COMMENT: RECENT ADVANCES IN THE ANTIMICROBIAL CHEMOTHERAPY OF LEPROSY

Sir,

Ji & Grosset must be congratulated for an illuminating editorial.[1] 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.

Ofloxacin 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[2] 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.[3] Therefore, most optimistically, lepromatous patients with 5×10^{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[4] in the presence of >750 ng/ml dapsone, according to evidence from mouse tests.[5-7] 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.[8]

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.[1] 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.[4]

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.[4] This prediction may only rarely have been tested[9,10] but remains to be refuted. Dapsone monotherapy using monthly injections[11] 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.[12–14] It is believed that 'primary dapsone resistance' was unknown before 1977,[15] whereas mouse tests in the early 1960s[16] demonstrated that the equilibrium frequency of 'full-dose' dapsone-resistant mutants lies between 1 in 100 and 1 in 10,000.[4]

Wherever mouse tests are done, dapsone-resistant *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 *M. leprae* probably decline in patients on dapsone monotherapy because dapsone reduces the relative fitness of the resistant mutants[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[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[19] is so low (0·76%/year $\pm$ 0·104, 95% c.i.[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.[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.

Does antimicrobial chemotherapy reduce the spread of *M. leprae*?

Reduced transmission of *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[20–21] (possibly because lepromatous leprosy can have inconspicuous signs) and since *M. leprae* can survive indefinitely outside human hosts (reviewed[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 *M. leprae* resistant to rifampicin and to multiple drugs.

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.[23] It has long been suggested[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 *M. leprae*.[25–30] Could the risk of disability in patients with 'low-risk' tuberculoid signs be increased by the inclusion of antimicrobial

chemotherapy in their treatment? A double-blind trial (such as that already suggested[4]) 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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References

[1] Ji B, Grosset JH. Recent advances in the chemotherapy of leprosy. *Lepr Rev*, 1990; **61:** 313–29.
[2] Grosset JH, Ji B, Guelpa-Lauras CC, Perani EG, N'Deli LN. Clinical trial of pefloxacin and ofloxacin in the treatment of lepromatous leprosy. *Int J Lepr*, 1990; **58:** 281–95.
[3] Finney DJ. Assays based on quantal responses. In: *Statistical method in biological assay*, Charles Griffin and Company Ltd, London. 3rd edn, 1978: pp. 394–401.
[4] Almeida JG. *Leprosy: short-term treatment. A quantitative scientific basis for anti-microbial chemotherapy in control programmes.* Plateau, UK, 1990: pp. 106.
[5] Colston MJ, Hilson GRF, Banerjee DK. The 'proportional bactericidal test': a method for assessing bactericidal activity of drugs against *M. leprae* in mice. *Lepr Rev*, 1978; **49:** 7–15.
[6] Colston MJ, Hilson GRF,L Lancaster RD. Intermittent chemotherapy of experimental leprosy in mice. *Am J Trop Med Hyg*, 1980; **29:** 103–8.
[7] Ji B, Chen J, Lu X and others. Antimycobacterial activities of two newer ansamycins, R-76-1 and DL 473. *Int J Lepr*, 1986; **54:** 563–77.
[8] Grosset JH, Ji B. Controlled clinical trial for evaluation of antimicrobial drug activity against *M. leprae*. *Int J Lepr*, 1989; **57:** 529–31.
[9] Lowe J. The chemotherapy of leprosy. Late results of treatment with sulphone and with thiosemicarbazones. *Lancet*, 1954; 1065.
[10] Dietrich M, Rangaraj J, Ganapati R *et al.* Combination therapy vs. monotherapy in BL and LL patients: a prospective randomized multicentre study. In: Abstracts of the XIII International Leprosy Congress, The Hague, 1988. *Quaderni di cooperazione sanitaria*, 1988; **9:** 629 (PO656).
[11] Pieters FA, Woonink F, Zuidema J. A field trial among leprosy patients in Nigeria with depot injections of dapsone and monoacetyldapsone. *Int J Lepr*, 1988; **56:** 10–20.
[12] Almeida JG, Christian M, Chacko CJG. Response to dapsone monotherapy in leprosy patients of Gudiyatham Taluk, south India: comparison between the 1960s and the 1970s. *Int J Lepr*, 1983; **51:** 378–81.
[13] Casabianca MN, Thomas A. Response to DDS monotherapy in bacteriologically positive cases registered between the 1960s and 1970s in leprosy control unit of the Philadelphia Hospital, Salur. *Indian J Lepr*, 1984; **56 (suppl):** 460–1.
[14] Reddy BN, Neelan PN. Role of dapsone in chemotherapy of leprosy: a comparison of responses to therapy in 2 cohorts in the 1960s and 1970s. *Ind J Lepr*, 1984; **56:** 912–8.
[15] Shepard CC, Rees RJW, Levy L, Pattyn SR, Baohong J, dela Cruz EC. Susceptibility of strains of *M. leprae*

