

## Response to Drs. Neelan and Reddy

TO THE EDITOR:

We welcome this letter with its painstaking critical approach. All the points raised can be answered.

We stated fully in our paper why the “exclusion” of some patients probably did not alter the findings. We repeat the most important points.

Of the patients enumerated 77.5% were fully studied. Of the remainder, 149 who had earlier escaped screening were not ignored but were pursued in 1981; 122 were screened, and the prevalence of DDS-resistant infection among them was no higher than among the fully studied patients. The 198 "absentees" were excluded from both the numerator and denominator of the estimates because methods had not yet been developed to distinguish between relapses due to a simple lack of treatment and those due to drug resistance. The "drug-resistant proportion test" using the mouse foot pad has been described only recently <sup>(1)</sup>, and will avoid the former problems of interpreting "mouse footpad drug resistance" <sup>(2)</sup>. Moreover, we found no association between regularity of treatment and incidence of drug resistance. The wisdom of our approach has subsequently been confirmed by the findings of Warndorff-van Diepen, *et al.* <sup>(4)</sup>, who showed that reliance on mouse foot pad test results leads to inflated estimates of drug resistance. The third group of patients said to have been excluded, those with a treatment regularity of less than 80%, were in fact included among the 1224 patients fully studied.

Treatment regularity in the initial period is claimed to be crucial to drug resistance. No reference or evidence is offered for this hypothesis. Until this claim is substantiated, treatment regularity following the "initial period" must be considered equally crucial.

Regarding the prevalence, contrary to the allegation we stated clearly the period concerned was 31 December 1977 to 28 February 1981. The use of person-years to work out rates in Tables 2 and 3 was considered by us to be quite necessary, to allow for standardization by duration of treatment. The difficulty said to be experienced by them in applying statistical tests for comparison was not shared by us. Many parametric as well as nonparametric techniques are appropriate to the data presented.

We are in total disagreement with their suggestion regarding Table 3, that cases with differing regularity of treatment should be pooled together in analyzing for association between initial dosage of DDS- and drug-resistant infection. The alternative preferred by us was to standardize first for reg-

ularity of treatment and, within a regularity "slab," to compare various initial dosages. This ensured that any differences found were not due to differing regularity of treatment. We would also want to consider tests for the statistical significance of differences before making declarations like the one suggested by the correspondents, about initial dosage of DDS and DDS resistance.

In our discussion, the inference that "attainment of smear negativity in a patient appears to be a favorable prognostic sign indicating a significantly reduced risk of DDS-resistant infection" seems inescapable. The prevalence of DDS-resistant infection among the group of 76 patients who never attained smear negativity was 12.4 times that among the group of 1148 who did attain smear negativity. Only if the group that remained smear positive had been treated on the average 12.4 times longer than the smear negative group, would the risk of DDS-resistant infection be equal in the two groups. On the contrary, we found that the 76 patients had a shorter average duration of treatment than the rest. Since our point was already made beyond reasonable doubt by the figures for prevalence, this supporting finding was judged superfluous.

We have investigated, with some success, the problem of obtaining quantitative rather than merely qualitative results from the mouse foot pad test for drug-resistant *Mycobacterium leprae*. We have demonstrated that the mouse test can classify strains with only 1 in 1000 drug-resistant *M. leprae* as drug resistant. Further, we have described the "drug-resistant proportion test" to quantify the proportion of *M. leprae* in a sample that are resistant to a drug. The correspondents' speculation on "multiplication factor" in positive harvests is not likely to be useful; no accurate estimate of the number of viable *M. leprae* inoculated can be made at the time of inoculation, and the final plateau of growth is not known to be different for drug-resistant *M. leprae* or drug-sensitive *M. leprae*.

The third part of their response to our discussion has been rendered an academic exercise by the paper of Warndorff-van Diepen, *et al.* <sup>(4)</sup>. That study demonstrated that 7 out of a sample of 18 patients who yielded DDS-resistant *M. leprae* in mouse foot pad tests subsequently responded to DDS

monotherapy for the entire duration of observation—5 to 9 years. When one considers that a single high-grade DDS-resistant *M. leprae* bacillus dividing once in 12 days should yield  $10^{12}$  *M. leprae* in only 1½ years, the observed response to DDS monotherapy seems spectacular. Previous assumptions that mouse test drug resistance was, in the long run, equivalent to clinical drug resistance in patients seem contrary to accumulating evidence.

Our criteria for growth in mouse experiments require a sixfold or greater increase in the number of *M. leprae* remaining in the foot pad 24 hr after inoculation (<sup>3</sup>). In fact, we observed a 12-fold or greater increase in every experiment. This is unlikely to be due to chance.

We are glad to know that the correspondents will publish findings similar to ours on the response to DDS monotherapy compared between the 1960s and 1970s. They agree that the efficacy of DDS monotherapy has not diminished over the years. We are content with the corroboration afforded by their observations. Our own inferences have been fully spelled out in the paper, and will be judged by the readers. We obviously do not oppose the use of DDS suggested by the correspondents.

The interesting claim that "mortality is higher among lepromatous cases who do not

respond to treatment and worsen clinically," is not supported by any evidence in the letter or by a reference.

We hope that previous papers by other workers on DDS resistance will receive a similar critical evaluation by the correspondents.

—J. G. Almeida, M.B., B.S.

—C. J. G. Chacko, M.D., Ph.D.

*Schieffelin Leprosy Research  
and Training Center  
Karigiri 632106, South India*

## REFERENCES

1. ALMEIDA, J. G., JOSEPH, P. S., SARANGAPANI, G. and CHACKO, C. J. G. "Drug-resistant proportion test" for *M. leprae* to quantify the proportion of drug-resistant *M. leprae* in a sample using the mouse foot pad. *Int. J. Lepr.* **52** (1984) 468–470.
2. ALMEIDA, J. G., JOSEPH, P. S., SARANGAPANI, G. and CHACKO, C. J. G. The mouse foot-pad test—sensitive to small proportions of drug-resistant bacilli in a sample of *M. leprae*. *Indian J. Lepr.* **56** (1984) 10–14.
3. EVANS, M. J., NEWTON, H. E. and LEVY, L. Early response of the mouse footpad to *Mycobacterium leprae*. *Infect. Immun.* **7** (1973) 76–85.
4. WARNDORFF-VAN DIEPEN, T., AREDATH, S. P. and MENGISTU, G. Dapsone-resistant leprosy in Addis Ababa: A progress report. *Lepr. Rev.* **55** (1984) 149–157.