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WHO Study Group



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Geneva, 1–5 November 1993

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1. **Introduction**

A WHO Study Group on Chemotherapy of Leprosy met in Geneva from 1 to 5 November 1993. Opening the meeting on behalf of the Director-General, Dr S. K. Noordeen, Chief Medical Officer, Leprosy Control, recalled that a WHO Study Group on Chemotherapy of Leprosy for Control Programmes had recommended the introduction of multidrug therapy (MDT) for leprosy in 1981, at a time when global efforts to control the disease were meeting with little success, owing to the widespread occurrence of dapsone resistance. Describing this as a bold and balanced decision, Dr Noordeen noted that the critical role of MDT in the successful control of the disease was now well recognized.

Some 4.3 million patients had already been cured through MDT¹ and the number of cases of leprosy had been reduced by two-thirds. Efforts still had to be made, however, to simplify the administration of MDT, to improve accessibility for patients with special needs (e.g. those living in remote areas), and to derive the maximum benefit from the new antileprosy drugs. Even though leprosy could be successfully controlled through chemotherapy, it was important to monitor the situation constantly for problems such as drug resistance and to develop even more effective drug combinations.

The objectives of the present Study Group were as follows:

- To review the information collected since 1981 (the year when the WHO MDT regimens were introduced) and to recommend any modifications of these regimens that seemed appropriate in the light of the data collected.
- To make recommendations regarding the use of the new antileprosy drugs in the chemotherapy of leprosy.
- To make recommendations regarding changes in the operational aspects of chemotherapy of leprosy which would further strengthen efforts to control and eliminate the disease.
- To identify further research needs in order to improve the chemotherapy and control of leprosy.

1.1 **WHO Study Group on Chemotherapy of Leprosy for Control Programmes, 1981**

When the WHO Study Group on Chemotherapy of Leprosy for Control Programmes met in 1981, leprosy control programmes faced a variety of serious constraints that not only threatened to hinder further progress but, left unchecked, could have resulted in a serious deterioration of the world leprosy situation. Widespread secondary dapsone resistance was being reported in up to 19% of patients previously treated with dapsone

¹ As of April 1994, it is estimated that over 5.6 million leprosy patients have been cured through MDT.

monotherapy. Of equal concern, primary dapsone resistance, mostly low degree, was being detected in some areas in as many as 50% of newly diagnosed, previously untreated cases (1). Furthermore, cases of resistance of *Mycobacterium leprae* to rifampicin and the thioamides had been reported among patients receiving these drugs as monotherapy. However, most control programmes had failed to appreciate the seriousness of the situation and thus had not implemented even the limited MDT regimens recommended in the fifth report of the WHO Expert Committee on Leprosy (2).

After reviewing the situation and data on the available drugs and from ongoing drug trials, the 1981 Study Group recommended that all leprosy patients (paucibacillary and multibacillary) be treated with regimens that would be effective in cases of dapsone resistance, but were also of relatively short duration. The recommended regimen for paucibacillary leprosy involved rifampicin and dapsone, administered for 6 months, while the regimen for multibacillary disease involved both these drugs, together with clofazimine, given for 24 months or until skin smears became negative. In addition, new simplified definitions of paucibacillary and multibacillary leprosy were introduced and operational guidelines were drawn up to help assure the successful implementation of the new regimens.

Within a few years these now standard WHO MDT regimens were widely implemented and the level of implementation has steadily increased over the past 12 years. The regimens have proved highly successful in preventing relapse. Indeed, the success of these regimens and the concurrent efforts by Member governments and nongovernmental organizations to strengthen leprosy control programmes led the World Health Assembly in 1991 to set a goal of elimination of leprosy as a public health problem (reducing the prevalence to below 1 per 10000 population) by the year 2000.

Although progress towards this goal has been excellent, it is appropriate at this time to review the chemotherapy of leprosy in the light of 12 years of experience with the current MDT regimens and the recent introduction of several new bactericidal antileprosy drugs.

2. **The present situation**

During the past 8 years, the numbers of estimated and registered cases of leprosy have fallen from 10-12 million to 2.7 million and from 5.4 million to 1.9 million respectively. On the other hand, approximately 690 000 new cases were detected in 1992. This represents no significant change from previous years. Intensified case-finding efforts and earlier detection of cases as a result of improved control programmes may, to some extent, have obscured any downward trend resulting from MDT. It is also likely that many cases now being detected are in people who were

infected before the introduction of MDT. None the less, in some long-standing, well organized control programmes where there has been a prolonged high level of coverage, there has already been a significant fall in the case-detection rate since the introduction of MDT. This trend may become more widespread in the future, although many factors other than the introduction of MDT are undoubtedly involved, such as improved case management.

Currently, the level of MDT coverage of estimated and registered cases is about 38% and 53% respectively and the cumulative MDT coverage¹ is around 76% and 86% respectively. Many of the patients not yet on MDT are those who are difficult to reach or who live in countries where efforts to control the disease have proved inadequate. There is therefore considerable room for improvement; this should be achievable through better control programmes, innovative systems of drug delivery, and adequate allocation of resources. Such improvement is essential to achieving the goal of eliminating leprosy as a public health problem by the year 2000.

