheless, it will still be necessary to ensure the uniformity and reliability of the examinations. In order to attain a satisfactory level of proficiency in all aspects of the examination procedure, retraining of staff will usually be essential. Provision of suitable laboratory equipment, such as microscopes and reagents, and recruitment and training of laboratory staff will be necessary in countries where facilities for bacteriological examination do not exist. A system of quality control by random checking of smear results and continuous supervision will have to be introduced. This can be done, for example, by establishing regional reference laboratories.

4.2.2 *Referral facilities for mouse-footpad studies*

Efforts should be directed towards developing referral laboratories equipped for undertaking mouse-footpad studies in endemic countries

where such facilities do not yet exist. The existing laboratories in other hyperendemic countries should be strengthened in order to monitor effectively and evaluate the occurrence of *M. leprae* resistance to dapsone and other drugs being used in the proposed multidrug regimens.

4.2.3 *Other laboratory facilities*

Essential laboratory facilities should be available for the screening of patients where clinical examination indicates the need for such investigations before starting chemotherapy. Certain special investigations may also be necessary should toxic manifestations or side-effects occur. The entire resources of the public health laboratories at the intermediate level and peripheral laboratory services should be made available to meet the demands when such situations arise. A harmonious working relationship and a close liaison between the staff of the leprosy control programme and that of the laboratory services within the existing infrastructure is vital for the success of leprosy control programmes.

4.3 **Drug delivery**

The recommended regimens require that the monthly doses of rifampicin and clofazimine in multibacillary leprosy and rifampicin alone in paucibacillary leprosy be administered under direct supervision: a leprosy worker should be present when the patient ingests the drug.

The convenience of the patient is the key to the success of intermittent multidrug therapy. The drug delivery system must be made flexible enough to ensure regularity of treatment. Clinic sites must be conveniently located and where necessary the full resources of the primary health care delivery system must be mobilized to meet the demands. In certain countries where the magnitude of the problem is vast and communications are difficult, it may be necessary to devise new treatment delivery systems different from the conventional medical network. Complementary systems of drug delivery through community health workers, schoolteachers, village headmen, etc. in the community may become necessary in special situations. Continuity, regularity, and completion of chemotherapy are the keys to the success of the proposed multidrug regimens.

There should be an efficient system of defaulter retrieval which should include home visits to the patients. Leprosy patients should have access to the nearest hospital, whether general or specialized, for the treatment of complications and side-effects of drugs. The patient should be monitored for side-effects periodically and should be seen by medical officers at specified intervals.

4.4 Medical care

Comprehensive medical care for leprosy patients, provision of simple physiotherapeutic measures to minimize deformities, and referral facilities for corrective surgery and rehabilitation should be integral components of the control strategy.

4.5 Records and follow-up

A suitable, simple system of collecting, recording and transmitting data is indispensable (40). Such a system will assist greatly in assessing the impact of the new regimens recommended. An effective mechanism should also be developed for the surveillance of both multibacillary and paucibacillary patients after chemotherapy has been discontinued.

4.6 Health education

Acceptance of the new concept of multidrug therapy by health professionals and patients will be critical for its successful implementation. Community participation at all levels will have to be ensured. In view of this it will be essential to promote health education using all available resources, including the mass media.

4.7 Equipment and drugs

Before the commencement of the programme an adequate supply of drugs and equipment must have been made to the peripheral level. A system to ensure a continuous supply of drugs and equipment should also have been established. The provision and maintenance of vehicles will be essential to ensure the easy mobility of workers and supervisors.

The Study Group suggested that the WHO Expert Committee on Essential Drugs consider the inclusion of ethionamide and protion-

amide in its model list of essential drugs and the transfer of rifampicin and clofazimine in that list from the category of complementary drugs to the main list (41).

4.8 Manpower and financial resources

Manpower and financial resources must be mobilized in countries where the infrastructure to implement leprosy control programmes is inadequate.

4.9 Planning and evaluation

Since the implementation of multidrug therapy will require more complex mechanisms for drug delivery and follow-up of patients, leprosy control activities should be reorganized in accordance with the new technical and logistic needs.

Proper planning and precise project formulation with intermediate objectives and operational targets will be necessary. One crucial consideration in project formulation is the need to provide adequate training to all categories of personnel involved in the programme.

