Reply by Gill, Mustafa and Godal

TO THE EDITOR:

The modern interpretation of the lepromin test is that it is a minimal vaccination ([1, 2]). This is the premise upon which our original study, i.e., the trial of a heat-killed, armadillo-derived vaccine, was based. In this study four groups of normal, healthy individuals were given graded doses (1.5×10^7, 5×10^7, 1.5×10^8, and 5×10^8) of heat-killed, armadillo-derived *Mycobacterium leprae* intradermally. The performance of the vaccine was assessed by measuring the skin-test responses of the volunteers to *M. leprae* soluble antigen (MLSA) before and after vaccination. This study therefore allowed us to measure a) the early and late responses to the killed-armadillo *M. leprae* vaccine (AML), b) the skin-test responses to MLSA and to PPD, and c) the lymphocyte transformation test responses to MLSA, whole *M. leprae,* and the various other antigens. Thus, the purpose of writing the article was to examine all of these parameters closely and to determine their relationships. We felt compelled to make this report since a) it supports the modern interpretation of the lepromin test, and b) it would benefit those centers in the world which use armadillo-derived *M. leprae* for lepromin testing. It is most important to grasp the fact that the vaccine in our study also functions as a lepromin. Unfortunately, Mistry and Antia failed to grasp this concept, and therein lies the reason for most of their criticisms of our report.

Mistry and Antia point out that "... a significant error in the study appears to be the consideration of the armadillo-derived *Mycobacterium leprae* (AML) vaccine as a representative of standard Mitsuda lepromin." We are cognizant of the differences between armadillo and human lepromin, and we have actually alluded to this fact in our paper. These differences aside, the AML vaccine elicits an early and a late response not unlike that elicited by "Mitsuda lepromin." We would say that while the AML vaccine is not equivalent to Mitsuda lepromin, it is sufficiently similar to be considered in the same category.

Mistry and Antia then remark that we failed to emphasize the reason for the fact that the majority of normals, who should be responders to lepromin, failed to respond satisfactorily to the AML vaccine. Actually, our study has shown, using Mistry and Antia's criteria of a cut-off point of 5 mm, that the majority of the subjects gave positive late responses to the vaccine. When the response to the vaccine was assessed by the difference in the skin-test response to MLSA, the conversion was statistically significant in the groups that received the three highest doses of vaccine, i.e., 5×10^7, 1.5×10^8, and 5×10^8 bacilli.

Mistry and Antia further point out that a major lapse in our study is the absence of a comparison of the pre- and postvaccination lepromin responses with the late reaction elicited by the AML vaccine. The purpose of the original study was to assess the per-

formance of the heat-killed, armadillo-derived vaccine. Testing the responses of the vaccinated volunteer to Mitsuda lepromin would have severely confounded the study, as the authors themselves have pointed out.

Mistry and Antia state that we suggested the use of a higher dose of Mitsuda challenge for testing vaccine potency. Bearing in mind the fact that our report is based on the premise that the lepromin test is a minimal vaccination, we state categorically that we never made such a suggestion. We did, however, point out to those centers which use armadillo lepromin to test the response of patients and their contacts that a negative lepromin response may be the result of the low dosage used rather than an indication of an inability to respond to *M. leprae*. We would, in such cases, recommend that these centers select their dose carefully and use a higher dose, if necessary. Bearing in mind our central premise, we would further add that we certainly do not recommend dose manipulation of lepromin to enhance the performance of a vaccine. And we have accepted a negative MLSA postvaccination skin-test response as a failure of vaccination.

Regarding the Fernandez reaction, the early lepromin response, which is believed to be a measure of previous sensitization to *M. leprae*, we found that the prevaccination MLSA responses do not correlate with the early lepromin reactions, except at the highest dose of lepromin used. We speculated that this was the result of the variability in soluble antigen content in lepromin preparations. There was also no correlation between the vaccinees' early lepromin response and their prevaccination skin-test responses to PPD. We concluded that the Fernandez response may not consistently measure previous sensitization and, therefore, its usage for this purpose was questionable. Mistry and Antia argue that our quotation of the work by Ponnighaus and Fine ([3]) vindicates the Fernandez reaction as a measure of previous sensitization and also supports our speculation on the variability of soluble antigen content in lepromin. It is not altogether apparent how they arrive at this conclusion, although this might be partly due to their confusing the early lepromin response with the MLSA response. There is no evidence to indicate that the two responses are identical. The authors have not provided convincing reasons for reconsidering our opinion of the Fernandez response.

Regarding MLSA, Mistry and Antia state that our work confirms the scepticism they feel about this reagent. The reasons for this conclusion, once again, are not very clear. It has behaved quite consistently in our hands, and we have no reason to question its credibility. While we look forward to using a well-characterized reagent, we do not share Mistry and Antia's enthusiasm for a "Mitsuda-like-agent." The longer time taken for such an agent to elicit a response may allow for an amplification. We would still be unable to distinguish a person with exposure to the disease from a person with no exposure to the disease.

Finally, we would like to say that we agree with Mistry and Antia that the antigenic preparations used in leprosy require much more study.

—Havindar Kaur Gill, M.Sc.
Division of Immunology
Institute for Medical Research
Jalan Pahang
50588 Kuala Lumpur
Malaysia

—Abu Salim Mustafa, Ph.D.
Whitehead Institute for Biomedical Research
Nine Cambridge Center
Cambridge, Massachusetts 02142
U.S.A.

—Tore Godal, M.D., Ph.D.
Director
Special Programme for Research and Training in Tropical Diseases
World Health Organization
1211 Geneva 27, Switzerland

REFERENCES

1. Bloom, B. R. and Godal, T. Selective primary healthy care for control of disease in the developing world. V. Leprosy. Rev. Infect. Dis. **5** (1983) 765–780.
2. Godal, T. Immunological aspects of leprosy—present status. Prog. Allergy **25** (1979) 211–242.
3. Ponnighaus, J. H. and Fine, P. E. M. The Karonga Prevention Trial—which BCG? Lepr. Rev. **57** Suppl. 2 (1986) 285–292.