Dr. Nelson, *et al.*'s Response

TO THE EDITOR:

We are interested in learning of the intriguing experiments reported by Converse, *et al.* (2), which examine the effects *in vitro* of various doses of cimetidine on lymphocyte transformation (LT) responses to *Mycobacterium leprae* and the generation of suppressor factors by lymphocytes stimulated with *M. leprae* in the presence or absence of cimetidine.

The *in vivo* studies we reported (1) are in agreement with the experiments reported by

Converse, *et al.*, in that no effect of cimetidine was shown in either study on the LT responses to *M. leprae*. However, Converse, *et al.* reported that cimetidine, especially in the lowest doses studied, was able to inhibit or reverse the release of suppressor factors from peripheral blood mononuclear cells of lepromatous patients when cultured with *M. leprae* antigens. These latter results are claimed to be in conflict with our *in vivo* studies.

However, it may not be possible to compare the two studies directly for several reasons. First, our studies were done in two groups of patients with well-characterized multibacillary leprosy (LL or BL) who had active disease or inactive treated disease. The studies reported by Converse, *et al.* were entirely *in vitro*. Peripheral blood mononuclear cells were exposed to various doses of cimetidine, and suppressor factors were measured after exposure to *M. leprae*. The authors quite arbitrarily characterized the responses into "high," "moderate," and "low or none." It is not possible to predict whether this *in vitro* effect of cimetidine, if it can be quantitated reproducibly, has any clinical relevance to the therapy of patients with leprosy, or even if it would be detectable in an *in vivo* study.

Secondly, our studies involved different types of patients. Converse, *et al.* studied six tuberculoid and six lepromatous patients, none of whom had experienced erythema nodosum leprosum (ENL) reactions. The patients from Ethiopia were not well described other than that they had long-term-treated disease without a history of reaction. They had been classified clinically by experienced leprologists and, in some cases, histopathologically.

We studied only multibacillary cases, but all of the inactive cases in our study had a history of having had a high bacterial index (BI) on skin smear and a well-characterized ENL reaction. All of the active multibacillary cases in our study were classified histopathologically as well as clinically by experienced leprologists. None of the active cases were experiencing reaction at the time of the study, nor had they had any reactions within at least 30 days. Converse, *et al.* suggest that patients with a history of having had an ENL reaction might respond differently to the immunomodulatory effects of a drug like cimetidine. Although patients may behave differently immunologically while they are undergoing or being treated for a reaction, we feel it is unlikely that they will continue to respond differently after their reaction has subsided in comparison to other patients of a similar leprosy class, bacterial load, and treatment status. We selected inactive lepromatous cases based upon their having had a high bacterial load in skin smear and an ENL reaction, in addition to their clinical classification by an experienced leprologist, to be certain that our patients had well-characterized lepromatous disease, since not all patients in Chiang Mai had been classified histologically until recently. Since none of the patients reported by Converse, *et al.* had reactions, it is entirely possible that these results are only applicable to a subset of lepromatous patients (i.e., those without reactions) or, alternatively, that some of the cases in their study had been misclassified.

Finally, we agree that it is possible that a different dosage regimen or duration of therapy with cimetidine might have some immunopotentiating effect in patients with multibacillary leprosy. Patients with active leprosy in our study were given cimetidine 400 mg four times a day, a dose similar to that used for ulcer therapy. The data of Converse, *et al.* [2], as well as others in the literature, suggest that the immunological effects of cimetidine are not dose related. Generally, immunological effects of the drug are more marked with smaller doses of the drug than that usually used for ulcer therapy. However, the studies recently reported by Jin, *et al.* [3] suggest that doses of 50 mg/kg of cimetidine were most active in inhibiting the generation of suppressor cells in a murine model. Mathur, *et al.* [5] recently reported no measurable effect of cimetidine when used with dapsone and rifampin chemotherapy in eight patients with lepromatous leprosy. This study confirms our *in vivo* results.

We agree with Converse, *et al.* [2] that it is possible that cimetidine or other pharmacological agents might be a useful adjunct in the treatment of leprosy in conjunction with effective chemotherapeutic agents. The reported immunological effects

of cimetidine in patients with chronic mucocutaneous candidiasis ([4]), and common variable hypogammaglobulinemia ([6]), gives cause for hope that the drug will also have some salutory effects in patients with lepromatous leprosy. However, if a clinically useful effect of cimetidine is to be demonstrated, it will be necessary to do so by *in vivo* study.

Another reason for studying the drug in a clinical trial, as we have done, is that cimetidine is a drug that is already licensed and very commonly used worldwide. We were interested to determine if the drug, used in doses commonly given to suppress gastric acid secretion, would have any adverse immunological effects in leprosy patients. In our study no effects, adverse or otherwise, were detected.

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