Evaluation should be built into the project at the time of project formulation. Progress should be continuously measured in relation to successive targets. Periodic assessment by independent teams should be encouraged.

4.10 Training

With the introduction of multidrug regimens, training and retraining of all categories of staff, including those working in the primary health care delivery system, must be undertaken. The training must be planned and organized so that each type of personnel is prepared to perform clearly defined tasks within the overall context of the programme. Training of medical students and organization of refresher courses for physicians on the newly recommended chemotherapy should also be encouraged.

A working manual should be prepared for the guidance of all personnel engaged in the programme. The manual should give in simple language detailed instructions regarding drug combinations, treatment delivery, and possible side-effects that may arise. The chain of referral and appropriate action to be initiated should be precisely indicated.

5. RESEARCH NEEDS

In the course of developing the recommended multidrug regimens for the treatment of paucibacillary and multibacillary leprosy patients, the Study Group recognized the need for further laboratory, clinical, and operational research. A particularly useful study in this regard would be an investigation into the effectiveness of the recommended regimens under varying operational conditions. Other needs will be met by the ongoing or planned research sponsored by THELEP.

Important knowledge was found to be lacking with respect to both clofazimine and ethionamide/prothionamide. The optimal dose of clofazimine for intermittent (monthly) administration is not known with certainty. The proportion of the dose absorbed from the gastrointestinal tract may decrease as the size of the dose is increased. Therefore, there may be a limit to the dose beyond which greatly increasing the quantity administered of this expensive drug may yield only a small increase in the quantity absorbed. Insufficient work has been done on the relationship between drug-dosage and rate of pigmentation on the one hand and ultimate intensity of pigmentation on the other. There may well be an optimal dosage which is active against *M. leprae* in man and which causes only minimum pigmentation. The smallest dose of clofazimine that is effective when the drug is administered monthly is not yet known. When it is administered in a dosage of 600 mg on 2 consecutive days every month the drug exerts measurable bactericidal effects. Additional studies should be carried out on the efficacy of smaller monthly doses of clofazimine. The minimum effective daily dose should also be established. Finally, studies of the compliance of dark-skinned patients with self-administered clofazimine, in reduced but effective dosage, and of the acceptability of clofazimine in such dosages to light-skinned patients should be undertaken.

Available data suggest that, in mice, ethionamide and prothionamide are not bactericidal when administered less frequently than three times weekly. These drugs do not lend themselves to administration by the patient, because of toxicity and expense. Moreover, they may lose their antimicrobial potency if administered intermittently. There is insufficient information on the bacteriostatic activity of these drugs against *M. leprae* when they are administered intermittently to mice. The minimum frequency of administration that exerts a measurable bacteriostatic effect is yet to be determined. At present, the daily dosage of ethionamide/prothionamide is based on the dosage found to be

effective in the treatment of pulmonary tuberculosis, and on the suggestion, based on the results of studies in *M. leprae*-infected mice, that *M. leprae* is more susceptible to these drugs than is *M. tuberculosis*. Thus, these drugs are now generally prescribed for the treatment of leprosy in a daily dosage of 500 mg, a dosage that is not universally well tolerated. Considerations of cost aside, self-administration of a poorly tolerated drug may lead to failure of compliance, not only with the drug in question, but with the entire therapeutic regimen. It is important to learn, therefore, whether these drugs are effective when administered in smaller daily doses. Also, studies of the compliance of patients with self-administered ethionamide/protonamide as a function of dosage should be carried out.

Several opportunities for the development of new drugs were recognized by the Study Group. A formulation of dapsone or a derivative of dapsone that, on monthly administration, would provide bactericidal concentrations of dapsone in the tissues, without risk of toxicity, is desirable. Also, the armamentarium of drugs that exert bactericidal effects against *M. leprae* is quite limited, and there is only a small number of drugs available for use in multidrug regimens. The development of additional drugs that are bactericidal against *M. leprae*, and that act by mechanisms distinct from those by which the already available drugs act, is much to be desired.

