Response to Dr. Grosset, *et al.*

TO THE EDITOR:

We thank the correspondents for their interest in our papers, and are happy to note that they do not dispute those of our findings of most practical importance. Our population-based study in an established leprosy control program directly observed dapsone resistance in a leprosy-endemic area. Previous estimates had relied on clinic- or hospital-based studies.

One thousand out of 1224 lepromatous and borderline lepromatous patients on dapsone monotherapy in the 1320 km^2 area of Gudiyatham Taluk, India, were found to have been smear negative for three years or more. Smear negativity was found to indicate a markedly reduced risk of dapsone (DDS)-resistant infection. Seventy-six patients, a very small group, remained continuously smear positive despite treatment, and only this group had a high prevalence of DDS-resistant infection.

This small "high-risk" group that emerges during dapsone monotherapy deserves the fullest possible concentration of efforts and resources. Theoretical predictions that dapsone-resistant infections would threaten every "multibacillary" patient are not supported by evidence from leprosy control programs in endemic areas. On the contrary, data showing the continuing efficacy of dapsone monotherapy, after two decades, were presented by independent investigators from Polambakkam, Chingleput, and Salur (all in South India) at the biennial conference of the Indian Association of Leprologists in November 1983.

The correspondents seem to feel that mouse test drug resistance is equivalent to clinical drug resistance in patients. In our view this is not supported by the evidence which, in fact, comes from several sources. Pearson, *et al.* [4] found patients who responded for over 53 months (4½ years) to DDS monotherapy, after the mouse foot pad test had grown high-grade DDS-resistant *Mycobacterium leprae.* Jacobson [3] observed that patients diagnosed by the mouse foot pad test to harbor primary dapsone-resistant *M. leprae,* and treated initially with DDS monotherapy, showed a response that was "completely normal as measured by all the usual criteria." Warndorff-van Diepen [6] showed that after even "high-grade" dapsone-resistant *M. leprae* grew in mice, patients yielding such organisms attained smear negativity and clinical inactivity despite continuing on dapsone monotherapy.

It seems to us that the mouse foot pad test for drug resistance has suffered from the omission of a control group of patients. While patients deteriorating on DDS monotherapy invariably yielded dapsone-resistant *M. leprae* in mice, it was assumed that patients responding favorably to DDS monotherapy would not do so. No "control" group of responding patients was ever tested. Such a control group has now become available from our study, and 5 out of 6 responding patients yielded *M. leprae* resistant to high-dosage dapsone (0.01% w/w) in the mouse diet.

The mouse foot pad test for drug resistance, as described by Pettit and Rees [5], seems exquisitely sensitive to the presence of a few drug-resistant *M. leprae* in predominantly drug-sensitive strains. We have subsequently demonstrated that strains of *M.*

leprae with only 1 in 1000 bacilli drug resistant can grow drug-resistant *M. leprae* in the mouse foot pad test ([1]). It is likely that the more carefully and expertly the mouse test is performed, the more exquisitely sensitive will it prove to minute proportions of drug-resistant *M. leprae*. In order that a distinction be made between predominantly drug-resistant and predominantly drug-sensitive strains, the "drug-resistant proportion" test ([2]) has now been described. The technique previously described by Pettit and Rees ([5]) required that harvests be done "at intervals of six to ten months from the day of inoculation." The reliability of that technique is likely to be enhanced by the "drug-resistant proportion" test ([2]), where harvests are performed before the plateau of bacillary growth is reached in untreated mice.

Theoretical predictions are often contradicted by practical experience. However, the evidence in this case comes over a long period, and from several independent sources. We feel that a more realistic view of dapsone resistance in leprosy is required.

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