Another encouraging observation is the extent to which disability in newly diagnosed patients is decreasing. Although treatment with MDT does not have a direct effect on disabilities, implementation of the standard WHO MDT regimens has indirectly led to a marked reduction in the prevalence of disabilities among leprosy patients. Earlier detection of the disease, a reduction in the frequency of reactions and very low rates of relapse – all consequences of the implementation of MDT – have contributed significantly to the prevention of disabilities. Moreover, as a consequence of the dramatic decline in prevalence, health workers should be able to devote more time to the management of reactions and the prevention of disabilities.

2.1 Experience with multidrug therapy (MDT) since 1981

Data collected by WHO from several countries on cohorts of patients completing the recommended MDT regimens between 1981 and 1993 have presented a very favourable picture (3).

Out of a total of 20 141 multibacillary patients (about 80 000 person-years), 67 were reported to have relapsed, yielding a cumulative risk of relapse of 0.74% over a 9-year period of follow-up. Among a total of 51 553 paucibacillary patients (about 180 000 person-years), 306 cases of relapse were identified, giving a cumulative risk of relapse of 1.09% over the same period of follow-up. Moreover, in both multibacillary and paucibacillary patients, the risk of relapse remained almost constant for every year of follow-up.

¹ A composite indicator defined as the proportion of leprosy patients who are, or have been, treated with MDT since the programme based on MDT started, among all patients registered during the same period.

In comparison, among multibacillary patients treated with dapsone monotherapy and followed up over a similar period after their skin smears became negative, the expected cumulative risk of relapse would be between 10% and 20%.

Data are also available from several trials sponsored by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases through its Scientific Working Group on the Chemotherapy of Mycobacterial Diseases (THEMYC).¹ Among over 7700 multibacillary patients involved in the trials, the risk of relapse was less than 1 per 1000 person-years, regardless of whether the patients were treated with the standard WHO MDT regimen for 2 years or until their skin smears became negative.

The generally excellent results reported with the WHO MDT regimens in the literature have clearly validated their efficacy, safety and acceptability. However, the results of studies on other MDT regimens have been variable. The interpretation of data from different studies is complicated by the use of a variety of regimens, including modifications of the WHO MDT regimens, the inclusion of variable numbers of patients previously treated with dapsone monotherapy for prolonged intervals, and confusion about the classification of paucibacillary and multibacillary cases, particularly since the definitions were changed in 1988 by the WHO Expert Committee on Leprosy (4). There has also been confusion about whether relapse or reaction was observed in those who reportedly relapsed, and uncertainty as to the level of patient compliance in some instances and, perhaps most important from the point of view of paucibacillary disease, whether treatment had been adequate. The Study Group therefore took all of these factors into account in reviewing the reports on paucibacillary and multibacillary disease.

2.1.1 **MDT for paucibacillary leprosy**

In general, the reports on MDT regimens for paucibacillary disease can be divided into three groups:

- those that found that MDT for less than 6 months was sufficient;
- those that found that the 6-month WHO MDT regimen was sufficient;
- those that found that MDT for more than 6 months was required by at least some, if not all, cases.

Among those reporting successful therapy in less than 6 months are Pattyn et al., whose regimens were generally markedly different from the standard WHO MDT regimen for paucibacillary leprosy and perhaps more potent (5–7). Thus, while their results do not relate directly to the

¹ Until 1991, this group was known as the Scientific Working Group on the Chemotherapy of Leprosy (THELEP).

question of the efficacy of the WHO regimen, they are of interest if the feasibility of devising a shorter MDT regimen for paucibacillary disease is to be considered.

Those in the second group, which reported excellent or satisfactory results with the standard WHO MDT regimen or a minor modification thereof, generally noted that, even if skin lesions had not totally cleared within 6 months, clearance continued eventually to complete healing (8-13).

Those in the third group found that up to 1 year or more of therapy, either with the standard WHO MDT regimen throughout or with dapsone monotherapy after the first 6 months, was necessary to obtain uniformly satisfactory results, although many of their cases may have shown a satisfactory response within 6 months (14-18). A key issue here is the question of what constitutes a satisfactory result. One definition is that all patients who comply with treatment should respond to MDT and that the relapse rate should be less than 1% per year (19). The Study Group considered that a satisfactory result from MDT in a patient who complies with treatment is one in which, after the start of therapy, bacteria begin to clear in multibacillary cases and lesions generally, though not necessarily rapidly, improve in both paucibacillary and multibacillary cases. Clearance of lesions is related more to the person's immune response than to the antileprosy treatment; all lesions and bacilli should eventually clear, even though clearance may be incomplete at the time therapy is discontinued.

The question of a higher frequency of relapse among patients receiving the 6-month WHO MDT regimen than among those receiving longer regimens is more difficult to address without knowing the level of compliance and having independent confirmation of such relapses. Some of the reported cases of relapse may have merely reflected lack of clearance of the lesions, while others may have been reversal reactions. Relapses occurring during the first year after completion of treatment, however, are rare. Furthermore, Ekambaram & Rao found no difference in the number of relapses among over 14000 patients receiving 6 or 12 months' therapy in India (12).

