500 mg 3 times daily was commenced, and 3 days later, 2 weeks after being admitted, her condition rapidly deteriorated, she began to cough blood and her blood pressure fell to 60/40 mmHg. Intravenous fluids were started and cloxacillin, gentamicin and chloramphenicol given. A repeat chest radiograph showed right upper lobe consolidation. Her white blood cell count was only 700/mm, with no neutrophils visible. Unfortunately she did not respond to treatment and died a few hours later.

Although there have been several reports of agranulocytosis due to dapsone, nearly all of these have been in patients taking dapsone for a reason other than leprosy. The first case of agranulocytosis secondary to dapsone occurred in a patient being treated for dermatitis herpetiformis. A total of 16 US soldiers serving in Vietnam developed agranulocytosis while taking 25 mg dapsone daily as malaria prophylaxis, of whom 8 died. Agranulocytosis has also been reported with weekly Maloprim (100 mg dapsone, 12.5 mg pyrimethamine) prophylaxis.

Serious reactions, numbering 103, with 11 deaths, were reported to the national registers of Sweden and the UK during 1965–1988, and 7 deaths were attributed to agranulocytosis. The incidence of serious reactions appeared to increase with higher doses.

In the last 4 years in Vanuatu we have been seeing a high incidence of the dapsone syndrome during leprosy treatment with nearly a quarter of patients reacting to dapsone (P Reeve et al. unpublished data). This usually rare syndrome has been reported in 2 brothers in Papua New Guinea and in an Aboriginal mother and son in Australia (J. C. Hargrave, personal communication). It is interesting that the only other case of agranulocytosis complicating leprosy treatment was reported in a Melanesian, and it is possible that there could be an increased susceptibility to dapsone reactions in Melanesians.

Because of the high incidence of reactions to dapsone all new leprosy patients in Vanuatu are being admitted to hospital for the first 2 months of treatment for close supervision.

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References

COMMENT: RECENT ADVANCES IN THE ANTIMICROBIAL CHEMOTHERAPY OF LEPROSY

Sir,

Ji & Grosset must be congratulated for an illuminating editorial. It was comforting to know that there are many anti-Mycobacterium leprae drugs already available for testing, but a few other aspects of their account raised some questions for me.
Oftoxacin trials

The authors suggest that not much more than a month of multidrug therapy (MDT), including daily ofloxacin and rifampicin, should be sufficient for lepromatous patients. This seems to be more optimistic than the evidence permits. Viable *M. leprae* in patients treated with ofloxacin at 400 mg/day are unlikely to decline at an exponential rate greater than 0.56 per day or less than 0.11 per day, according to standard calculations. Therefore, most optimistically, lepromatous patients with $5 \times 10^{11}$ viable *M. leprae* are predicted to need at least 6 weeks of daily ofloxacin and rifampicin, for viable *M. leprae* to be eliminated. A shorter duration seems unduly adventurous, although it may suffice in patients with a smaller initial number of *M. leprae*. More cautious investigators may wish to assume the most pessimistic rate of bacterial decline, by which the corresponding safe duration of daily ofloxacin with rifampicin is up to 8 months. These calculations disregard re-infection and persisters, both of which can be dealt with by subsequent treatment.

The authors suggest that trials of new regimens should include patients treated up to 1 year with dapsone monotherapy. This is a mistake which would seriously weaken any inferences drawn from the trials. Viable *M. leprae* decline at a rate of no less than 0.032 per day in the presence of >750 ng/ml dapsone, according to evidence from mouse tests. Even 6 months of dapsone monotherapy is therefore predicted to give a 3000-fold reduction in the number of viable *M. leprae*, and a whole year of dapsone a 10 million-fold reduction.

The inclusion of dapsone-treated patients in trials of new regimens is expected to exempt the regimens from serious testing. This mistake has already been made once in the THELEP trials of WHO-MDT (which mainly included smear-negative patients who had previously received several years of dapsone monotherapy). It would be a pity to repeat that mistake.