isolated prior to 1977 from patients with previously untreated lepromatous leprosy. *Int J Lepr*, 1986; **54:** 11–15.

[16] Rees RJW. Recent bacteriologic, immunologic and pathologic studies on experimental human leprosy in the mouse foot pad. *Int J Lepr*, 1965; **33:** 646–57.

[17] Almeida JG, Chacko CJG, Christian M, Taylor PM, Fritschi EP. DDS-resistant infection among leprosy patients in the population of Gudiyatham Taluk, south India. Part 3. Prevalence, incidence, risk factors and interpretation of mouse foot-pad test results. *Int J Lepr*, 1983; **51:** 366–73.

[18] Almeida JG, Christian M, Chacko CJG. Results of long-term domiciliary dapsone (DDS) monotherapy for lepromatous leprosy in Gudiyatham Taluk, south India. *Int J Lepr*, 1983; **51:** 385–6.

[19] Madrid classification. Report on the Madrid Congress technical resolutions. *Int J Lepr*, 1953; **21:** 504–16.

[20] Leprosy Division, DGHS. Leprosy status report, 1985–6. National leprosy eradication programme in India. Ministry of Health and Family Welfare, New Delhi, 1986: pp. 36–9.

[21] Rodriguez JN. Evaluation of the leprosy control programme of the Philippines. II. Application and manner of analysis. *Int J Lepr*, 1962; **30:** 418–41.

[22] Blake LA, West BC, Lary CH, Todd JR, 4th. Environmental nonhuman sources of leprosy. *Rev Inf Dis*, 1987; **9:** 562–87.

[23] Radhakrishna S, Nair NGK. Association between regularity in dapsone (DDS) treatment and development of deformity. *Int J Lepr*, 1987; **55:** 425–34.

[24] Arnold HL. The Madrid classification. *Int J Lepr*, 1954; **22:** 473 (correspondence).

[25] Lara CB, Nolasco JO. Self-healing, or abortive and residual forms of childhood leprosy and their probable significance. *Int J Lepr*, 1956; **24:** 245–63.

[26] Gomez L, Avellana Basa J, Nicolas C. Early lesions and the development and incidence of leprosy in the children of lepers. *Philippine J Sci*, 1922; **22:** 233–55.

[27] Souza Campos N. Aspects cliniques de la lepre tuberculoide chez l'enfant. *Rev Brasileira Leprol*, 1937; *5 (special no.):* 99–113.

[28] Davey TF. A repeated leprosy survey in southeastern Nigeria. The progress of untreated cases of leprosy. *Int J Lepr*, 1941; **9:** 77–86.

[29] Fernandez JMM. *La infeccion leprosa en el nino*. Editorial Rosario, SA: Rosario, Argentina. 1947: pp. 187.

[30] Guinto RS, Doull JA, Bancroft H, Rodriguez JN. A field study of leprosy in Cordova, Philippines. Resurvey in 1941 after eight years. *Int J Lepr*, 1951; **19:** 117–36.