On the basis of the data available, the Study Group concluded that the 6-month WHO MDT regimen for paucibacillary disease has been very effective and recommended that it should continue to be used. The Study Group noted that a recent review confirmed this view (20).

2.1.2 **MDT for multibacillary leprosy**

The results of trials of the standard WHO MDT regimen for multibacillary leprosy are easier to analyse than those for paucibacillary disease. There seems to be less disagreement about this regimen's efficacy, which may in part be because treatment is open-ended: unlike

the recommended regimen for paucibacillary disease, which is given over 6 months, the regimen for multibacillary disease is administered over a period of at least 2 years and preferably until skin smears are negative. Consequently, there have been fewer modifications of the standard regimen for multibacillary leprosy and even those implemented are now being dropped. For example, the initial 14-day course of daily rifampicin used in India has proved to be of questionable value and is now being phased out (20, 21). In general, the WHO MDT regimen for multibacillary disease has been highly successful. As with paucibacillary disease, some very short-term regimens have been investigated by Pattyn et al. (7, 22-24), often with excellent results. This may be a reason to expect that the results of ongoing or future trials of other very short-term regimens will also be satisfactory. However, Pattyn et al. have argued that follow-up 9-10 years after completion of therapy is necessary to evaluate the efficacy of any MDT regimen for multibacillary disease.

A key question for the Study Group, however, was whether the WHO MDT regimen for multibacillary disease could now be fixed at 24 months and the proviso to continue it until skin smears are negative could be dropped. Most control programmes have already taken this step, but while an overview of the literature may give the impression that 24 months of treatment should be sufficient, specific data addressing this question are limited. A trial in Bamako, Mali, for example, reported only one relapse among 44 multibacillary patients treated with the WHO MDT regimen, but follow-up averaged only 42 months (25). This group also noted, on evaluating relapses after a variety of rifampicin-containing MDT regimens, that while relapses occurred an average of 5.5 years after completion of treatment, they occurred earlier in those who received the shortest period of treatment with rifampicin. Relapse was more likely if the bacterial index (BI)¹ was high (5-6+) at the completion of treatment. Nearly all strains of *M. leprae* isolated from patients who relapsed remained fully sensitive to rifampicin, including the patient who relapsed after treatment with the WHO regimen (26).

Li et al. reported no relapses among 80 patients treated for 24-27 months and followed-up for 33 months (27). Katoch et al. reported on 15 highly bacillated (BI 4-6+) multibacillary cases lost to follow-up after 12-44 months of treatment. Those patients who were retrieved after being given only 12-18 months of therapy all deteriorated, whereas all those who had received at least 24 months of therapy continued to improve (28). Becx-Bleumink (9, 29) reviewed the literature and recommended that treatment for multibacillary patients should be limited to 2 years for operational reasons. Since increasing numbers of programmes are now limiting

¹ Refers to the density of bacilli in smears or tissues. The BI is generally scored on Ridley's logarithmic scale, at one end of which the demonstration of 1-10 leprosy bacilli in 100 oil-immersion fields is graded as 1+ and at the other end the demonstration of over 1000 bacilli in a single oil-immersion field is graded as 6+.

therapy to 24 months in all multibacillary cases, more data will be forthcoming, but available information suggests that 24 months are sufficient.

2.1.3 **Toxic and lepra reactions during MDT**

Drug toxicity has not been a major problem with MDT. In one large study involving 10426 patients with multibacillary disease and 35013 with paucibacillary disease, 17 patients had hepatitis (two of whom died), three had renal failure and four had dermal hypersensitivity reactions (30). Toxic reactions to rifampicin such as renal failure or thrombocytopenia are occasionally reported but are rare. It has been reported (31, 32) that delayed-type hypersensitivity reactions to dapsone are more common among patients receiving MDT than among those given monotherapy, but there are relatively few data to support this.

The prevalence of lepra reactions does not appear to have increased following the introduction of MDT. Indeed, erythema nodosum leprosum (ENL or type II lepra reaction) is less common now, perhaps because of the clofazimine component of the MDT regimen for multibacillary leprosy, but the extent of this protection is not clear (33). Perhaps the most extensive data on reactions among patients receiving the WHO MDT regimens are those of Becx-Bleumink & Berhe, who report the findings from the All Africa Leprosy Research and Rehabilitation Training Centre (ALERT) leprosy control programme. During the first 2 years of therapy, reversal reactions occurred in 43.6% of 266 borderline lepromatous cases and 19.2% of 109 lepromatous leprosy cases, whereas ENL developed in 2.7% and 11.1% respectively. Reversal reactions were most common in multibacillary patients in the first year of MDT and then gradually declined, but were still occurring in the fifth year of treatment. Among 438 borderline tuberculoid patients, the prevalence of reversal reactions was 10.3% during the 6 months of treatment and 7.3% during the first year after completion of treatment. Among paucibacillary patients, the risk was highest during treatment with MDT followed by the first 6 months after completion of treatment; however, reversal reactions were occasionally observed up to 4 years after therapy was discontinued. Other studies have found reactions to be relatively uncommon; for example, Ramesh et al. report that only 10.4% of 855 multibacillary cases treated with MDT developed ENL or reversal reactions. Few details are available of this study, however, and it is not clear whether this population and the ALERT cases were comparable in terms of disease activity, etc.

