Neuron-specific Enolase-immunoreactive Fibres in Uremic Patients

Sir,

We have read with interest the recent study by M. Ståhle-Bäckdahl (1), in particular the immunohistochemical findings in patients with uremic pruritus who were undergoing maintenance haemodialysis. The author found a striking difference in the histotopographical distribution of neuron-specific enolase (NSE)-immunoreactive skin nerve terminals when comparing haemodialysed patients and control volunteers. Specifically, NSE-positive fibres were observed to enter and sprout throughout the epidermis in all patients, whereas they could be detected only in the stratum basale of the healthy controls. Such findings would suggest an anatomical explanation for uremic pruritus, although NSE intra-epidermal immunoreactivity was found, irrespective of itching (2, 3).

We would like to report results on NSE skin immunoreactivity in 24 patients and 10 control subjects, which are at variance with these observations. We could observe a pattern of intra-epidermal 'sprouting' of NSE-positive varicose nerve endings, as described by M. Ståhle-Bäckdahl and co-workers, in only 3 patients. In a few of the remaining patients, isolated epidermal fine positive terminals were occasionally detected. No difference in the distribution of dermal NSE immunoreactivity between uremic patients and controls was seen. However, we did find a certain reduction in the total number and intensity of NSE-stained fibres in the uraemic group, compared with the control group. Interestingly, in agreement with previous reports (4), we could observe sporadic NSE-immunoreactive free nerve endings also in the epidermis of control samples collected from various body areas (Fig. 1). Furthermore, intra-epidermal free nerve endings have been observed by other authors, not only in lesional skin (5, 6) but also in normal specimens (7).

In conclusion, these data would suggest that it is

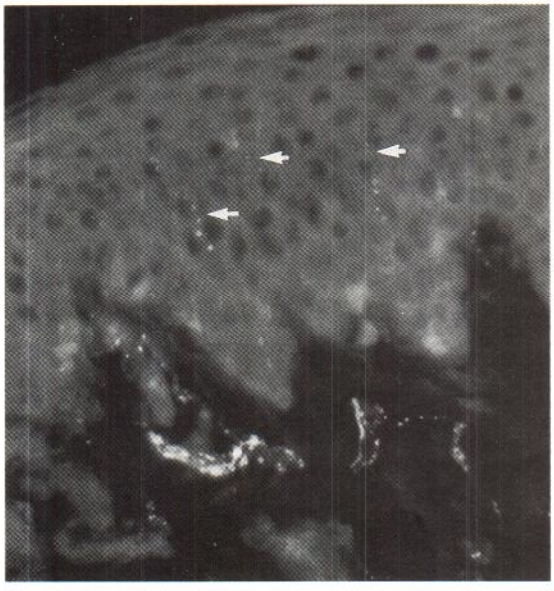

Fig. 1. Normal skin: NSE-immunoreactive fibres (*arrows*) in the epidermis (×400).

difficult to correlate intra-epidermal NSE-containing fibres to uremic pruritus. Nevertheless, the minor changes in cutaneous innervation observed in the present study might be related to distal axonopathy, which occurs frequently in uremic patients (8).

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Response to the letter by Fantini et al.

Sir,

The present study by Fantini et al., "Neuron-Specific Enolase-Immunoreactive Fibres in Uremic Patients", questions our results published in *Neuroscience Letters*, 99 (1989) 281–286 (Johansson et al., "Intraepidermal Neuron-Specific Enolase (NSE)-Immunoreactive Nerve Fibres: Evidence for Sprouting in Uremic Patients on Maintenance Hemodialysis"). Since the letter presently submitted to Acta Dermato-Venereologica does not contain information regarding immunogen or antibody employed, site of excision, fixation, immunohistochemistry, etc., it is, of course, very difficult for us to make a correct comparison of the two studies. Nevertheless, we would like to comment upon their interesting data:

In accordance with the Italian group, we did not report any difference in the dermal distribution between uremic patients and controls. Fantini et al., however, find a certain reduction in the total number and intensity of neuron-specific enolase stained fibres in the uremic as compared to the control group. It is not obvious where this reduction was seen, however, taken from their text it could be the epidermis or the entire skin. At the same time they also report intraepidermal sprouting, however only in three patients (not in the normals), and in a few of

the remaining patients isolated epidermal thin positive terminals were occasionally detected. Again, as these two studies were most probably done with different types of antibodies generated and against different types of neuron-specific enolases, it is naturally very difficult for us to make a true comparative evaluation. Finally, also the possibility of differences in sensitivity and detectability has to be taken into consideration, an issue many times addressed in the field of neuroscience, and recently by us in dermatology (cf. Ljungberg & Johansson, "Immunohistochemistry in Dermatology with Special Reference to Neuronal Markers: Methodological Aspects, Sensitivity and Detectability", *Histochemical Journal*, 1990, to be submitted).

The authors furthermore report the observation of neuron-specific enolase immunoreactive free nerve endings in the epidermis of *control* samples, supported by their photomicrograph. It is well-known, from several studies, that neuron-specific enolase will stain nerve fibres in the basal parts of the epidermis (also reported by us). The authors give no information, if any care was taken to examine the consecutive 'mirror-image' sectional plane, to rule out the possibility that fibres observed within the epidermis were not merely following, e.g., a dermal papilla present on the next section. Regarding findings from other types of *lesional* skin, we can also support this by mentioning observations from other types of itching diseases, which seem to be in parallel with the findings from uremic pruritus (most recently reported at the international conference on *"Neural Regeneration and Transplantation – The Morphological and Functional Bases"*, Singapore, February 11–14, 1990 (Johansson et al., "Evidence for Sprouting of Neuron-Specific Enolase (NSE)-Immunoreactive Nerve Fibers in Uremic Patients on Maintenance Hemodialysis" (abstr.))).

It may be mentioned, that since our first study was published, we have continued these investigations, employing other types of antigens/antibodies, and our preliminary observations from such studies support our own original findings, however, as the material is too small yet, it is not possible to publish these data here.

Perhaps all types of pruritic lesions will show the same type of neuronal change, namely sprouting of nerve fibres throughout the upper layers of the skin, thus, producing a situation where nerve fibres or the free nerve ending type will be very close to any kind of physical or chemical interaction with the surrounding universe? Only future studies, like the above-mentioned ones, can solve this question, and we strongly look forward to the publication of a full paper from Fantini and colleagues!

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