

paragraph 5 of Dr. Chatterjee's comments. However, we do not accept his opinion that "a field study can substitute for a hospital-based trial." In our view, both clinical (or hospital-based) trials and field trials are interlinked but are not interchangeable. In developing new combined regimens, one must begin somewhere; determining the comparative effectiveness of various drug regimens through controlled clinical trials seems to be the most rational and feasible starting point.

With respect to paragraphs 6 and 7 of Dr. Chatterjee's comments, we emphasize that the aim of the clinical trial is to compare the effectiveness of various drug regimens against *M. leprae*. It is beyond argument that the response of organisms to antimicrobials cannot be directly measured in most treated lepromatous or untreated nonlepromatous patients, but only in previously untreated lepromatous patients.

Certainly, more effective regimens should be developed for those patients who have failed to respond properly to the standard multidrug therapy. Nevertheless, the majority of these failures have occurred among paucibacillary patients whose clinical response is unsatisfactory; at the moment, it is not clear that the inadequate response results from insufficient antimicrobial treat-

ment. It is likely that protocols with different approaches (e.g., immunotherapy) and parameters should be developed for studies among these patients.

Although one should not exaggerate the complexity of planning and conducting a controlled clinical trial, the complexity should not be underestimated. In our limited experience, due to various limitations, very few institutes in the world are capable of conducting a controlled clinical trial independently and properly. Multi-institute collaboration probably is the most feasible approach to solve the potential problems, technical and logistic, faced by a trial.

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## Relapses in Multibacillary Leprosy

TO THE EDITOR:

I wish to offer the following comments on the paper entitled "Rate and Time Distribution of Relapses in Multibacillary Leprosy," by Kurz, *et al.* published in the *INTERNATIONAL JOURNAL OF LEPROSY* **57** (3) 1989, 599–606.

In the life table analysis used in the analysis of the data, it is assumed that the probability of undergoing an event is constant. Factors such as initial bacterial load, age, and immunological status of the patient would have certainly influenced the occurrence of the event, in addition to the treatment and its regularity. Because of the rigid selection criteria, large numbers of patients were excluded from the study. It would be interesting to know whether the group excluded had any particular attributes and the

extent to which their exclusion has influenced the figures of relapse rates.

Regarding the statement of the authors in the summary, "The results show no evidence that relapses occurring after 3 years of negativity could be reinfections . . .," I failed to find any evidence from the data published in the paper that supports this statement except probably the continuation of treatment after negativity. Nowhere is it mentioned as to whether all the patients who have relapsed were on dapsone (DDS) until the occurrence of the relapse. Certainly there must be some cases where the treatment was stopped. Add to this the possibility of 20% of the cases (as per the authors' own experience) not consuming the drugs. Then so-called relapses from these two groups could as well be reinfections. In addition, from

among the patients on monotherapy the reinfection could have occurred by the DDS-resistant organisms, although this is a rare possibility.

I shall be much obliged if the authors can kindly offer their comments.

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## Dr. Kurz Replies

### TO THE EDITOR:

We are thankful to Dr. B. N. Reddy for his valuable comments on our paper on relapses in multibacillary leprosy (<sup>2</sup>). We wish to offer the following clarifications.

Our topic was relapses—their rate and time distribution in relation to regularity of treatment—not a discussion of their possible causes. Whether the underlying phenomenon is reinfection, resistance, or any other mechanism had no bearing on the question at issue: Do multibacillary (MB) patients really benefit from life-long dapsone monotherapy after negativation? From our data, the answer is yes, and at any time after negativation relapse occurrence was affected by regularity during both smear-positive and -negative periods. As discussed in the paper, this result contrasts with the proposition that relapses occurring beyond the first 3 years of negativation could well be reinfections (<sup>1</sup>). It explains our statement on reinfections pointed out by Dr. Reddy.

We did not include an initial bacterial index (BI) in our analysis. A first reason was the skewness of the BI distribution, most patients being in the 2+ and 3+ categories and, following current practice, it did not seem necessary to go beyond the MB classification. A second reason was the impact of case-finding activities on the BI at diagnosis, and thus the difficulty of interpreting results of relapse rates by BI categories.

Dr. Reddy suggests that “rigid” selection criteria could have biased our results. We do not share his view. We wanted to study relapses in true negative subjects, not a mix of relapses and reactivations in patients falsely declared negative in a single examination. Hence, our admissibility criteria emphasized specificity rather than sensitivity. In no way do they affect the validity of the results. Rather, they enhance it by se-

curing homogeneity of the study base (the 1883 MB patients who showed 2 consecutive years of BI = 0).

Comparability would be an issue only if eligible subjects were not enrolled, whatever the reason, and it was not the case. The only subjects of concern in this study are 160 enrolled patients who dropped out somewhere after negativation. They would bias the results only in case of their dropping out being related to relapse occurrence. In view of the organization of leprosy services in the Polambakkam Leprosy Centre area, we consider it unlikely, although we cannot be quite certain.

During the study period (1955–1982), MB cases in Polambakkam received life-long dapsone monotherapy. As proposed by Dr. Reddy, surely some of them did not consume their drug, and there must be some cases where the treatment was stopped. Our purpose was to assess a policy (life-long dapsone monotherapy), not dapsone effectiveness. Those behaviors being inherent to the policy, they are part of its assessment. They were taken into account by dividing the study base into groups of different regularity.

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