2.2 **Drug resistance**

Although primary dapsone resistance is thought to be widespread, patients infected with dapsone-resistant *M. leprae* have, to date, responded satisfactorily to the WHO MDT regimens.

Small numbers of cases of secondary rifampicin resistance have been reported among patients treated with rifampicin monotherapy or among dapsone-resistant cases treated with rifampicin and dapsone. Whenever rifampicin resistance is suspected, patients should be referred for full investigation, including drug-susceptibility tests in the mouse-footpad model. An appropriate MDT regimen incorporating new antileprosy drugs should be substituted for the WHO regimen (see section 4.3.1).

No confirmed cases of clofazimine resistance have been reported.

Relapses after treatment with the WHO MDT regimens have been rare. Among those who have been studied after relapse (including patients infected with dapsone-resistant *M. leprae*), no new cases of resistance have been detected by drug-susceptibility tests in mice. In addition, re-treatment with the WHO MDT regimen has been effective in all cases.

2.3 Persistence of *Mycobacterium leprae*

Data from the clinical trials organized by THEMYS (see page 4) in Bamako, Mali, and Chingleput, India, suggest that small numbers of drug-susceptible *M. leprae* often persist in patients treated with the WHO MDT regimen for multibacillary leprosy (35). However, the very success of this regimen so far indicates that persistence of *M. leprae* is not a frequent cause of relapse when treatment is completed.

2.4 Immunotherapy

A number of immunotherapy studies are in progress, but there are, as yet, insufficient data available to indicate the role of immunotherapy in the treatment of leprosy. In any case, immunotherapy is unlikely to play a significant role in leprosy control programmes.

2.5 Lepra reactions

Corticosteroids, clofazimine and thalidomide remain the mainstays of reaction management, with no promising alternatives in sight. The use of standardized prednisolone regimens has been proposed for the treatment of reversal reactions and neuritis under field conditions (36), and should help to prevent disabilities among leprosy patients until such time as better anti-reaction drugs or other treatments are found.

3. Currently available antileprosy drugs

Several new highly bactericidal drugs have become available since 1981, but only a limited amount of additional information is available on the five drugs that were considered for inclusion in MDT at that time, i.e. dapsone, clofazimine, rifampicin, ethionamide and prothionamide.

3.1 Dapsone

Dapsone is inexpensive and relatively non-toxic in the doses used, although occasional cases of delayed hypersensitivity reactions and less commonly agranulocytosis have been reported. Mild haemolytic anaemias are common following treatment with the drug, but severe haemolytic anaemias are rare except in patients with severe glucose-6-phosphate dehydrogenase deficiency. When given in a dosage of 100 mg daily, dapsone is weakly bactericidal against *M. leprae*. Such a dosage results in peak serum levels that exceed the minimum inhibitory concentration (MIC) of dapsone against *M. leprae* by a factor of about 500. Such high levels of the drug will also 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.

3.2 Rifampicin

Rifampicin is expensive, but even a single 600 mg dose monthly is highly bactericidal against *M. leprae* and is almost as effective as daily rifampicin for treatment purposes. The toxicity of the drug is relatively low, but is related to the size of the dose and the interval between doses. The standard dose of 600 mg monthly has proved relatively non-toxic, although occasional cases of renal failure, thrombocytopenia, influenza-like syndrome and hepatitis have been reported. Its effect on the metabolism of other drugs, such as dapsone, corticosteroids and oral contraceptives, is not a problem when it is administered monthly. A number of rifampicin derivatives have been prepared, such as rifabutin (37), which are also highly bactericidal against *M. leprae* and have longer half-lives than the parent drug. There is no evidence to suggest that these drugs would be more effective for the treatment of leprosy, however, and their cost is higher.

3.3 Clofazimine

In the dosage employed for the MDT regimen for multibacillary leprosy, clofazimine is virtually non-toxic. Pigmentation of the skin, particularly within skin lesions, is common but it clears completely after treatment is discontinued. The higher doses of clofazimine sometimes used for the control of lepra reactions may occasionally produce severe gastrointestinal side-effects. A recent study (38) found that when the drug was administered in a dosage of 1200 mg once-monthly, the results were comparable to those obtained with the standard MDT regimen (300 mg once-monthly plus 50 mg daily). Although only small numbers of patients were involved, the results of studies on *M. leprae* activity in the mouse-footpad model were very similar in the two groups. This suggests that the total dose of clofazimine could be reduced, without the need for self-administration of the drug.

3.4 Thioamides (ethionamide and protionamide)

The two available preparations ethionamide and protionamide are similar in terms of activity, dose and toxicity. They are intermediate in bactericidal activity between dapsone and rifampicin but are more costly than dapsone. They are frequently hepatotoxic; because of their toxicity, the WHO Expert Committee on Leprosy, at its sixth meeting, recommended that ethionamide and protionamide should not be substituted for clofazimine in the MDT regimen for multibacillary leprosy “unless absolutely necessary” (4). The toxicity of protionamide has recently been confirmed by a study in which 694 multibacillary patients were treated for 6 months with a combination of dapsone, protionamide and rifampicin. Approximately half of the patients also received isoniazid. Irrespective of the inclusion of isoniazid, hepatotoxic effects were observed in 10% of the patients, which were sufficiently severe to warrant stopping of treatment (39).

