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## Acute Renal Failure and Multidrug Therapy for Leprosy

TO THE EDITOR:

Brasil, *et al.* <sup>(2)</sup> 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 <sup>(3)</sup>, 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.* <sup>(1)</sup>]. 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.* <sup>(5)</sup>] or, alternatively, by a Bayesian approach <sup>(4)</sup>, 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

to other drugs, the knowledge of which would help to eventually identify groups at risk. This could be achieved by the undertaking of a case-control study in a population of individuals with leprosy in which the cases would be those who had ARF, and the controls a sample of those who did not. It is important to use incident cases and appropriate controls in such studies, but even cases which already occurred, such as those detected by the São Paulo state surveillance system, could be used insofar as the selection of controls is adequate (<sup>6</sup>). The identification of risk groups could be extremely helpful for health professionals, who could use this information to identify individuals who should either be monitored as to their renal function during WHO/MDT or should receive an alternative drug schedule to treat their leprosy with a lower risk of developing ARF as a drug reaction.

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## Bacillary and Histopathological Findings in the Peripheral Nerves of Armadillos Experimentally Infected with *M. leprae*

TO THE EDITOR:

The article by Scollard, *et al.* in the June 1996 edition of the *JOURNAL* (<sup>2</sup>) raises a number of interesting points concerning the presence or absence of *Mycobacterium leprae* in the peripheral nerves of armadillos found to have disseminated infection at the time of sacrifice. The Table (page 147) indicates that of the three animals with disseminated infection at sacrifice, number 632 had bacilli in all 4 nerves, but number X5 had bacilli in only 3 out of 6 and number X6 in only 1 out of 7 nerves examined. Thus, out of a total of 17 nerves examined, no fewer than 9 (i.e., over 50%) were negative for *M. leprae*, despite disseminated infection at sacrifice.

These findings are strikingly reminiscent of those in a series of armadillos experimentally infected in the 1970s and 1980s by Dr. R. J. W. Rees, Laboratory for Mycobacterial Research, National Institute for Medical Research, London, U.K., as part of the Immunology of Leprosy (IMMLEP) arm of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), with the main objective of establishing a bank of *M. leprae* sufficient for leprosy projects worldwide, including efforts to develop a specific vaccine for human trials (<sup>3</sup>). The protocol included the submission to Oxford of a wide range of tissues for histopathological examination from all animals sacrificed (<sup>1</sup>). This invariably included right and left main