CORRESPONDENCE

This department is for the publication of informal communications that are of interest because they are informative and stimulating, and for the discussion of controversial matters. The mandate of this JOURNAL is to disseminate information relating to leprosy in particular and also other mycobacterial diseases. Dissident comment or interpretation on published research is of course valid, but personality attacks on individuals would seem unnecessary. Political comments, valid or not, also are unwelcome. They might result in interference with the distribution of the JOURNAL and thus interfere with its prime purpose.

Controlled Clinical Trials

TO THE EDITOR:

The clinical note on controlled clinical trials of drugs against leprosy by Grosset and Ji (IJL 1989 57:529–531) needs to be commented on for a number of reasons. In the first place, the observation that people should not give up the "intention" to conduct clinical trials if "concepts of new combined regimens are available" is a welcome development, even though in the rather lengthy discourse on the obvious need for controlled trials this concession on the part of THELEP leaders is almost "inaudible" unless one reads the note carefully. There are assertions and observations made that are both inaccurate and unrealistic. I would like to identify these weaknesses:

1. Three major factors have been identified as causes of treatment failure, namely, a) poor activity of drugs; b) resistance of the organisms to the drug(s) used; c) patient noncompliance with treatment. In the context this note has been produced, which is multidrug combinations against leprosy, a very important factor has not been identified, that of incompatibility of drugs in a combination. As a matter of fact, this is the most important factor that calls for generation of "concepts of new drug regimens."

2. To observe that immunological parameters are not relevant to antimicrobial activity of drugs in leprosy is being unrealistic. The immunopharmacology of antileprosy drugs, their antagonism and synergism, and the relevance of these to the ultimate outcome of antileprosy treatment seem to continue to be neglected and unappreciated. Leprosy being a disease where everything begins and ends in tune to the host's immune response, it is strange how the authors could think of this as irrelevant. Let me quote Grosset himself on this: ". . . rapid spontaneous killing of the organisms in untreated mice, once the *Mycobacterium leprae* have multiplied to the plateau level, renders the assessment of drug activity very difficult" (IJL 1987 55:847–851). What is it that kills *M. leprae* in the untreated mice? It is the host immune response. Why does *M. leprae* multiplication in the mouse foot pad stop at 10^6 organisms? Again, it is the immune response. So, is it not going to influence the result in the drug-treated mice, as well as in the human patient?

3. The statement that "drug activity in humans can be predicted, at least to date, from the activity obtained in the mouse foot pad system" contradicts Grosset's recent observation that "The results of these experiments show clearly that established infection of normal mice with *M. leprae* is not a convenient system by which to compare the activities of different drug regimens" (IJL 1987 55:849).

4. The observation that "it is necessary to ascertain that the causative organisms are susceptible to the tested drug(s) and therefore patients harboring organisms resistant to these (as a consequence of primary or secondary resistance) must be excluded, otherwise assessment of the drug activity will be distorted" is, to say the least, baffling. Because, by doing so, you are already in the study and will have already achieved your objective of knowing if the drug(s) possess antimicrobial activity. Since you do not ex-

pect the bacilli from all the patients in your trial to display uniform resistance or susceptibility to the drug(s) being tested, bacilli from each patient will need to be tested individually, and that is your trial! The other objectives of a drug trial are determining the length of treatment, the extent of persister survival, and the rates of relapse. That would be outside the scope of a trial primarily designed to know the bacteria-killing efficacy of drug(s). The most vital thing one needs to know, after the antimicrobial efficacy of the drug(s) is established, is the efficacy of the drug(s) in the treatment of the disease, which in leprosy adds up to more than just antimicrobial activity.

5. Treatment of leprosy in a control/eradication program is a large-scale operation, a population-based activity. The biggest drawback, and consequently the vulnerability to criticism of the WHO's only regimen, is that it was based on only small-scale, hospital-based trial results, and before prescribing it for large-scale field use it was never put to field testing. In the first place, hospital-based trials can never be a substitute for field trials which have their own relevance and requirements. Field trials evaluate logistic, epidemiologic and social dimensions of the leprosy eradication project through mass treatment. Things like length of therapy that will guarantee inactivation, prevent relapse, make the community of patients nontransmitters and safe to the community at large, educate and build community confidence in the treatment, are all very vital objectives of your therapeutic trials and none is possible of achievement sitting in a hospital. It is high time problems of leprosy of all sorts be tackled from within the population without any further time loss. The ultimate criteria to evaluate the efficacy of a treatment regimen is its ability to interrupt transmission, bring about a decline in incidence, prevent relapse and deformity, and the social acceptability of the treatment regimen through rapid and appreciable beneficial effect on the individual patient. All these can only be achieved through field-based trials, without which we will continue to be uncertain about the feasibility of control/eradication through therapeutic interruption. In this scheme of things, bacillary viability and persistence, the persister phenomenon and its relevance, are all matters of theoretical curiosity. Have not studies already indicated that in ± 9% of biopsy specimens persisters remain, notwithstanding the type of drug combination and length of treatment? (Gelber and Levy, IJL 1987 55:872–878). As a matter of fact, all parameters that need to be put to the test in a therapeutic trial in leprosy, such as clinical, experimental, epidemiologic, logistic and social, can be tested through a field study. Therefore, while a field study can substitute for a hospital-based trial, it is impossible through a hospital-based study to get answers to so many vital questions at the same time.

6. The requirement that ". . . the activity of drug regimens against *M. leprae* should be assessed only in previously untreated lepromatous leprosy patients" is almost impossible to meet. In the first place, at least in most leprosy-endemic parts of India, we are seeing far fewer lepromatous patients these days; secondly, treatment is easily available if the patient knows that leprosy is treatable; thirdly, in those patients who failed to respond to the WHO/government of India's regimen, an experiment with alternative regimens is not only relevant, urgently necessary and of high priority, it also promises to be highly rewarding if one's "intention" is really to try out "concepts of new combined regimens."

7. I have already pointed out the relevance of considering the immunopharmacology of antileprosy drugs. Conducting trials with alternative regimens for paucibacillary patients, a potentially immunologically unpredictable group, is inescapable. In India, a significant majority of leprologists of standing are in uniform agreement that the current multidrug regimen for paucibacillary leprosy is inadequate and insufficient, and an alternative approach and regimen must be researched. Moreover, "paucibacillary" under the skin can be highly bacillated deep down (see my review of the proceedings of the THELEP-Indian scientist's meeting at Karigiri, March 1988: Indian J. Lepr. 1989 61:249–257).

I should like to end by emphasizing once again that it is not going to help by making therapeutic trials appear like an extraordinarily complex, complicated and demanding exercise. Even if it is so, there is no escape from therapeutic trials on alternative

regimens. If the will to do a good job is there, and a good idea and infrastructure with supportive staff exist, it should be a relatively routine task for a group to organize and execute a drug trial. Problems are there, and the earlier WHO trials at Chingleput and Mali were not free from such problems. The majority of patients who attend Chingleput, JALMA, Karigiri, or other clinics have had dapsone monotherapy or various lengths of multidrug therapy previously, and everybody knows that any assertion on their part of having had no treatment is never taken seriously. That, of course, does not mean fresh cases do not arise or are not seen in clinics. But to get a number sufficiently large to be assigned to one or more treatment groups and a control group is next to impossible, unless one resorts to a modified life-table approach spread out over years. So, a controlled trial in a field situation with patients whose status of bias is considered and adjusted as much as is possible, seems to be the only possibility at this moment. And it is certainly possible to obtain results from such studies on which alternative treatment strategies can be based.

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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