3.5 Fluoroquinolones

Although a large number of fluoroquinolones have been developed, some such as ciprofloxacin are not active against *M. leprae*; of those which are, most interest has focused on ofloxacin. Like all fluoroquinolones, ofloxacin interferes with bacterial DNA replication by inhibiting the A subunit of the enzyme DNA gyrase. It was used in a clinical trial by Ji & Grosset in a dose of 400 mg daily (40). A single dose had some bactericidal activity, although less than that of a single dose of rifampicin, and 22 doses killed 99.99% of the viable *M. leprae*. Ofloxacin is well absorbed, reaching a peak serum concentration of 2.9 µg/ml after 2 hours, and has a half-life of 7 hours. Most of the dose is excreted unchanged in the urine. Side-effects include nausea, diarrhoea and other gastrointestinal complaints, and a variety of central nervous system complaints including insomnia, headaches, dizziness, nervousness and hallucinations. Serious problems are infrequent and do not usually require discontinuing the drug.

3.6 Minocycline

Minocycline is the only member of the tetracycline group of antibiotics that has significant bactericidal activity against *M. leprae*. This may be because of its lipophilic properties, which allow it to penetrate cell walls (41). The standard dose is 100 mg daily, which gives a peak serum level that exceeds the MIC of minocycline against *M. leprae* by a factor of 10–20. Its bactericidal activity against *M. leprae* is greater than that of clarithromycin, but much less than that of rifampicin (42). It was shown to be very effective clinically when administered as monotherapy in eight patients with lepromatous leprosy, although 2 months of therapy was required before all patients became negative for *M. leprae* as determined in the mouse-footpad model (43).

Like the other tetracyclines, minocycline inhibits protein synthesis via a reversible binding at the 30S ribosomal subunit, thereby blocking the binding of aminoacyl transfer RNA to the messenger RNA ribosomal complex. It is well absorbed, with a half-life of 11-23 hours. Side-effects include discoloration of teeth in infants and children, occasional pigmentation of the skin and mucous membranes, various gastrointestinal symptoms and central nervous system complaints, including dizziness and unsteadiness. Minocycline is commonly used for the long-term treatment of acne, which indicates that in general it is well tolerated.

3.7 **Macrolides**

Several members of this group, including erythromycin, have been evaluated as antileprosy drugs, but only clarithromycin shows significant promise at this time. Studies in the mouse-footpad model have demonstrated the potent bactericidal activity of clarithromycin, but it is clearly less bactericidal than rifampicin (41). When clarithromycin was administered at a dose of 500 mg daily to lepromatous leprosy patients, 99% of bacilli were killed within 28 days and 99.9% by 56 days (44).

Clarithromycin is readily absorbed from the gastrointestinal tract and converted to its active metabolite, 14-hydroxyclearithromycin. A single dose of 500 mg produces a peak serum concentration of about 1.0 µg/ml in 1-4 hours, which subsequently decays with a half-life of 6-7 hours. About 38% of the dose is excreted in the urine and 40% in the faeces. Tissue concentrations are higher than those in serum.

Clarithromycin inhibits bacterial protein synthesis by linking to the 50S ribosomal subunit, thereby preventing elongation of the protein chain. It is relatively non-toxic. Gastrointestinal irritation, nausea, vomiting and diarrhoea are the most common problems, but they usually do not necessitate discontinuation of the drug.

3.8 **Other drugs**

With the possible exception of fusidic acid (45), other drugs available or under study with known activity against *M. leprae* are much less potent than those mentioned above or purely bacteriostatic. They include amoxicillin plus clavulanic acid, brodimoprim, thioacetazone and deoxyfructoserotonin. Given the large number of much more potent antileprosy drugs available which have the potential in MDT regimens for further marked shortening of the length of therapy, there is no justification for using any of these other drugs.

4. **Recommended chemotherapeutic regimens**

4.1 **Multibacillary leprosy**

The WHO MDT regimen for multibacillary leprosy has been very successful and has been widely implemented as recommended. Most data on the effects of limiting therapy to a 24-month course (rather than continuing until skin smears are negative) are favourable. The Study Group therefore recommended that all multibacillary patients be given the standard WHO regimen for 24 months, since it considered that such a change was safe and would increase the use of the regimen under field conditions.

The Study Group also recommended that there should be no changes in the composition or doses of drugs, or in the “rhythm” (i.e. frequency and pattern) of therapy. Although the various new bactericidal drugs now available may alter this situation in the future, the Study Group pointed out that clinical trials would be needed before these drugs could be employed in MDT regimens.

For adults the recommended standard regimen for multibacillary leprosy is:

- rifampicin: 600 mg once a month, supervised;
- dapsone: 100 mg daily, self-administered;
- clofazimine: 300 mg once a month, supervised, and
50 mg daily, self-administered.

Duration: 24 months.

