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EDITORIALS

Editorial opinions expressed are those of the writers.

XIV LEPROSY CONGRESS STATE-OF-THE-ART LECTURES

We are pleased to have the opportunity of publishing the full texts of the state-of-the-art lectures presented at the XIV International Leprosy Congress in Orlando, Florida, U.S.A., 29 August–4 September 1993. The first two of these lectures appear in the March 1994 issue. Remaining lectures will appear in subsequent issues.— RCH

Progress in the Chemotherapy of Leprosy*

Although they are a minority in number, patients with lepromatous or multibacillary leprosy are the main sources of infection with *Mycobacterium leprae* and those in whom drug-resistant mutants are the most easily selected. The rationale that supports modern chemotherapy for leprosy [6, 7, 15, 24, 42] is the same as that of chemotherapy for patients with cavitary pulmonary tuberculosis. In both cases, the multibacillary character of the disease is the crucial point.

Microbial Population in Multibacillary Leprosy

In a patient with multibacillary (MB) leprosy the maximal number of acid-fast bacilli (AFB) could be 100 billion (10^{11}) or 1 trillion (10^{12}), of which on average only 1% (10^9 or 10^{10}) are viable [36]. The proportion of *M. leprae* mutants resistant to dapsone, clofazimine or rifampin among those 10^9–10^{10} viables has not yet been established because until now *M. leprae* cannot be cultivated *in vitro*. However, by analogy with what is known about *M. tuberculosis* [3, 4, 16, 27] the mean proportion of drug-resistant mutants within a wild strain of *M. leprae* was estimated to be 1 per 10 million, 10^{-7} to rifampin and 10^{-6} to dapsone, clo-

* Based on state-of-the-art lecture presented at the XIV International Leprosy Congress on 1 September 1994, Orlando, Florida, U.S.A.

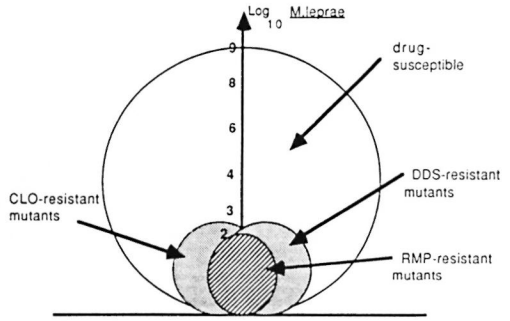

FIG. 1. Bacillary populations in multibacillary leprosy.

TABLE 1. *Quantitative importance of drug-resistant mutants in a normal strain of* M. leprae.

Drug(s)	Resistant mutant	
	%	Total no.[a]
Rifampin (RMP)	1 per 10^7	10^3
Dapsone (DDS)	1 per 10^6	10^4
Clofazimine (CLO)	1 per 10^6	10^4
RMP + DDS	1 per 10^{13}	10^{-3}
RMP + CLO	1 per 10^{13}	10^{-3}
DDS + CLO	1 per 10^{12}	10^{-2}
RMP + DDS + CLO	1 per 10^{19}	10^{-9}

[a] In a MB patient harboring 10^{10} viable *M. leprae*.

fazimine or thioamide, either ethionamide or prothionamide. Thus, a patient with MB leprosy harbors, at most, 10^9 drug-susceptible organisms, 10^3 rifampin-resistant mutants, and 10^4 dapsone-, clofazimine- or thioamide-resistant mutants (Fig. 1).

Basis of Chemotherapy for Leprosy

In order to cure a patient microbiologically, chemotherapy should be capable of killing all viable organisms, the drug-resistant mutants as well as the drug-susceptible organisms. Killing the drug-susceptible organisms requires a drug or a combination of drugs with bactericidal activities. The more bactericidal against all forms of drug-susceptible organisms the prescribed drug(s), the shorter the total duration of treatment and the more effective the chemotherapy, the smaller the percentage of relapses with drug-susceptible organisms after stopping treatment. It should be clearly understood therefore that the length of treatment is highly dependent upon the capability of the drug therapy to sterilize the lesions.

