Dapsone Susceptibility of *M. leprae* Before and After 1977

TO THE EDITOR:

Interesting points are raised by a recent paper in the JOURNAL ([13]). The authors argue, from data on dapsone susceptibility of *Mycobacterium leprae* isolated before 1977, that there has been an increase in the frequency of strains "primarily resistant" to dapsone since 1977. However, not all observations seem consistent with the authors' view.

First, the paper claims that the post-1977 "prevalence of primary resistance to dapsone" is "30 to 50 per 100 patients at risk." This is not true of The Philippines, the country which supplied more of their "pre-1977" *M. leprae* isolates than any other (24 out of 74 isolates). The reported post-1977 prevalence of "primary resistance to dapsone" in The Philippines is only 3.6 per 100 patients at risk (95% confidence limits 0.0 to 9.1 per 100) ([3]).

Secondly, in presenting the table showing all pre-1977 isolates as susceptible to dapsone, they discount publications from the London laboratory. In that laboratory, previously untreated *M. leprae* isolates in the 1960s were not inhibited in all foot pads among mice fed high concentrations of dapsone—0.01 to 0.1 g% ([10]). In 1965, the London laboratory reported on previously untreated isolates that "the overall result on nearly 100 foot pads has been complete inhibition in only 82 per cent": despite mouse dietary concentrations of dapsone as high as 0.025 to 0.1 g% ([9]).

It is instructive to look more closely at the methods involved. The paper ([13]) notes differences between various laboratories, in techniques as well as in criteria for interpretation of results. At least two distinct methods can be discerned which can be traced back in the literature to Atlanta ([11, 12]) and London ([8]), respectively. The pre-1977 data in the paper seem to be based largely on the Atlanta method (at least 44 out of 74 isolates). The post-1977 results cited in the paper are based largely on the London method. The pooling of results from the two methods, as done in the paper ([13]), may not be justified.

If results from the Atlanta method are used to compare the dapsone resistance of untreated *M. leprae* before and after 1977, then claims of an increase in dapsone resistance cannot be substantiated. Namely, 24 out of 24 pre-1977 Philippine isolates showed no dapsone resistance ([13]), while 53 out of 55 post-1977 Philippine isolates also showed no dapsone resistance ([3]). The difference is not statistically significant ($p = 0.4821$, Fisher's exact test).

The London method, used on post-1977 isolates of untreated *M. leprae* from Chingleput (South India) and Bamako (Mali), showed that 1 of 96 isolates grew in mice treated with 0.01 g% dapsone in their diet (roughly equivalent to the recommended adult human dose of 100 mg dapsone per day), although 36 out of 96 isolates grew in mice treated with 0.0001 g% dapsone in their diet ([14]). Unfortunately, no comparable data for the period before 1977 seem to be available for these two areas.

The Atlanta and London methods of mouse foot pad drug sensitivity testing differ in some important respects. The Atlanta method harvests untreated mice at monthly intervals, and treated mice as soon as the organisms in untreated mice have multiplied to "a level near 1×10^6 acid-fast bacilli" per foot pad ([12]). This reduces the danger of comparing treated and untreated mice after growth in untreated mice has reached the plateau of about 1×10^6 bacteria per foot pad. The London method, in contrast, harvests treated as well as untreated mice at some predetermined interval—"usually 8 to 12 months" after inoculation ([13]). This difference may be crucial, particularly when resistance is diagnosed at low concentrations of dapsone in mouse diet (e.g., 0.0001 g%) ([14]).

A single bacterium with a doubling time of 11.1 days ([5]) would reach the plateau of 10^6 bacteria in a foot pad within less than 8 months from inoculation. Given a sufficient delay until harvest, e.g., 9 months from inoculation, no more than 1 of the 1000 or more bacteria inoculated need multiply at the low concentration of dapsone in order to simulate "resistance." Further, the assumption that mouse serum levels of dap-

sone are maintained adequately by the low concentration (0.0001 g%) of dapsone in the mouse diet seems precarious. The half-life of dapsone in the mouse is as short as 2 to 4 hours ([6]). Perhaps the "primary resistance" of post-1977 isolates from Bamako and Chingleput to low concentrations of dapsone is not beyond question.

If "primary dapsone resistance" has increased after 1977, the data so far do not seem to demonstrate this. Despite theoretical predictions to the contrary, the most remarkable feature of "primary dapsone resistance" to date is its apparent rarity ([3]), and the continuing efficacy of dapsone monotherapy ([1, 2, 7]), even among patients with "primary dapsone resistance" in mouse foot pad tests ([4]).

—Joel G. Almeida, M.B.B.S.

Department of Tropical Hygiene
London School of Hygiene and
Tropical Medicine
Keppel Street
London WC1E 7HT, U.K.

REFERENCES

1. 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.
2. Casabianca, M. N. and Thomas, A. Response to DDS monotherapy in bacteriologically positive cases registered between 1960's and 1970's in leprosy control unit of the Philadelphia Hospital, Salur. Indian J. Lepr. **56** Suppl. (1984) 460–461.
3. 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.
4. Jacobson, R. R. The effectiveness of dapsone in patients with primary dapsone resistant leprosy. Int. J. Lepr. **52** Suppl. (1984) 710.
5. Levy, L. Studies of the mouse foot-pad technique for cultivation of *M. leprae*. 3. Doubling time during logarithmic multiplication. Lepr. Rev. **47** (1976) 103–106.
6. Levy, L., Biggs, J. T., Jr., Gordon, G. R. and Peters, J. H. Disposition of the antileprosy drug, dapsone, in the mouse. Proc. Soc. Exp. Biol. Med. **140** (1972) 937–943.
7. Neelan, P. N. and Reddy, B. N. Response of multibacillary leprosy patients to dapsone monotherapy. Comparison of 2 cohorts registered in 1960's and 1970's. Indian J. Lepr. **56** Suppl. (1984) 463–464.
8. Pettit, J. H. S. and Rees, R. J. W. Sulphone resistance in leprosy; an experimental and clinical study. Lancet **2** (1964) 673–674.
9. Rees, R. J. W. Recent bacteriologic, immunologic and pathologic studies on experimental human leprosy in the mouse foot pad. Int. J. Lepr. **33** Suppl. (1965) 646–657.
10. Rees, R. J. W. A preliminary review of the experimental evaluation of drugs for the treatment of leprosy. Trans. R. Soc. Trop. Med. Hyg. **61** (1967) 581–594.
11. Shepard, C. C. and Chang, Y. T. Effect of several anti-leprosy drugs on multiplication of human leprosy bacilli in footpads of mice. Proc. Soc. Exp. Biol. Med. **109** (1962) 636–638.
12. Shepard, C. C., McRae, D. H. and Habas, J. A. Sensitivity of *M. leprae* to low levels of 4-4′ diaminodiphenyl sulfone. Proc. Soc. Exp. Biol. Med. **122** (1966) 893–896.
13. Shepard, C. C., Rees, R. J. W., Levy, L., Pattyn, S. R., Ji, B. and dela Cruz, E. C. Susceptibility of strains of *M. leprae* isolated prior to 1977 from patients with previously untreated lepromatous leprosy. Int. J. Lepr. **54** (1986) 11–15.
14. 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 resistance to dapsone among untreated lepromatous patients in Bamako and Chingleput. Lepr. Rev. **54** (1983) 177–183.