Dr. Grosset Replies for the Isoprodian Study Group

TO THE EDITOR:

The questions raised by Dr. Verduin are highly pertinent. However they are difficult to answer. First, the majority of the patients included in the Isoprodian study were not newly diagnosed patients. Second, the study was not a field trial but, to the contrary, a double-blind controlled clinical trial aiming to demonstrate whether or not the addition of isoniazid was detrimental. Only patients selected for possible supervised daily intake of drugs were included. Therefore, in their conclusion, the authors have been careful enough neither to extrapolate their findings to routine field conditions nor to recommend that thioamide-containing regimens should replace the World Health Organization-recommended regimens.

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How Effective Is Monthly Rifampin? Response to the Letter to the Editor by Dr. J. G. Almeida

TO THE EDITOR:

I write in response to the Letter to the Editor by Dr. J. G. Almeida, entitled "How effective is monthly rifampin?"[1], in which he concludes that daily administration is many times more effective than monthly administration. Dr. Almeida's argument is flawed in that he draws conclusions with respect to the activity of the drug against *Mycobacterium leprae* in man from data obtained from work in mice. That rifampin is less active against *M. leprae* in the mouse than in man has been reported previously by Grosset [2, 4], among others. Dr. Almeida's extrapolation of the initial rates of bacterial killing in mice leads him to the outlandish conclusion that patients treated with monthly rifampin harbor at least 10^8-fold more viable *M. leprae* after treatment for 14 weeks than do those treated with daily rifampin. In fact, the available data [3, 6–9] demonstrate that the rate at which *M. leprae* are killed in man decreases abruptly, after the number of viable organisms has been reduced 1000–10,000-fold, at which time the population of "persisters" is unmasked [10]. The decrease of the rate of bacterial killing and the size of the population of *M. leprae* surviving after the initial kill are indistinguishable in patients treated by a variety of rifampin-containing regimens [3, 9].

One cannot be entirely confident that monthly rifampin is as effective as daily rifampin. Were I to become ill with multibacillary leprosy, I would very likely prefer my rifampin daily rather than monthly. However, the difference of effectiveness cannot be great, and administering the drug monthly both "stretches" the supply and permits supervision of drug administration.

Moreover, there is room for serious argument with respect to the antimicrobial activity of rifampin against *M. leprae.* None of us is comfortable with the discrepancy between man and mouse. In fact, as Grosset has pointed out [1, 5], the pharmacokinetic behavior of rifampin is more favorable in the mouse than in man, a fact that is inconsistent with the apparently greater efficacy of the drug in man. Is the discrepancy between mouse and man the result of crossing species barriers—i.e., one demonstrates the viability of *M. leprae* by inoculating mice, whether the organisms have been recovered from mice or man? Or is it possible that shipment of the specimen, often if not always required when organisms are to be recovered from human lesions and inoculated into mice, and rarely if ever required when organisms are to be transferred from mouse to mouse, is injurious, particularly to *M. leprae* that have been exposed to rifampin? On the other hand, the available