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.

At Twenty Years after Shepard's Method of Inoculation of *M. leprae* in the Foot Pads of Mice

TO THE EDITOR:

At twenty years after Shepard's ([4]) discovery of the growth of *M. leprae* in the foot pads of mice (1960) and its further use as an experimental model in leprosy, Bergel ([1]), Murohashi and Yoshida ([3]), and Chang ([2]) have pointed out some fundamental limitations to its application.

Among others, there are the following technical limitations:

1) The growth of *M. leprae* in the foot pads of mice is limited and regressive and does not generate the characteristic histopathological structure of lepromatous leprosy, i.e., the vacuolization of the histiocyte and the formation of Virchow cells. Thus the model does not reproduce lepromatous leprosy bacteriologically or histologically.
2) The exact inoculation of a given amount of bacilli is technically very difficult, the amount of lost bacilli at inoculation is variable (but may be considerable), and this factor may create imprecision in the results obtained. Besides it is often quite difficult to break up any globi in the inoculum, and this may make it difficult to count the exact number of bacilli to be inoculated.
3) The number of bacilli harvested from foot pads after the growth of *M. leprae* does not follow a normal frequency distribution, and this may make interpretation of results doubtful in statistical analyses.
4) The same amount of inoculum arising from the same source in some cases may give a quite different harvest in one foot pad as compared to the contralateral one in the same animal. An inoculum from the same source inoculated into individual animals may give quite variable results from one to the other, the difference in harvests being up to even a thousand fold.
5) The detection of bacilli through histobacteriological examinations in the foot pad only shows the presence of bacilli when the bacilli are above a threshold concentration. Conversely, there can be bacilli in the foot pad without their being detectable histobacteriologically.

In connection with these fundamental technical limitations in this experimental model, results obtained in hundreds of experiments done in the major leprosy centers of the world allow one to make the following observations:

1) With the use of this method, practically no new drug for the treatment of leprosy has been discovered so far. The only one that has been discovered utilizing this method has been acedapsone (DADDS), which is related to dapsone. Acedapsone, when administered every 75 days, liberates a few milligrams of dapsone per day. It is

now known that the administration of low doses of dapsone is not advisable in order to minimize the emergence of sulfone resistant bacilli.

2) Through the use of this experimental model, no vaccine has been discovered, so far, to prevent leprosy, and neither could the possible preventive activity of BCG be exactly evaluated.
3) With this experimental model it is not possible definitively to resolve the controversy as to whether or not nonsolid leprosy bacilli are viable.
4) With this experimental model it is not possible definitively to resolve the controversy as to whether or not environmental temperature is the main factor in the growth of *M. leprae*.
5) In this experimental model it has not been possible to determine the mechanism of action of sulfones against *M. leprae*.

In our view the fundamental limitation in this experimental model is that we are dealing with a normal animal. *M. leprae* are inoculated into normal mice which lack the biochemical alterations characteristic of the lepromatous condition. Without these biochemical changes, limited bacillary multiplication can occur, as it does in the foot pads of normal mice, but disseminated infection or disease cannot take place.

In summary, it seems to us that any experimental model which ignores the biochemical alterations characteristic of lepromatous leprosy will inevitably be limited in its applicability. This seems to be the case with Shepard's method in addition to the technical limitations outlined earlier.

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Reply to Dr. Bergel's Letter to the Editor

To the Editor:

The Editor has asked me if I wish to reply to Dr. Bergel's letter. I am reluctant to do so because I believe that communications of this sort too easily degenerate into useless exchanges of personally motivated assertions. The only really suitable scientific communication is a full-scale publication with adequate description of methods, full presentation of results, cogent discussion, and conclusions; the paper should be published in a journal that requires review by knowledgeable scientists before possible revision and acceptance. The reader is thereby provided with the evidence that he needs to form his own conclusions about what has been written in the paper.

If I did not reply to the statements of Dr. Bergel, however, some readers might conclude that I have at least partially accepted his assertions. To avoid such confusion let me simply state that, with one exception, I think all of the limitations and observations listed by Dr. Bergel are either wrong (entirely or in substantial part) or trivial. The exception, of course, is his first limitation; as far as I know, no one has claimed that the experimental *M. leprae* infection in normal mice resembles human lepromatous disease histologically. The concentration of *M. leprae* in mice is usually lower, but the values in mouse-foot-pad lesions and in human lepromatous tissue overlap.

Because Letters to the Editor often are political rather than scientific, the reader is well-advised to consider their purpose. I have given the reason for my reply. It may be that Dr. Bergel feels that the infection