Killing the drug-resistant mutants requires a more sophisticated approach. It requires the use of a combination of drugs to kill mutants resistant to each drug in order to prevent the selection of resistant mutants that would lead to treatment failure. The killing of drug-resistant mutants and the prevention of their selection is, therefore, the first objective of chemotherapy.

Killing drug-resistant mutants

To kill resistant mutants one takes advantage of a basic rule of genetics, the independence of mutation. According to that rule, a mutant resistant to a given drug remains fully susceptible to another drug on the condition that the latter has a mechanism of action different from that of the former. In other words, each drug acts against the mutants resistant to the others. Because of the relatively limited size of the drug-resistant mutants in multibacillary leprosy before treatment, the combination of two drugs, for example, rifampin and dapsone, is in theory sufficient to kill the resistant mutants (Table 1). However, one should keep in mind the possibility of primary and secondary dapsone resistance. In practice, to overcome possible dapsone resistance the recommendation is to combine three drugs, rifampin, dapsone and clofazimine ([42]) (Fig. 2).

Dapsone, being poorly bactericidal, has to be given at a daily dose of 100 mg in adults. Clofazimine, also poorly bactericidal, has to be given daily at a dose of 50 mg with a monthly supplement of 300 mg, but might be given monthly at a dose of 1200 mg ([23]). For rifampin, a single dose of 600 mg kills more than 99% of the susceptible

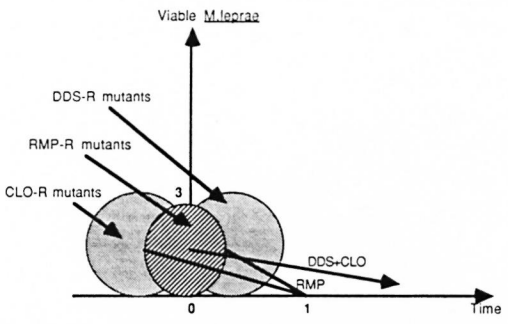

FIG. 2. Outcome of drug-resistant mutants in patients on combined chemotherapy (MDT).

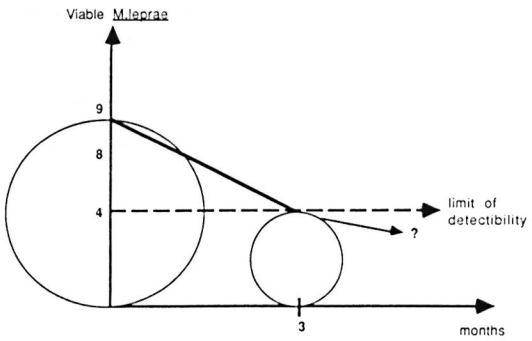

FIG. 3. Outcome of drug-susceptible *M. leprae* in patients on combined chemotherapy (MDT).

organisms present at the start of treatment, that is as much as 3 to 6 months of daily treatment with the combination dapsone plus clofazimine ([7, 28, 37–39]). Since daily treatment with rifampin did not demonstrate to be more bactericidal than monthly treatment ([39]), there is no need to give rifampin daily, even during the initial phase of chemotherapy. By definition, mutants resistant to dapsone and clofazimine are fully susceptible to rifampin and are killed by the first dose(s) of rifampin; whereas it takes a much longer duration of daily administration of dapsone and clofazimine to get rid of rifampin-resistant mutants. This explains why in the control programs it is recommended to give only monthly supervised pulses of 600 mg rifampin, a rhythm of administration that fits well with the regular field visits of the medical team. On the other hand, since the length of time needed to kill rifampin-resistant mutants cannot be determined precisely, in order to remain on the safe side it is recommended to administer the combination dapsone-clofazimine during the whole course of therapy.