The above regimen is suitable for the treatment of all categories of multibacillary patients except for those referred to in section 4.3. Cases of relapse should be confirmed by a referral centre and the patients should be re-treated with the same regimen, since drug resistance is unlikely.

4.2 **Paucibacillary leprosy**

The 6-month WHO MDT regimen for paucibacillary leprosy has yielded excellent results wherever it has been appropriately used, and there is no convincing evidence to suggest that it should be extended beyond 6 months. The Study Group therefore recommended that the regimen be retained, with no changes in the duration or rhythm of therapy, or in the composition or doses of drugs.

For adults the recommended standard regimen for paucibacillary leprosy is:

- rifampicin: 600 mg once a month, supervised;
- dapsone: 100 mg daily, self-administered.

Duration: 6 months.

If any patients relapse, they should be re-treated with the same regimen, provided their disease is still paucibacillary. If, however, multibacillary leprosy is diagnosed at the time of relapse, treatment should be in accordance with the recommended regimen for that disease.

4.3 **Alternative MDT regimens**

The availability of potent new drugs makes possible the formulation of alternative regimens for use when it is impossible or inadvisable to employ the standard MDT regimens described above.

4.3.1 **Rifampicin resistance or toxicity**

Multibacillary patients who have relapsed, and who have been shown to be infected with rifampicin-resistant *M. leprae* (by testing in the mouse-footpad model), and those in whom rifampicin has toxic effects require treatment with a new regimen. On the basis of the available information, the Study Group recommended the following regimen for adults:

- daily administration of 50 mg of clofazimine, together with two of the following drugs – 400 mg of ofloxacin, 100 mg of minocycline, or 500 mg of clarithromycin – for 6 months;
- daily administration of 50 mg of clofazimine, together with 100 mg of minocycline or 400 mg of ofloxacin for an additional 18 months.

This regimen should be administered under direct supervision in a referral centre.

4.3.2 **Severe dapsone toxicity**

If dapsone has severe toxic effects in any patient (paucibacillary or multibacillary), the drug should be stopped immediately. No further modification of the regimen is required for patients with multibacillary disease. However, clofazimine in the dosage employed in the standard MDT regimen for multibacillary disease may be substituted for dapsone in the regimen for paucibacillary disease for a period of 6 months.

4.3.3 **Refusal to accept clofazimine**

Every effort should be made to persuade multibacillary patients to agree to treatment with clofazimine. When clofazimine is totally unacceptable owing to pigmentation of the skin, the available evidence suggests that ofloxacin, 400 mg daily, or minocycline, 100 mg daily, may be substituted for the clofazimine component of the standard MDT regimen. Because of the limited information available, these drugs should be administered only under supervision in a referral centre. In view of the severe hepatotoxicity of ethionamide and protionamide, the Study Group considered that these drugs should no longer be recommended as substitutes for clofazimine.

5. **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. Given the effectiveness of the standard WHO MDT regimens for paucibacillary and multibacillary leprosy, and WHO's goal of elimination of leprosy as a public health problem by the year 2000, leprosy control programmes of the highest quality become even more important.

5.1 **Classification**

The current system for classifying patients as either paucibacillary or multibacillary based on skin smears has proved satisfactory. In this system, patients showing negative smears at all sites are classified as having paucibacillary leprosy, while those showing positive smears at any site are classified as having multibacillary disease. The Study Group therefore recommended that this system should be continued. However, it is possible in most cases to distinguish multibacillary and paucibacillary leprosy on clinical grounds, and approaches based on clinical classification may be required where reliable facilities for the bacteriological examination of skin smears are not available. When classification is in doubt, the patient should be treated as having multibacillary disease.

5.2 **Laboratory facilities**

5.2.1 ***Facilities for bacteriological examination***

A service for the bacteriological examination of skin smears is not a prerequisite for initiating an MDT programme. However, with the widespread implementation of MDT, many leprosy control programmes have established or improved their services for processing skin smears. To ensure that the services offered are of high quality, however, they must be regularly monitored by reference laboratories. Provision of suitable laboratory equipment and training will be necessary in countries where such services do not exist.

In view of the increasing prevalence of human immunodeficiency virus (HIV) and hepatitis B infection in many countries where leprosy remains endemic, the number of skin-smear sites and the frequency of smear collection should be limited to the minimum necessary for diagnostic purposes. To prevent cross-infection, technicians should take care to avoid injury when taking skin smears (46).

5.2.2 ***Referral facilities for mouse-footpad studies***

Unless the patient is part of a special study, routine drug-susceptibility

studies in the mouse-footpad model are generally not useful for leprosy control programmes.

5.2.3 **Other laboratory facilities**

Whenever possible, the laboratory facilities of primary health care services should be used for routine screening for contraindications to MDT and evaluating any cases of drug toxicity that arise.

5.3 **Re-treatment of multibacillary cases previously treated only with dapsone monotherapy**

Relapse of multibacillary patients previously treated only with dapsone monotherapy continues to be a significant source of new cases in many leprosy control programmes (47-49). Re-treatment of such patients with the standard WHO MDT regimen for multibacillary leprosy would probably prevent nearly all such relapses. The Study Group therefore recommended that multibacillary patients previously treated with dapsone monotherapy and showing negative skin smears should be given a 2-year course of the standard WHO MDT regimen for multibacillary leprosy wherever resources permit, provided that this activity does not prevent newly diagnosed cases from receiving treatment.

