Response to "Topical Phenytoin in Diabetic Foot Ulcers"

We read with interest the report by Muthukumarasamy et al. (1), in which the authors concluded that topical phenytoin may promote healing of diabetic foot ulcers. However, we are concerned that their conclusions do not seem to be justified on the basis of the data reported.

Because subjects with vascular disease were excluded, it would appear that this study is concerned mainly with the treatment of neuropathic foot ulceration. We are disappointed that the patients were not randomized to the treatment or control group, and the strength of this study is diminished further by the fact that it was not blinded. The problems associated with nonrandomized open trials in the assessment of new treatments is well recognized (2). Furthermore, Table 1 of the article shows the control subjects to have had larger ulcers to begin with. (Perhaps this is a typographical error?) A randomized, placebo-controlled, double-blind trial is necessary to prove that topical phenytoin is indeed effective in healing neuropathic foot ulcers.

Finally, we cannot share the optimism expressed by the authors for the usefulness of topical phenytoin in rural areas where ready access to hospitals or clinics is not available. In their study, the subjects were treated in a hospital where bed rest is usually part of treatment in addition to daily dressings and prompt antibiotic therapy. It is not justified to extrapolate from the findings of this study to a rural setting where it is quite likely that patients with insensitive feet will walk on their ulcers and aggravate their problem; besides, they will not receive optimal foot care or antibiotic therapy. Thus, we fear that in such situations a diabetic patient with neuropathic ulceration is more likely to lose his limb, regardless of whether he receives topical phenytoin. We believe that in such a setting, amputations due to neuropathic ulcers may be reduced by identifying those at risk, teaching these individuals how to protect their feet, and by establishing a mechanism for early referral to a hospital or clinic (3).

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Reply

We appreciate the interest shown in our paper and the careful reading it has been given.

Drs. Kumar and Boulton are correct to point out that our study is concerned mainly with the treatment of neuropathic foot ulceration. This, of course, does not exclude some small vessel involvement by the diabetic process as both a contributor to the neuropathic process and to the failure of a skin ulceration to heal. The prominent neovascularization seen with phenytoin treatment on the light and electron microscopic examination of the biopsies of the patients' ulcers is of interest and encouraging in this respect.

The authors are also correct to point out that there is a typographical error in Table 1. For "Initial ulcer size (cm^2)" in the "Control" column, the number should be "10," and not "20." In fact, the two groups, as can be seen from the Table, were matched in all respects, making our study quite strong. Matching with respect to a variety of factors such as ulcer size, age, sex, metabolic and nutritional status and ulcer chronicity is critical to conducting an interpretable, reliable study of the healing of skin ulcers, especially in patients with less than optimal access to good therapeutic and preventive health care services.

We are well aware of the dangers of open trials in the assessment of new, and not-so-new, therapeutic modalities and with the advantages of randomization and blinding of both patient and observer. Careful matching of patients is a reasonable alternative in studies such as ours, where the sample size is relatively small. Uniform control of diabetic status and removal of variables related to infection also are crucial. Secondly, the planimetry was, in effect, blind. The clinical observations could not be blinded because it is very difficult to remove all traces of phenytoin powder prior to each observation and the wounds are so clearly different after three to four days that true blinding is impossible to achieve. Just to say a trial is "blind," when it really cannot be so, is misleading in itself. As a double-check on the validity of our conclusions in this trial, biopsies were submitted to a pathologist for blind evaluation. As the paper points out, his conclusions were supportive of both the evidence provided by the ulcer area measurements during treatment and the clinical impressions.

Placebo control in wound healing trials is problematic. We are not aware of

a true placebo powder that can be applied to wounds. Even a chemically or biologically inert powder may have irritant effects in an ulcer that could promote or hinder healing. Some have argued that dermatologic bases could serve as inert comparisons, but they are not necessarily inert either, and they can interfere with the action of the agent to be tested.

Finally, we should point out that we said in our paper that "Phenytoin should prove especially useful in rural areas where daily attendance at clinic or hospital is not possible." The emphasis is on the "should." We quite agree that proper preventive foot care is important for diabetic patients, and we do not make the claim that phenytoin replaces the need for antibiotics, as the letter implies. Both preventive care and ulcer treatment need to be available in rural, poor areas. Consistent with this, we do state that phenytoin's low cost, ease of use, and safety are important features for use in rural areas where poverty is a constant companion—and indeed they are. Rather substantial experience with phenytoin in different parts of the world, as documented in some of the references in our paper, as well as others (personal communications) since, indicates that neither strict bedrest nor daily dressing changes are necessary with topical phenytoin therapy. We feel that our "should" merits further evaluation in the rural setting.

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Measuring Subjective Symptoms

We read with interest the article by Tandan et al. (1) on the subject of topical capsaicin in painful diabetic neuropathy. They reported that no difference was found in visual analogue pain scores between the capsaicin- and placebo-treated groups, but those who applied capsaicin received a more favorable evaluation by their physicians. They also reported improvement or cure of painful symptoms in almost half the patients who subsequently took part in an open-label study. Despite the lack of subjective improvement, and based on the physician's evaluation of the patients and the results from the open-label study, the authors concluded that capsaicin may be of value in treating patients with painful diabetic neuropathy.

According to Huskisson (2), "Pain is a personal psychological experience and an observer can play no legitimate part in its direct measurement." Prospective double-blind studies using visual analogue pain or symptom score scales have been suggested as the appropriate methods to evaluate new treatments (3,4). In view of these recommendations, failure of subjective improvement should be interpreted as a negative finding, and the physician's global evaluation should not be considered as a valid endpoint. Similarly, results from open-label studies, given the placebo effect and the lack of proper control, cannot be regarded as surrogates for positive efficacy of new treatments of highly subjective symptoms—such as pain.

Therefore, we think that the conclusions of this otherwise interesting study are not supported by the results, and, in agreement with the authors, we believe that further studies are needed to clarify the efficacy of capsaicin in painful diabetic neuropathy.

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Semantics of Plasma Glucose Thresholds for Counterregulatory Responses

Webster's dictionary defines *threshold* as "the point at which a physiologic or psychologic effect begins to be produced" (1).

Thus, if during decrements in plasma glucose, a lower than normal glucose level is required to cause a response, then the plasma glucose (or glycemic) threshold for that response is lowered or reduced. Conversely, if higher than normal glucose levels are required to elicit a response, then the glucose threshold for that response is higher or increased. Therefore, use of the opposite terminology (e.g., lower glucose level equals