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 clofazidine 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 \textit{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 \textit{Mycobacterium leprae}

Data from the clinical trials organized by THEMYC (see page 4) in Bamako, Mali, and Chingleput, India, suggest that small numbers of drug-susceptible \textit{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 \textit{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, clofazidine 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, clofazidine, rifampicin, ethionamide and protonamide.
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 prothionamide)**

The two available preparations ethionamide and prothionamide 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 prothionamide should not be substituted for clofazimine in the MDT regimen for multibacillary leprosy "unless absolutely necessary" (4). The toxicity of prothionamide has recently been confirmed by a study in which 694 multibacillary patients were treated for 6 months with a combination of dapsone, prothionamide 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-hydroxyclarithromycin. 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, brodlimoprim, thioacetazone and deoxyfructoserdotonin. 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 prothionamide, the Study Group considered that these drugs should no longer be recommended as substitutes for clofazimine.