5.4 **Drug delivery**

The recommended regimens require that the monthly doses of rifampicin and clofazimine for multibacillary patients and of rifampicin alone for paucibacillary patients be administered under direct supervision: a health worker should be present when the patient ingests the drug. All registered and newly diagnosed cases must be started on an appropriate MDT regimen immediately. Because the WHO MDT regimens are “robust” (i.e. their efficacy is not impaired by minor modifications and their application requires little in the way of infrastructure), it is possible to devise new treatment delivery systems outside the conventional medical network in certain countries where primary health care services are limited and communications are difficult. If normal monthly supervision by a health worker is not possible, every effort should be made to find a responsible person, such as a village chief or schoolteacher, to supervise the monthly drug intake. Continuity, regularity, and completion of chemotherapy continue to be the keys to the success of the MDT regimens.

To be effective, treatment must be given regularly. Multibacillary patients should receive 24 monthly doses of combined therapy within 36 months and paucibacillary patients six monthly doses within 9 months. If any patients drop out before completion of therapy, they should be re-evaluated when retrieved to determine whether further treatment is needed.

There should be an efficient system for identifying patients who drop out of treatment, 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. They should also be monitored for side-effects periodically and should be seen by medical officers at specified intervals.

5.5 Management of reactions and prevention of deformity

If deformity is to be prevented, reactions must be promptly diagnosed and treated. This is a vital part of every leprosy control programme, since patient compliance will often depend on how well reactions are managed.

Usually the diagnosis of reactions is relatively straightforward but occasionally, in patients who have completed treatment, differentiation of a reversal (type I) lepra reaction from relapse may be difficult. Guidelines exist (50) to assist programme staff in this regard and a referral source for evaluation of problematic cases should be available.

Reversal reactions and erythema nodosum leprosum (ENL) can be treated using corticosteroids, or in some cases, clofazimine. For patients with severe ENL, however, thalidomide is the most effective drug. Corticosteroids and clofazimine are readily available, and thalidomide should be made available at referral centres. Detailed guidelines for their use should be given during training and in field manuals. It must be pointed out, however, that because of its teratogenic effects, thalidomide should never be given to women of childbearing age. All patients must be fully informed of its side-effects and this drug must be given only under close supervision at the nearest referral centre. If supervision and appropriate use of thalidomide cannot be assured, it should not be used.

Clinical trials have shown that, in general, patients with reactions or neuritis can be treated successfully using standard courses of corticosteroids. The Study Group noted that such standard courses (36) have safely been used by appropriately trained health workers, even under very difficult field conditions, and therefore recommended their use. On the basis of experience with tuberculosis, the Study Group considered that, when treatment with corticosteroids was started after a patient had completed MDT, there might be some risk of relapse in multibacillary patients. It therefore recommended that, wherever possible, 50 mg of clofazimine daily be started as a prophylactic measure if the duration of steroid therapy is expected to exceed 4 months, and be continued until the course of steroids is completed. However, these patients should not be re-entered into the case registry.

The Study Group also recommended that care for iridocyclitis, lagophthalmos and other eye problems and access to specialized ophthalmology services should be available to all leprosy patients. Care and advice about measures to prevent injuries to insensitive hands and feet are also required.

5.6 Follow-up after completion of therapy

Because the risk of relapse after completion of the WHO MDT regimens has been shown to be negligible, it is no longer necessary to continue routine annual surveillance of patients. Instead, the Study Group recommended that patients should be taught, at the time of release from treatment, to recognize the early signs of possible relapse or reactions and to report promptly for treatment.

Health services, for their part, must ensure that health workers are aware of the possibilities of reactions and relapse after completion of MDT. They must also be able to diagnose and treat these conditions and to refer patients when necessary.

5.7 Health education and medical care

Acceptance of MDT by health professionals and patients has generally been excellent, as has community participation. For MDT regimens to be implemented successfully, however, a good health education programme must be developed and/or maintained, using all available resources, including the mass media.

Before starting MDT, patients should be informed of the possible side-effects of the treatment they will receive, the possibility of lepra reactions or disabilities occurring, and what to do if such problems arise. Patients should also be advised about the consequences of interrupting or stopping MDT. This information is essential to ensure that patients cooperate with health workers. Throughout their treatment, patients should be advised about how to take care of insensitive hands, feet and eyes.

5.8 Household contacts of patients

Household contacts of leprosy patients are at significant risk for the development of the disease. Thus, contacts of newly diagnosed cases should be examined for evidence of leprosy at that time. They should then be advised of the early signs of the disease and told to return if any suspect skin, motor, sensory or other lesions occur. Chemoprophylaxis with rifampicin or other antileprosy drugs is not recommended for contacts of leprosy patients in leprosy control programmes.

5.9 Training

With the introduction of MDT, training is needed for all categories of staff, especially those working in the primary health care delivery system. The training should be planned and organized so that each category of personnel is able to perform certain tasks competently within the overall context of the programme. Adequate training for all management personnel involved in the programme is crucial. Several training modules

for managers of leprosy control programmes are available from WHO.¹ Training of medical students and organization of refresher courses for physicians on MDT for leprosy 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. The manual should be updated as necessary.