Shorter MDT with rifampicin, clofazimine and dapsone

The authors claim that MDT with rifampicin, clofazimine and dapsone should not be shortened below 2 years. This is unduly pessimistic. The measured rates of decline in viable *M. leprae* during treatment with each of these drugs suggest that, even most pessimistically, as little as 14 months of clofazimine and dapsone with rifampicin included for an initial 100 daily doses should be sufficient to eliminate viable non-persister *M. leprae* in lepromatous patients. The most optimistic assumptions suggest that as little as 3 months of daily rifampicin and clofazimine or even 5 months of regular daily clofazimine and dapsone following a single initial rifampicin dose could prove sufficient against viable *M. leprae* in lepromatous patients.

MDT with rifampicin, clofazimine and dapsone is itself fairly expensive. Trials to shorten such MDT seem to deserve a higher priority than the authors seem to concede. Enthusiasm for more expensive drugs should not stand in the way of trials to establish the minimum required duration of MDT with rifampicin, clofazimine and dapsone.

Dapsone monotherapy of limited duration

So far a glaring deficiency in nearly all trials of MDT has been the omission of a control group on dapsone monotherapy of limited duration. Quantitative analysis suggests that 3 years of regular full-dose dapsone monotherapy could prove more than sufficient for the elimination of non-persister viable bacteria in lepromatous patients. This prediction may only rarely have been tested but remains to be refuted. Dapsone monotherapy using monthly injections also provides the only opportunity at present for fully supervised intermittent anti-microbial chemotherapy in leprosy.

The objections to dapsone monotherapy in leprosy do not bear scientific scrutiny. It is believed that campaigns of dapsone monotherapy were losing efficacy by the late 1970s, where the evidence
shows that their efficacy was undiminished or even increasing.\textsuperscript{12}-\textsuperscript{14} It is believed that 'primary dapsone resistance' was unknown before 1977,\textsuperscript{15} whereas mouse tests in the early 1960s\textsuperscript{16} demonstrated that the equilibrium frequency of 'full-dose' dapsone-resistant mutants lies between $1$ in 100 and $1$ in 10,000.\textsuperscript{4}

Wherever mouse tests are done, dapsone-resistant \textit{M. leprae} are found, as expected. Nevertheless, wherever dapsone is taken regularly and in adequate dosage by patients, it succeeds, except in a handful of 'slow-responding' lepromatous patients who do poorly on any regimen including MDT. Dapsone-resistant \textit{M. leprae} probably decline in patients on dapsone monotherapy because dapsone reduces the relative fitness of the resistant mutants\textsuperscript{4} and because leprosy patients (unlike mice with small bacterial inocula) show significant rates of bacterial clearance.

Dapsone monotherapy is observed to be adequate for about 99\% of all patients starting treatment in India (where nearly half of the registered leprosy patients in the world live), since the cumulative probability that dapsone will fail within 20 years of starting monotherapy is observed to be under 10\% for L patients\textsuperscript{17,18,4} and under 1\% for all leprosy patients in India. In 1991, millions of patients in India and elsewhere remain on dapsone monotherapy without the predicted catastrophe of widespread failure of dapsone monotherapy. The measured incidence of dapsone-resistant failure of treatment among L patients\textsuperscript{19} is so low (0.76\%/year ± 0.104, 95\% c.i.\textsuperscript{17,4}) that dapsone-resistance will probably continue to present an infrequent threat to dapsone monotherapy in the foreseeable future.

The objections to monthly injections of dapsone seem unduly pessimistic. Injections are so frequently and widely demanded (and conceded) in India that it is doubtful whether the risk of infection with HIV can be lowered significantly by the avoidance of monthly dapsone injections (which need not be administered by untrained staff).

Up to 30 million US dollars per year would be freed in India alone if 3-year dapsone monotherapy were used instead of WHO-MDT.\textsuperscript{4} In fact, 3-year fully supervised dapsone monotherapy is so suited to Indian needs that its omission from trials seems not only unscientific but also economically unwise. The cost and sustainability of regimens of antimicrobial chemotherapy deserve more attention than they have received: the enthusiasm and prosperity of donors cannot be relied upon.