TABLE 2. *Relation between duration of treatment with rifampin and incubation period of relapse ([29]).*

Duration of treatment with RMP	No. patients	No. relapses with incubation period		
		Total	≤ 5 yr	> 5 yr
< 3 mos.	283	50	32 (64%)	18
> 3 mos.	101	18	4 (22%)	14
Total	384	68	36 (53%)	32

Killing drug-susceptible organisms

During the initial phase of MDT, in addition to the killing of drug-resistant mutants there is also an extremely rapid killing of drug-susceptible organisms (Fig. 3). For example, in patients of the Bamako-Chingleput study ([39]), the proportion of *M. leprae* remaining capable of multiplying in the foot pads of mice after the few initial doses of 600 mg rifampin was in the range of 10^{-7}, i.e., 1 per 10,000,000. Since about 10^{-2} (1 per 100) were able to multiply before treatment, then the first doses of rifampin have reduced the proportion of viables from 10^{-2} to 10^{-7}, in other words have killed 99.999% of them. The initial population of viable *M. leprae* in a MB patient has therefore been reduced from 10^{10} to 10^{5}. The objective is then to eliminate the remaining 10^{5} viable drug-susceptible *M. leprae* in order to prevent relapse after stopping treatment.

After the initial rapid killing of *M. leprae* in the Bamako-Chingleput study ([39]), the proportion of *M. leprae* capable of multiplying in mice remained constant during the 2 years of treatment, suggesting that chemotherapy was mostly ineffective against the remaining organisms. These organisms were not drug-resistant *M. leprae* selected by the chemotherapy because the few bacilli that grew in the foot pads of mice were normally susceptible to rifampin and other drugs. They are unresponsive to the drugs to which they are fully susceptible, perhaps because of the strong post-antibiotic effect ([31]) of rifampin. The suppression of metabolic activity, that persists after short exposure of organisms to antimicrobials and might be due to the nonlethal damage caused by antimicrobials, has been observed in leprosy after long-term dapsone therapy and in many other infectious diseases including tuberculosis ([30, 40]) and staphylococcus infection.

Faced with the apparent secondary unresponsiveness of *M. leprae* to chemotherapy after the initial doses of rifampin, the crucial question is whether or not it is worth it to continue the treatment, in other words, what is the optimal duration of chemotherapy? There is no definite answer to that question but only some suggestion that it is useful to continue treatment beyond the first doses of rifampin. For example, in a recent

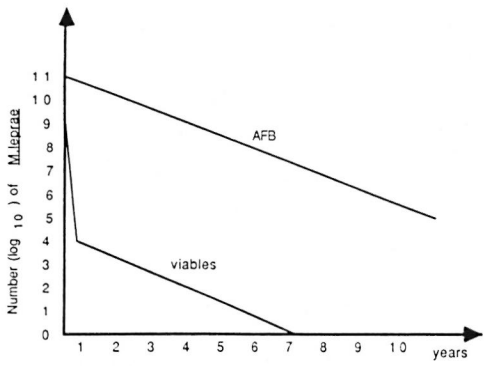

FIG. 4. Possible outcome of *M. leprae* AFB and viables in a multibacillary patient on combined chemotherapy (MDT).

study of MB patients who relapsed after very short-course MDT ([29]) it was clear that the shorter the duration of treatment with rifampin, the shorter the incubation period of relapse (Table 2).

There is, therefore, a contradiction between the apparent unresponsiveness of a tiny proportion of *M. leprae* to chemotherapy and the apparent benefit of prolonging chemotherapy. A hypothesis to reconcile these apparently opposite facts would be that the role of drug therapy, after initial doses of rifampin that have killed 99.999% of the bacillary population, is to maintain the remaining organisms in their dormant state so that the clearing mechanisms of the host can eliminate them progressively. If such a hypothesis was valid then it might be possible to determine the optimal length of treatment. In the Bamako-Chingleput study, the load of acid-fast bacilli (AFB) in the serial skin smears decreased by 0.62 $\log_{10}$ per year. Because the proportion of viable *M. leprae* among AFB remained constant (10^{-7}) for the 2 years of the study, then the clearing of the remaining viable *M. leprae* should be parallel to the clearing of AFB in the skin smears, also 0.62 $\log_{10}$ per year. The time required to clear 10^5 *M. leprae* at a speed of 0.62 $\log_{10}$ per year is about 7–8 years for a MB case of leprosy with maximal bacterial load (Fig. 4). This is more or less the time necessary for a MB patient with a bacterial index (BI) of 4 to 5+ to reach skin-smear negativity. Of course, for MB patients with a lower initial BI, the optimal length of chemotherapy would depend upon the initial load of AFB. For previously dapsone-treated patients with already negative skin smears, the optimal length of combined chemotherapy could well be still shorter.