5.10 Drugs and drug supplies

Availability of an uninterrupted supply of drugs is the most important prerequisite for an MDT programme.

Drugs for MDT regimens should be ordered at least 6 months in advance to ensure that the necessary amounts are obtained in time. This means that every leprosy control programme should have a long-range plan of its drug needs. In addition, every programme should try to keep a reserve stock of at least 6 months' supply of drugs in order to prevent an interruption of MDT in the event of a delay in the drug supply.

Since substandard products exist on the world market, care should be taken to ensure that the drugs procured by the programme are of adequate quality. All drugs should be properly stored to prevent deterioration and the stock managed so that supplies are utilized before their expiry date. Blister packs containing a month's supply of drugs should be used wherever possible, since they are convenient for the health workers and may aid patient compliance.

5.11 Planning and human and financial resources

In general, experience has shown that MDT can be readily implemented, with some programme modifications, wherever monotherapy is now utilized. Countries planning to increase MDT coverage must first mobilize the necessary human and financial resources.

Proper planning and precise formulation of projects with intermediate objectives and operational targets will be necessary.

5.12 Monitoring and evaluation

A suitable, uniform system of collecting, recording and transmitting data to programme managers is indispensable and will greatly assist in

¹ Available on request from Leprosy Control, Division of Control of Tropical Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

assessing the impact of MDT. In order to monitor compliance, a record should be kept of the number of patients who drop out of treatment.

A system for evaluation should be developed when the programme is planned. Progress should then be continuously measured in relation to specific targets at different stages of the programme. Periodic evaluation by independent teams should be encouraged.

5.13 **Treatment of patients with human immunodeficiency virus (HIV) infection or tuberculosis**

HIV infection is a significant problem in many countries where leprosy is endemic. As yet, leprosy has not been found to be more common in such countries, but occasionally, patients may be encountered who both are HIV-positive and have active leprosy. The information available (51) indicates that the initial response of such patients to MDT is similar to that of other leprosy patients and treatment of reactions does not require modification.

Patients suffering from both leprosy and tuberculosis will also occasionally be encountered. They will require standard antituberculosis therapy in addition to MDT for their leprosy. At present only rifampicin will be common to the two regimens and it must be given in the doses required for tuberculosis.

6. **Research trends and needs**

6.1 **New bactericidal drugs**

Progress continues in all areas of leprosy research but particularly in chemotherapy. The availability of three powerful new bactericidal drugs has led to considerable work to define their role in the treatment of this disease. Ji et al. recently reported the results of mouse-footpad studies, which showed that a single combined dose of minocycline and clarithromycin is only slightly less bactericidal than rifampicin, while adding a single dose of ofloxacin yields a combination similar to rifampicin in terms of activity. They suggested that this three-drug combination could be given once monthly for treating multibacillary patients infected with rifampicin-resistant *M. leprae*, and that this same combination or perhaps just minocycline plus clarithromycin could be given together with rifampicin once monthly to treat other multibacillary patients (52).

Although there is less need for new drugs now than in 1981, the potential for finding new drugs is greater. This is because thousands of preparations are currently being screened for antituberculosis activity, some of which are likely to be effective against *M. leprae*. Such drugs may permit the duration of therapy to be reduced further. A drug to eliminate persistent *M. leprae* would also be extremely useful.

6.2 Shorter therapy

Currently, a regimen consisting of 600 mg of rifampicin plus 400 mg of ofloxacin, both given daily for 1 month, is being evaluated as a treatment for both paucibacillary and multibacillary leprosy. If successful, this would markedly shorten leprosy chemotherapy, although it would still fall considerably short of the theoretical ideal of single-dose treatment for this disease. Supervising daily therapy for 1 month would of course be costly and labour-intensive, and innovative approaches to this limitation of the regimen would have to be sought. Whatever the results of such trials, the quest for ever shorter regimens will undoubtedly continue. The Study Group recommended that attempts should be made to develop very short-course regimens, particularly for early paucibacillary leprosy, which is a significant problem in certain countries.

6.3 Intermittent supervised therapy

Monthly supervised therapy, without the need for self-administration of drugs, would eliminate the problems of compliance with the current MDT regimens for multibacillary cases, where only the monthly administration of rifampicin and clofazimine is supervised. Several possible regimens based on supervised intermittent administration of ofloxacin, minocycline, clarithromycin and rifampicin are noted in section 6.1. As noted earlier (see page 9), rifampicin plus clofazimine might be added to that list, at least for paucibacillary disease. However, such regimens are unlikely to have a major impact on leprosy control unless their costs are acceptable and they are significantly shorter than standard MDT.

6.4 Improved reaction therapy

The best method of preventing disability is to diagnose leprosy as early as possible using the methods now available, and then provide appropriate treatment, including drugs for the control of reactions and neuritis. Corticosteroids and thalidomide are excellent drugs for these purposes, but may have severe toxic effects. The Study Group therefore recommended that priority should be given to finding an acceptable alternative to these drugs.

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