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.

Dapsone Susceptibility of *Mycobacterium leprae* Isolated Before 1977

TO THE EDITOR:

In his letter ([1]) in response to our paper ([7]), Almeida raised several arguments by which to deny the conclusions reached in this paper—namely, that the susceptibility to dapsone of strains of *Mycobacterium leprae* isolated from previously untreated patients has changed since the years preceding 1977. First, he has correctly called attention to the fact that the available data ([5]) do not, in fact, suggest that the susceptibility to dapsone of strains of *M. leprae* isolated since 1977 from previously untreated patients in The Philippines is different from that of strains of *M. leprae* isolated earlier. Our statement that the prevalence of primary resistance to dapsone is currently 30 to 50 per 100 patients at risk was not based on data obtained from The Philippines.

His second argument—that strains of *M. leprae* resistant to dapsone had been isolated at the National Institute of Medical Research (NIMR), London, is based on a single review paper ([6])—in which *M. leprae* described as having been isolated from previously untreated patients, and representing an unstated number of patients, are reported to have multiplied in mice administered dapsone in dietary concentrations ≥0.0001 g per 100 g diet. Almeida cited this same paper in earlier efforts to prove that the importance of resistance to dapsone has been exaggerated ([2]). However, when the relevant laboratory records were reviewed, in order to assemble the data on strains isolated prior to 1977 at the NIMR, the data that had been presented in the 1965 publication were not found. In fact, the *M. leprae* reported in the 1965 paper to have multiplied in dapsone-treated mice may well have represented only a single strain, and the possibility of a laboratory error cannot be excluded. Therefore, these data cannot be employed to prove Almeida's contention that dapsone resistance has always been with us ([2]).

Almeida's third, and more serious, argument is methodological. In brief, he argues that "Rees' method" may be more sensitive than "Shepard's method" to the presence in a specimen of small proportions of dapsone-resistant *M. leprae* because, by the former method, harvests are performed later, providing more time for the drug-resistant individuals in the population of *M. leprae* to multiply. Because, so goes the argument, the susceptibility of most of the pre-1977 isolates had been measured by Shepard's method, whereas most of the more recent measurements [i.e., those made in the course of the THELEP-sponsored trials in Chingleput and Bamako ([8])] have been made by Rees' method, the prevalence of dapsone resistance among pre-1977 isolates may simply have been underestimated, or that among post-1977 isolates overestimated. On the other hand, employing Shepard's technique, Grosset and his colleagues recently found the prevalence of primary dapsone resistance to be approximately 40 per 100 patients at risk in the French West Indies, French Oceania, and Francophone Africa ([4]). In addition, because the inocu-

lum of 5000–10,000 *M. leprae* probably includes no more than 50–100 viable organisms ([3] and J. Grosset, personal communication), resistant individuals cannot be detected unless they are present in a proportion no smaller than 1:100; a strain including so great a proportion of resistant *M. leprae* cannot be considered susceptible to dapsone.

Finally, Almeida wonders if it is possible, by incorporating the drug into the mouse diet, to maintain a given concentration of dapsone for the long period of administration required. He implies that, should the concentration of dapsone slip below the minimum, *M. leprae* susceptible to dapsone would be permitted to multiply, thus "simulating" resistance. Although, as he points out, the $T_{1/2}$ of dapsone in the mouse is short, the mouse eats more-or-less continuously, so that incorporating the drug in the mouse diet should provide as continuous a level of drug in plasma and tissues as is possible, without resorting to continuous infusion. Although plasma levels of the drug have not been monitored at sufficiently close intervals during administration of dapsone incorporated in the mouse diet to demonstrate that effective levels are maintained throughout the 24 hours of the day, nevertheless, the demonstration ([7]) that some strains of *M. leprae* are inhibited from multiplying when the drug is administered in the minute concentration of 0.00001 g per 100 g diet [10 ng per 100 g, or approximately 0.5 ng per day (approximately 20 ng per kg body weight)] suggests that this method of administering dapsone is indeed efficient, and that there are in fact differences of susceptibility among strains.

Thus, the weight of evidence suggests that, despite methodologic differences and problems, the susceptibility to dapsone of the strains of *M. leprae* isolated during recent years from previously untreated patients with lepromatous leprosy is different from that characteristic of the strains isolated and tested during the first years of susceptibility testing. Whether or not the current isolates, largely resistant to only the lowest concentration of dapsone, are killed during treatment of patients with dapsone in full dosage is irrelevant. In the course of many years' use of dapsone monotherapy, more resistant strains appear to have been selected, and one can predict that continued use of dapsone monotherapy will lead to the selection of even more resistant strains, so that, finally, dapsone monotherapy will be totally without effect.

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REFERENCES

1. Almeida, J. G. Dapsone susceptibility of *M. leprae* before and after 1977. Int. J. Lepr. **55** (1987) 726–727.
2. Almeida, J. G. and Chacko, C. J. G. Evaluation of dapsone monotherapy for lepromatous leprosy in Gudiyatham Taluk. Indian J. Lepr. **56** Suppl. (1984) 454–458.
3. Committee on Experimental Chemotherapy. Experimental chemotherapy in leprosy. Bull. WHO **53** (1978) 425–433.
4. Guelpa-Lauras, C.-C., Cartel, J.-L., Constant-Desportes, M., Millan, J., Bobin, P., Guidi, C., Brucker, G., Flageul, B., Guillaume, J.-C., Pichet, C., Remy, J.-C. and Grosset, J. H. Primary and secondary dapsone resistance of *M. leprae* in Martinique, Guadeloupe, New Caledonia, Tahiti, Senegal, and Paris between 1980 and 1985. Int. J. Lepr. **55** (1987) 672–679.
5. Guinto, R. S., Cellona, R. V., Fajardo, T. T. and de la Cruz, E. C. Primary dapsone-resistant leprosy in Cebu, Philippines. Int. J. Lepr. **49** (1981) 427–430.
6. Rees, R. J. W. Recent bacteriologic, immunologic and pathologic studies on experimental human leprosy in the mouse foot pad. Int. J. Lepr. **33** (1965) 646–655.

7. Shepard, C. C., Rees, R. J. W., Levy, L., Pattyn, S. R., Ji, B. and de la Cruz, E. C. Susceptibility of strains of *Mycobacterium leprae* isolated prior to 1977 from patients with previously untreated lepromatous leprosy. Int. J. Lepr. **54** (1986) 11–15.
8. Subcommittee on Clinical Trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Primary dapsone resistance in Bamako and Chingleput: final report. Lepr. Rev. **58** (1987) 209–218.