TABLE 3. *Relation between BI upon completion of very short-course MDT and risk of subsequent relapse ([29]).*

Bacterial Index (BI)	No. patients	Relapse	
		No.	%
≥ 5+	197	42	21.3[a]
< 5+	184	25	13.6

[a] $p < 0.05$.

A recent finding of the Marchoux Chemotherapy Study Group ([29]) gives an indirect support to the hypothesis of a relation between bacterial load and optimal length of treatment. As shown in Table 3, relapses after very short-course MDT were significantly earlier and more numerous among MB patients whose BI upon completion of treatment was 5+ or more than among those with a BI <5+, suggesting that the higher the BI the longer the required length of treatment.

In the control programs it is difficult to adapt the length of treatment to the bacterial load for each patient. Operationally it is easier to standardize the duration of treatment for the two main categories of patients, those whose BI is negative and considered as paucibacillary and those whose BI is positive and considered multibacillary. According to the recommendations of the Sixth Report of the Expert Committee on Leprosy ([41]), the former should treated for months whereas the latter should be treated for at least 2 years and at best until smear negativity. To prolong treatment up to smear negativity might be especially beneficial for the most bacillary cases of leprosy because those cases have the lowest specific immunity against leprosy and have likely the least capacity to maintain the remaining *M. leprae* in a dormant state.

Present Results of Combined Chemotherapy (MDT) for Leprosy

Since the WHO recommendations ([41, 42]) multidrug therapy (MDT) has become routine practice in a majority of endemic countries. By the middle of 1993, about 4.2 mil-

lion patients have been treated with success. Clinical improvement has been rapid, side effects rare and mild, and compliance satisfactory. The mean cumulative risk of relapse has been 1% over 9 years of follow up (S. K. Noordeen, personal communication, 1993).

Among PB cases of leprosy, clinically active skin lesions were still present at the end of the 6-month course of MDT among 4% to 28% of the patients ([2, 26]). For patients and health workers, these lesions were still considered as active and requiring treatment even though they usually improved or disappeared after stopping MDT ([1]). In addition, reversal reactions may happen after stopping treatment ([2, 26]) and cause nerve damage. Because of the relatively low frequencies of these findings, it is not recommended to extend the 6-month duration of treatment for PB leprosy up to 12 months. Nevertheless, prolongation or reintroduction of MDT may be considered on an individual basis ([41]).

Among MB cases of leprosy, less than 1% of relapses have been observed within the first 5 years of follow up after completion of treatment in field programs as well as in field trials conducted by WHO, and even among newly diagnosed patients who received only 2 years of MDT. Such a finding is strong evidence of the potent bactericidal activity of the recommended regimen, and of its capacity to cope with persisters. Another finding of crucial importance is that, among MB patients who relapsed after an extremely short course of MDT containing rifampin ([29]), and in the single patient who relapsed after 2-year daily MDT in Martinique ([5]) whose *M. leprae* strains were isolated on mice and their drug susceptibility tested, all strains remained fully susceptible to the prescribed drugs. MDT is, therefore, capable of reaching its first objective, the killing of drug-resistant mutants.

Research in Chemotherapy of Leprosy

Because of the excellent activity of the WHO-recommendation regimens, the priority in the chemotherapy for leprosy is to implement MDT as rapidly and as extensively as possible in all endemic countries. It is also important to conduct operational research and health system research, aiming to improve the average of MDT implementation, and assessing its results in terms of compliance, completion and epidemiologic impact.