\textbf{Does antimicrobial chemotherapy reduce the spread of \textit{M. leprae}?}

Reduced transmission of \textit{M. leprae} has so far seemed to depend more on secular factors than on antimicrobial chemotherapy. Since infective patients are generally diagnosed well after they have become infectious\textsuperscript{20-21} (possibly because lepromatous leprosy can have inconspicuous signs) and since \textit{M. leprae} can survive indefinitely outside human hosts (reviewed\textsuperscript{22}) antimicrobial chemotherapy is expected to generally have only a trivial impact on the secular decline of leprosy. This prediction has yet to be refuted by any report with an adequate description of methods, and 3-year dapsone monotherapy would give the same cosmetic reduction in number of patients on antimicrobial chemotherapy as does WHO-MDT, but at far lower cost and with far less risk of selecting \textit{M. leprae} resistant to rifampicin and to multiple drugs.

\textbf{Are some disabilities attributable to antimicrobial chemotherapy?}

The authors overlook important new evidence on the positive association between the risk of disability and the regularity of antimicrobial chemotherapy.\textsuperscript{23} It has long been suggested\textsuperscript{24} that tuberculoid patients can be classified on the basis of simple prognostic criteria (e.g. single well-defined patch, positive lepromin reaction, no nerve involvement). Self-healing is known to occur in up to 75\% of persons developing tuberculoid signs of infection with \textit{M. leprae}.\textsuperscript{25-30} Could the risk of disability in patients with 'low-risk' tuberculoid signs be increased by the inclusion of antimicrobial
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chemotherapy in their treatment? A double-blind trial (such as that already suggested) could answer this important question.

Research priorities in antimicrobial chemotherapy

The priorities for research in the antimicrobial chemotherapy of leprosy seem to go beyond the testing of newly available drugs. In particular, the authors may wish to consider the need for:

a careful predictions of cost for various strategies of antimicrobial chemotherapy;

b trials to test the predicted minimum duration for MDT (with clofazimine and dapsone, including daily rifampicin for an initial period);

c quantitative theoretical models to suggest appropriate durations and subjects for trials of new regimens;

d a controlled double-blind trial to refute the suggestion that antimicrobial chemotherapy increases the risk of disability among persons with signs of low-risk tuberculoid infection;

(and, perhaps most importantly for countries such as India):

e the inclusion of a control group on 3-year fully supervised dapsone monotherapy in trials of more expensive regimens.

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**REPLY: B JI and J-H GROSSET**

Sir,

The following is in response to the above letter from Dr Almeida regarding our editorial entitled ‘Recent advances in the chemotherapy of leprosy’.\(^1\)

The backbone of the current multidrug therapy (MDT) regimens is rifampicin (RMP) because of its great potency; the major objective to combine it with other drugs is to prevent the selection of RMP-resistant mutants during RMP-monotherapy, due to the huge bacterial population in untreated multibacillary (MB) leprosy patients.\(^1\) Both pefloxacin and ofloxacin displayed very powerful bactericidal activities in lepromatous patients: 99-99\%, or 4 ‘logs’, of organisms viable on DO were killed by 22 doses of either pefloxacin 800 mg or ofloxacin 400 mg; and the average size of RMP-resistant *Mycobacterium leprae* in an untreated lepromatous patient is no more than \(10^4\), or 4 ‘logs’. By definition, RMP-resistant mutants should be killed by fluoroquinolones at the same speed as RMP-susceptible organisms, thus, all the RMP-resistant mutants may be eliminated after 22 doses of either pefloxacin or ofloxacin. It is, therefore, possible that the combination of RMP and ofloxacin may considerably shorten the duration of MDT.

However, we have never claimed that 1 month of ofloxacin will be able to eliminate \(5 \times 10^{11}\) viable (non-persister) *M. leprae* as described by Dr Almeida. Because of the limitations of the tools, we know that at best, we are only able to measure the initial 5 or 6 logs of the killing even using nude mice for monitoring the bactericidal activity.\(^2\)

Dr Almeida has calculated the declining rates of viable organisms during treatments with various drugs. It is difficult to verify the validity of these calculations simply because of the lack of a sensitive tool. Nevertheless, it is unlikely that the declining rate of viable organisms remains the