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REFERENCES

1. WHO Technical Report Series, No. 607, 1977.
2. PETTIT, J. H. S. & REES, R. J. W. *Lancet*, **2**: 673-674 (1964).
3. PETTIT, J. H. S. ET AL. *International journal of leprosy*, **34**: 375-390 (1966).
4. PEARSON, J. M. H. *International journal of leprosy*, **49**: 417 (1981).
5. MEADE, T. W. ET AL. *International journal of leprosy*, **41**: 684 (1973).
6. PEARSON, J. M. H. ET AL. *Lancet*, **2**: 69-72 (1975).
7. PEARSON, J. M. H. ET AL. *International journal of leprosy*, **44**: 140-142 (1976).
8. PEARSON, J. M. H. ET AL. *Leprosy review*, **50**: 183-199 (1979).

9. PETERS, J. H. ET AL. *International journal of leprosy*, **44**: 143–151 (1976).
10. LEVY, L. ET AL. *Leprosy review*, **48**: 107–112 (1977).
11. TAYLOR, P. M. ET AL. *Leprosy review*, **47**: 5–11 (1976).
12. BALRAJ, V. ET AL. *International journal of leprosy*, **48**: 397–401 (1980).
13. LI WENZHONG ET AL. *Chinese journal of dermatology*, **14**: 75–79 (1981).
14. BAQUILLON, G. ET AL. *Leprosy review*, **51**: 315–319 (1980).
15. GUELPA-LAURAS, C. C. ET AL. *Acta leprologica* (in press).
16. HASTINGS, R. C. & JACOBSON, R. R. *Health cooperation papers*, **1**: 47–54 (1981).
17. PATTYN, S. R. ET AL. *Acta leprologica*, No. 76–77: 321–324 (1979).
18. PATTYN, S. R. ET AL. *Médecine d'Afrique noire*, **28**: 147–148 (1981).
19. JACOBSON, R. R. & TRAUTMAN, J. R. *International journal of leprosy*, **39**: 726–737 (1971).
20. LONDONO, F. *Leprosy review*, **48**(1): 51 (1977).
21. RUSSELL, D. A. ET AL. *International journal of leprosy*, **44**: 170–176 (1976).
22. PEARSON, J. M. H. ET AL. *Leprosy review*, **48**: 129–132 (1977).
23. GIRDHAR, B. K. ET AL. *Leprosy in India*, **50**: 352–355 (1980).
24. GUINTO, R. S. ET AL. *International journal of leprosy*, **49**: 427 (1981).
25. PATTYN, S. R. ET AL. *Médecine d'Afrique noire*, **26**: 687–691 (1979).
26. WATERS, M. F. R. ET AL. *Leprosy review*, **49**: 127–130 (1978).
27. JACOBSON, R. R. & HASTINGS, R. C. *Lancet*, **2**: 1304 (1976).
28. ROLLIER, R. & ROLLIER, M. *Maroc médical*, **52**: 148–166 (1972).
29. PATTYN, S. R. ET AL. *International journal of leprosy*, **43**: 356–363 (1975).
30. PATTYN, S. R. & COLSTON, M. J. *Leprosy review*, **49**: 324–326 (1978).
31. WATERS, M. F. R. ET AL. *Leprosy review*, **45**: 288–298 (1974).
32. WATERS, M. F. R. ET AL. *British medical journal*, **1**: 33 (1978).
33. FREERKSEN, E. & ROSENFELD, M. *Chemotherapy* (Basel), **23**: 356–386 (1977).
34. SHEPARD, C. C. *International journal of leprosy*, **35**: 429–435 (1967).
35. REES, R. J. W. *Leprosy review*, **46** (Supplement): 121–124 (1975).
36. WORLD HEALTH ORGANIZATION. *A guide to leprosy control*. Geneva, 1980.
37. RIDLEY, D. S. *Skin biopsy in leprosy*. Basel, Ciba-Geigy, 1977 (Documenta Geigy).
38. PATTYN, S. R. ET AL. *Annales de la Société Belge de Médecine tropicale*, **59**: 79–85 (1979).
39. WARNDORFF, J. ET AL. *Leprosy review*, **53**: 9–17 (1982).
40. *Weekly Epidemiological Record*, No. 34, 1981, pp. 265–270.
41. WHO Technical Report Series, No. 641, 1979.

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