Meanwhile, research in chemotherapy is conducted with the following two major objectives: to shorten the duration of the present regimens and to improve their supervision. Compared to life-long dapsone monotherapy, the 2-year MDT for MB leprosy has made considerable progress but it will take a long time and will be difficult to implement in some areas ([24]), and in the areas where it is implemented the patients' compliance is often questionable ([8]). In addition, the classification of patients into PB and MB leprosy requires microscopic examination of skin smears. To have a shorter and/or fully supervised treatment applicable to both PB and MB patients would, therefore, represent great progress.

With the presently available drugs (rifampin, dapsone and clofazimine) there is not much hope to shorten the overall duration of MDT because only rifampin has very strong bactericidal activity. It is not possible to strengthen MDT activity by adding a thioamide because thioamides are poorly bactericidal drugs and have the potential for liver toxicity. On the other hand, compliance with MDT might be improved, for example, by giving only monthly supervised doses of clofazimine. The recent study by Jamet, *et al.* ([23]), demonstrating that clofazimine was as bactericidal at 1200-mg monthly doses as at 50-mg daily doses combined with a 300-mg monthly dose, is encouraging in that respect.

New drugs with bactericidal activity against *M. leprae*

Actually to shorten treatment duration and develop fully supervised intermittent regimens, new drugs with strong bactericidal activity against *M. leprae* are needed. Such drugs are presently available, namely, fluoroquinolones, minocycline and clarithromycin. All of them are lipophilic drugs, thus capable of penetrating eukaryotic cell membranes and the cell wall of mycobacteria.

Fluoroquinolones. Fluoroquinolones, nalidixic acid derivatives, inhibit bacterial DNA gyrase, an enzyme which is involved in DNA replication. They have a mecha-

TABLE 4. *Bactericidal activity of fluoroquinolones given daily against* M. leprae *as measured by three short-term trials in humans.*

Adzopé trials	Drugs	Dose size (mg)	No. patients	Bactericidal activity
N'Deli, *et al.* [32]	Pefloxacin	800	10	>99% Killing in 2 months
Grosset, *et al.* [19]	Ofloxacin	400	10	99.99% Killing by 22 doses
	Pefloxacin	800	10	
Ji, *et al.* (submitted)	Ofloxacin	400	8	>99.99% Killing by 28 doses
	Ofloxacin	800	8	
	O + DDS + CLO[a]	400	8	

[a] Ofloxacin 400 mg + dapsone 100 mg + clofazimine 50 mg daily and 300 mg monthly.

nism of action totally different from that of other antileprosy drugs. Among them, pefloxacin and ofloxacin have a powerful bactericidal activity against *M. leprae* in the mouse model ([10, 17, 20, 33, 35]). As shown in Table 4, 22 daily doses of pefloxacin 800 mg or ofloxacin 400 mg are killing 99.99% of viable *M. leprae* present in MB leprosy at the start of treatment ([19, 32]). Definite clinical improvement was observed in all patients, and the morphological index (MI) drastically decreased to the baseline during treatment. Increasing the daily dose of ofloxacin up to 800 mg did not increase the bactericidal activity, and the combination with dapsone and clofazimine did not enhance or reduce its activity (Ji, *et al.*, submitted).

It is important to emphasize that, except for rifampin, no other drug so far tested in humans has demonstrated such a degree of bactericidal activity. Since daily ofloxacin for 4 weeks is capable of killing 99.99% or 4 $\log_{10}$ *M. leprae,* i.e., as many organisms as the maximal number of rifampin-resistant mutants in a MB patient, then it is possible that the daily combination of ofloxacin and rifampin may permit us to shorten considerably the duration of MDT. A multicenter field trial is being organized under the auspices of WHO to test this hypothesis.

