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CORRESPONDENCE

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Regarding Brasil, *et al.*'s Adverse Effects in Leprosy's WHO/MDT and Paramedic's Role in Leprosy Control Program

TO THE EDITOR:

The June 1996 INTERNATIONAL JOURNAL OF LEPROSY (Vol. 64, pp. 97–104) published an article entitled "Results of a Surveillance System for Adverse Effects in Leprosy's WHO/MDT." In this article one of the hypotheses given by Brasil, *et al.* ([1]) to explain the low number of reported acute renal failure cases as an adverse effect of WHO/MDT was the fact that most of the leprosy program has been carried out by paramedics. We would like to make some comments regarding this article.

The state of Amazonas covers an area of 1,564,445 km^2 in the north of Brazil. It is the largest state in the Amazon Basin with 2,424,817 inhabitants (1995) and its population density is a low 1.55 inhabitants/km^2. Half of the population lives in the capital city, Manaus, and the rest are unevenly distributed between the interior towns (nearly 60%) and the rural areas.

The Instituto de Dermatologia Tropical e Venereologia Alfredo da Matta is one of the National Reference Centres for Leprosy and the Reference Centre for Skin Diseases in the state. The management of the leprosy control program is the responsibility of this Institute.

The WHO/MDT in Amazonas started in 1982. The implementation was initiated by pilot studies in four areas: two areas in the capital at the Institute and in the Aleixo District, an ex-leprosarium which reported the first six cases of dapsone resistance in Brazil ([6]); two areas in the interior (in Lábrea and Tefé) both of which are municipalities with the highest prevalence and incidence rates for leprosy in the state. From the satisfactory results with the new therapeutic scheme, WHO/MDT was gradually implemented and expanded to all 62 municipalities of the state. In order to ensure efficient implementation of the new scheme, reorganization of the health infrastructure was necessary to enable the staff to cope with the revised strategy. When there were constraints, priorities were formulated so that available resources were put to the best use. Training of program personnel (physicians, nurses, social workers, biochemists, paramedics and laboratory technicians) has been carried out regularly in Manaus and in the interior over the past 10 years, with regular 5- to 10-day courses on general aspects of the disease, including its treatment. During the various courses, special attention is given to the rare but possible adverse effects of WHO/MDT. It is made clear to the participants that if they should come across any side effects they must interrupt the treatment, and this they have indeed done. They also are advised to refer the patients to the referral hospital in case of severe adverse effects or severe leprosy reaction, in addition to contacting the staff of the Institute by telephone in order to receive infor-

THE TABLE. *Cases of adverse effects to WHO/MDT which caused the interruption of the treatment from December 1982 to August 1996, Manaus, Amazonas, Brazil.*

Adverse effects	No.	%
Gastrointestinal complaints	22	31.88
Hemolytic anemia	13	18.84
Flu-like syndrome	11	15.94
Toxic hepatitis	8	11.59
Cutaneous reactions	6	8.70
Thrombocytopenic purpura	3	4.35
Methemoglobinemia	3	4.35
Acute renal failure	1	1.45
Respiratory syndrome	1	1.45
Psychotic syndrome	1	1.45
Total	69	100.00

mation about the correct procedures. More complicated cases that are unusual have, where necessary, been removed from the interior to Manaus by plane.

Most of the health centers and hospitals in the interior have two physicians who are responsible for the general medical assistance of the whole community. At these health units, the WHO/MDT has been administered, mainly by the paramedics.

Systematic and routine follow-up supervisionary activities of the health units in Manaus and in the interior have been carried out by the Institute's staff or from the regional health team.

From December 1982 to August 1996, a total of 20,019 patients were on or had completed WHO/MDT in Amazonas state. Of these, 10,864 (54.26%) received MDT in Manaus, where they could be monitored by physicians.

For the purpose of this letter, we are reporting 69 cases of adverse reactions (The Table) to WHO/MDT which resulted in treatment being interrupted by a physician in Manaus. These data can be compared with data collected in other regions where patients have been followed up by physicians ([1–5]).

Regarding the progress of the patients who had their treatment suspended, 65 had their treatment re-introduced with alternative regimens, which excluded those drugs suspected of causing their adverse effects. One patient refused further treatment and 3 patients died (1 due to acute renal failure, 1 to thrombocytopenic purpura and 1 to hemolytic anemia). If, besides the case already reported, more cases of renal damage due to WHO/MDT had occurred in Manaus, they probably were mild cases and the patients probably had minimal symptoms which they did not complain about.

More than half of the leprosy cases in the state of Amazonas live in the capital and, therefore, have access to a physician. Taking this into consideration and also the results shown in The Table lead us to think that the hypothesis given in the article, regarding the role played by paramedics, cannot explain the reduced incidence of acute renal failure as a consequence of adverse reactions to MDT in the state.

From the large number of patients under WHO/MDT in Manaus, it could be said that the current regimen has remarkably few side effects. However, side effects should be diagnosed as soon as they arise and treated appropriately in order to prevent dire results.

In order to try to explain the greater number of acute renal failure cases observed in São Paulo compared with Manaus, new hypotheses need to be formulated and new studies should be carried out to verify them. It may be possible to include ethnic characteristics or differences in the levels of severity of the renal damage.

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Acute Renal Failure and Multidrug Therapy for Leprosy

To the Editor:

Brasil, *et al.* ([2]) reported that a surveillance system for adverse drug reactions detected 20 cases of acute renal failure (ARF) among 20,667 patients treated for leprosy with World Health Organization multidrug therapy (WHO/MDT) in the state of São Paulo, Brazil, during an 18-month period. Assuming that the incidence of ARF in the general population in Brazil is around 140 per million, the same as that observed in Britain ([3]), these events follow a Poisson distribution, and one can calculate that the probability of the finding of 20 or more cases being due to chance is almost nil [calculations not shown, formula provided in Bégaud, *et al.* ([1])]. Brasil, *et al.* did not report whether the diagnosis of ARF was validated or simply accepted according to what was written on the notification. But even if only 7 cases out of the 20 were valid, the probability of a value as or more extreme than 7 (i.e., the p value) would still be less than 5%, which can be interpreted as an association between ARF and MDT for leprosy is likely.

The finding of an incidence of 1 per 1000 of ARF among patients under treatment for leprosy in São Paulo deserves, therefore, attention. Although not a common side effect, it is a severe one, and can lead to death if not adequately treated. It can be argued though that the available data are too crude and subject to biases. By this reasoning, one should not accept the data, which could eventually result in interference with the MDT program and may compromise the effort to control leprosy, because the cases of reported ARF are clearly associated to the drugs, and that an excess risk of developing ARF among users of WHO/MDT, supposedly due to the intermittent use of rifampin, is better demonstrated.

There should then be a next step in the investigation of the association between ARF and MDT. A detailed study of the reported cases would be of extreme interest in order to assess whether renal failure did occur and, if so, whether it was really acute and not previously unrecognized chronic renal failure. For each case, if the diagnosis of ARF was correct, then it would be necessary to assess whether WHO/MDT was correctly imputed as causally related to this complication. Other factors, such as other drugs, toxins, infections, dehydration, and so on, could be present simultaneously, and the likelihood of each should be compared, which could be done using one of several algorithms available in the literature [e.g., in Kramer, *et al.* ([5])] or, alternatively, by a Bayesian approach ([4]), or by both. Validation of case reports is essential for establishing whether there is an excess risk of ARF associated with WHO/MDT and, if so, what is its magnitude.

If this excess risk is confirmed, it would be interesting to investigate whether there are predictors of ARF among patients being treated with WHO/MDT, such as age, underlying diseases, or simultaneous exposure