Drs. Grosset and Ji's Response to Dr. Chatterjee's Comments

TO THE EDITOR:

The comments by Dr. Chatterjee regarding our Clinical Note entitled "Controlled clinical trial for evaluation of antimicrobial drug activity against *M. leprae*," published in the June 1989 issue of the JOURNAL ([2]), are most welcome. However, we feel that his comments reflect more misunderstanding than disagreement.

For example, we agree entirely with Dr. Chatterjee that incompatibility of drugs in a combination is a possible cause of treatment failure. For this reason, we emphasized that treatment failure may be attributed to "poor antimicrobial activity of the drug(s)" and that evidence of the antimicrobial activity should be firmly established before undertaking a clinical trial.

We also agree that the immune responses of the host play an important role throughout the course of leprosy infection. Because of the immune response, rapid spontaneous killing of *Mycobacterium leprae* occurs once *M. leprae* have multiplied to the plateau level in immunologically intact (normal) mice; therefore, we concluded that established infection of normal mice is not a convenient system in which to compare the activities of different drug regimens ([1]). On the other hand, established infection is not the only system in which to study experimental chemotherapy, and we certainly did not intend to imply that other systems could not provide highly predictable results of drug activity in humans. Furthermore, because, to the best of our knowledge, none of the current immunological parameters is well correlated with the antimicrobial activity of a drug against *M. leprae*, we believe that the immunological parameters are irrelevant to the measurement of antimicrobial activity of the drug in a clinical trial, this despite our full awareness of the important impact of the immune responses of the host on the disease.

Another example of misunderstanding is given in paragraph 4, concerning the requirement of establishing the drug susceptibility status of the organisms before treatment. As described in our paper, because the evidence of the antimicrobial activity of the tested drugs has already been firmly established before conducting a clinical trial, and to exclude the patients who are harboring organisms resistant to these drugs, the pretreatment drug susceptibility status of the organisms should be tested. Although it is absolutely correct that the treatment of leprosy is "more than just antimicrobial activity," one must nevertheless measure the antimicrobial activity of regimens to be employed. As described in the title of our paper, the aim of the controlled clinical trial is to compare the effectiveness of various drug regimens against *M. leprae*.

We have never underestimated the importance of field trials in the development of new combined regimens as suggested in

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 treatment. 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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