Minocycline. Among the tetracyclines, minocycline is unique in being active against *M. leprae* ([11, 12]). It acts in inhibiting protein synthesis by a mechanism different from that of other antileprosy drugs. In mice, its bactericidal activity is similar to that of ofloxacin ([11, 25]). In humans given a daily dose of 100 mg minocycline ([13] and Ji, *et al.*, submitted), definite clinical improvement was seen in some patients as early as 14 days after beginning treatment, in all patients by 1 month, and marked improvement in all patients by 2 months. As also observed with fluoroquinolone treatment, the change in the MI was spectacular. Table 5 summarizes the results of mouse subinoculations from serial skin samples, showing that clearance of viable *M. leprae* was rapid. More than 99% and 99.9% of the viable *M. leprae* had been killed by 28 and 56 days of treatment, re-

TABLE 5. *Bactericidal activity of daily 100 mg minocycline in MB leprosy patients.*

Study	No. patients	No. cases showing multiplication of *M. leprae* after inoculation into mouse				
		Before treatment	1 wk.	1 mo.	2 mos.	3 mos.
Gelber, *et al.* [13]	8	8/8	7/8	5/8	2/8	0/8
Ji, *et al.* (submitted)	11	11/11	ND[a]	1/11	0/11	ND

[a] ND = Not done.

TABLE 6. *Comparative bactericidal activities of a single dose of rifampin, the combinations minocycline, clarithromycin and/or minocycline against* M. leprae *in the mouse* ([28]).

Drug[a]	Killing activity
RMP	99.5%
Mino + clari	96%
Oflo + mino + clari	98.4%
RMP + oflo + mino + clari	99.5%

[a] RMP = Rifampin 10 mg/kg; mino = minocycline 25 mg/kg; clari = clarithromycin 100 mg/kg; oflo = ofloxacin 150 mg/kg.

spectively, a result similar to that obtained with ofloxacin.

Clarithromycin. A derivative of erythromycin, clarithromycin is a new macrolide that inhibits protein synthesis by a mechanism different from that of minocycline. In mice, its bactericidal activity is of the same order as that of ofloxacin and minocycline ([9, 25]). In MB leprosy patients treated daily with 500 mg clarithromycin, the clinical response, the MI decrease and the killing of viable *M. leprae* are also of the same order as that of ofloxacin and minocycline (Ji, *et al.*, submitted). Although some synergism between minocycline and clarithromycin was demonstrated in the mouse model, the combination of 100 mg minocycline and 500 mg clarithromycin was not more active in man than each component alone, perhaps because the potency of each individual drug was too strong.

Research for new drug regimens

New drug regimens for leprosy have potential interest only if they are better than the WHO-recommended regimens in terms of antimicrobial activity, acceptability and safety, overall cost-effectiveness, length of treatment, compliance and/or if they may replace them in case of proven resistance to rifampin.

It is clear that the three new drugs ofloxacin, minocycline and clarithromycin are individually and in combination much more active than dapsone and clofazimine. They are, therefore, natural candidates to replace dapsone and clofazimine for improving leprosy chemotherapy. Among numerous possible improvements, the following might be considered.

Improved supervision of present MDT regimens. A disadvantage of the presently recommended MDT regimens in that only the monthly doses of 600 mg rifampin and 300 mg clofazimine are supervised. If a patient is not at all compliant in the intake of daily unsupervised doses of dapsone and clofazimine, then his treatment actually might be in practice monotherapy by rifampin, with the risk of developing secondary resistance to rifampin. A possibility, already discussed, is to administer clofazimine monthly at a dose of 1200 mg. But the tolerance of such a high dose of clofazimine is questionable in the long term. Another, more tempting, possibility is to administer monthly doses of a combination of the new drugs ofloxacin, minocycline and clarithromycin. A single dose of ofloxacin alone did not demonstrate sufficient bactericidal activity ([19]) to be recommended. On the other hand, as shown in Table 6, a single dose of either the double-drug combination (minocycline and clarithromycin) or triple-drug combination (ofloxacin, minocycline and clarithromycin) displays a bactericidal activity close to that of a single dose rifampin in the mouse. In addition, a single dose of the combination of all four drugs is not antagonistic, suggesting that daily dapsone and clofazimine might well be replaced by monthly doses of ofloxacin, minocycline and clarithromycin. The activity of monthly doses of the new drugs given in combination with and without rifampin is presently being tested in the field.

Short-course chemotherapy for leprosy. As already discussed, the daily regimen of 600 mg rifampin and 400 mg ofloxacin for 1 month might be as active as the 2-year drug regimen recommended by WHO. With the former, the patient would receive 28 doses of rifampin and ofloxacin; with the latter the patient would receive 24 doses of rifampin and more than 730 doses of dapsone and clofazimine. Since daily ofloxacin for 1 month is considered as capable as 2 years of dapsone plus clofazimine to kill the rifampin-resistant mutants present at the start of treatment, the patient treated for 1 month with daily rifampin and ofloxacin may well be overtreated compared to the

patient treated with the WHO-recommended MDT. To remain still more on the safe side while keeping the advantage of short-course chemotherapy, an increase of the bactericidal activity of the drug combined with rifampin has to be considered. Such an increase cannot be obtained by increasing the 400 mg daily dose of ofloxacin to 800 mg, because 800 mg ofloxacin did not demonstrate a better bactericidal activity than 400 mg (Ji, *et al.*, submitted) but might be less well tolerated. On the other hand, it is possible to combine minocycline and clarithromycin with ofloxacin. In spite of the limited sensitivity of the mouse model in measuring strong bactericidal activity, there are some indications that the combination clarithromycin + minocycline (Ji, *et al.*, submitted) and the combination ofloxacin + clarithromycin + minocycline ([25]) are more powerful than ofloxacin alone ([19]). These remain to be demonstrated in the field and evaluated in terms of antimicrobial activity, acceptability and tolerance by the patients, and cost effectiveness.

Long-course, fully supervised, intermittent regimens. To successfully treat patients living in remote areas and/or regions where monthly supervised treatment or intensive short-course chemotherapy are difficult to implement, it would be useful to develop new regimens based on rifampin and the newer drugs given with long intermittencies between each pulse of the drugs. In that respect, two findings should be taken into consideration. First, a single pulse of ofloxacin, minocycline plus clarithromycin is as bactericidal as a single pulse of rifampin, thus is capable to kill rifampin-resistant mutants as rapidly as rifampin kills the susceptible organisms. Second, a single pulse of rifampin is capable of rendering for months *M. leprae* harvested from skin biopsies not cultivable in the mouse. The post-antibiotic effect of rifampin, that is due to the persisting damages induced by the drug, is particularly important in the case of *M. leprae*. Taking advantage of both findings, why not design rifampin-containing regimens including two or three of the newer drugs that would be given under supervision once a month, every 2 months, every 3 months and perhaps every 6 months or even once a year? Of course a number of questions should be answered before introducing such regimens in the field. To the question of the length of drug administration, the answer might be until the skin smear becomes negative. Arguments supporting that answer have been given previously. The question of the prerequisites before testing the regimens in the field might be answered when it has been demonstrated that there is no regrowth of *M. leprae* within the 3, 6, or even 12 months between each pulse of the drug combinations. Experimental studies presently conducted in nude mice will provide the answer.

Chemotherapy for rifampin-resistant leprosy. From a still limited number of patients ([18, 22]), rifampin-resistant *M. leprae* have been isolated. Because of their epidemiologic importance, these patients should benefit in priority of the newly developed drugs. After having demonstrated the rifampin-resistance of the organisms, an effective drug regimen ([21]) for rifampin-resistant leprosy might be as follows. During the first 2 or 3 months, treatment would be daily 400 mg ofloxacin, 500 mg clarithromycin, 100 mg minocycline and 100 mg clofazimine. During the following 6 months treatment would be daily 500 mg clarithromycin, 100 mg minocycline and 50 mg clofazimine and then, up to smear negativity, either 100 mg minocycline and 50 mg clofazimine or 50 mg clofazimine alone, or 100 mg minocycline alone.

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