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In Reply.—We would like to comment on the letter of Doctor Chrubasik, as this provides an excellent forum for bringing forth a number of specific issues.

First, in spite of what appears to be extensive citations, the basic animal experiments conducted prior to the application of intrathecal (IT) or epidural somatostatin (SST) in humans were by any index inadequate and insufficient. Only two studies, one in dogs and one in rats, were conducted, and they provide only limited information. Thus, as we read that literature, the intrathecal dog experiments only included one animal that received IT SST (at total of 30 mg over a period of 3 h) under anesthesia, and which was killed immediately thereafter. This experimental preparation precludes assessment of behavior, analgesia, and motor function. Further, spinal cord histology cannot be assessed for pathological changes due to the abbreviated period of survival. The situation may be somewhat better regarding epidural administration. Thus, in the same paper, chronic epidural infusion study in dogs was described, but there is neither information as to the infusion volume nor evidence that the pathological analysis was carried out in a blinded fashion, nor is any representative histology presented with which the saline and drug treated animals may be compared. More importantly, in those animals in which epidural infusion occurred and that were allowed to survive, there is no systematic description of animal behavior. Interestingly, in light of the proposed use of the drug, no apparent efforts were made to assess changes in the pain response. Thus, the doses of the drug employed and alleged to be safe may not have been pharmacologically active. In rat experiments, only one behavioral endpoint (tail pressure) was assessed. Ten micrograms SST IT increased the tolerated pressure from "13.4" to "18.5" (arbitrary units) only between 5 and 10 min after SST administration. However, 29 µg SST IT caused acute death due to respiratory arrest in four out of six rats. Thus, these studies only provide evidence for a mild short-lasting analgesia possibly confounded with motor dysfunction and high toxicity of SST with a small margin of safety and no spinal cord histology. In that regard, all of the animal data we have presented are in essential agreement with Doctor Chrubasik's own data.

We agree that there may be species differences with regard to the susceptibility to toxic and analgesic effects of SST. In order to evaluate possible species differences, we conducted, in addition to studies in rats, further studies in cats and mice, evaluating analgesia, motor function, behavior, and spinal cord histology following IT SST. Results show that the three species do not qualitatively differ with regard to SST toxicity, which occurs at concentrations of 10 µg/µl of IT SST and that changes in pain sensitivity, if present, only occur in the toxic range.

Due to the fact that SST at low dosages was ineffective in our animal studies, higher dosages than those apparently used in humans had to be employed. It is interesting to note, however, that dosages employed in humans in recent clinical studies are far higher than those initially reported. Thus, doses of up to almost 10,000 µg of SST epidurally have been infused intraoperatively over unspecified time periods for abdominal procedures. Cumulative dosing may be significant, for with regard to receptor action, toxicity is best expressed as a function of local concentration. Of similar interest is the reported relative clinical potency of SST given epidurally and intrathecal. Thus, in human experiments, equal doses (250 µg) were administered as a bolus IT and epidurally with subsequent infusions of 10 and 125 µg/h, respectively. The reported equivalency of the resulting analgesia is surprising, given that the reported CSF transfer of SST is 2/10,000 (0.02%) of the epidural dose. The reason for this similarity between the effects reported with intrathecal and epidural doses and the progressively increasing dose requirements being reported in subsequent publications has never been addressed. We, however, would note that should this tendency continue, there will be little difference between these doses and those reported toxic even in the animal models.

Secondly, we raise the issue of which molecule is actually being examined. In 1985, Doctor Chrubasik kindly provided us with vials of "SST." We found the content to contain approximately 3.5 mg of material and about 250-275 µg of SST-like immunoreactivity. We do not know the identity of this excess material, but it is not responsible for the toxicity we have observed. As we have documented in all publications, the peptide we have examined is the 1-14 cyclized SST form. We have employed SST from different manufacturers, we have examined the chemical identity to the extent of having assessed its immunoreactivity and its elution on an HPLC column, and we have indicated the vehicle (saline). Outcome was similar in all cases. In none of the studies reported by Doctor Chrubasik et al. in rat, dog, or humans is there any indication of the identity of the molecule, purity

of the material in the vis, or the vehicle in which the drug was injected. Such information is fundamental in trying to assess the characteristics of drug action.

Finally, we do not question the good intention of relieving pain in suffering patients, but we are fundamentally concerned about the impression left by the sequence of events leading to the clinical use of spinal SST or any such agent in humans. SST was given to rats and short-lasting analgesia was observed, while at slightly higher doses the animal died acutely. Moreover, there was other literature that emphasized possible toxicity of SST administered into the neuraxis. Yet, 1 and 2 yr preceding the publication of the rat and dog studies, a paper appeared reporting both epidural and intrathecal data. All of this occurred without addressing the fundamental issue of toxicity observed in animals. While there may be true differences between the response to certain drugs in human and non-human models, it is our position that the bulk of evidence shows marked similarity. Thus, in a novel situation, the burden of proof regarding toxicity must be borne by the investigator-clinician, addressed and resolved before proceeding to humans. That toxicity has not been reported in humans to date is no excuse for allowing such studies in patients where adequate alternatives exist.

As outlined, the purpose of our study was to provide data that were lacking as to the effects of IT SST in animals. Results from rat, cat, and mouse experiments indicate a high toxicity of IT SST across species mediated by an unknown mechanism, and a lack of analgesic effects of IT SST in the non-toxic range. In our opinion, animal data at this time provide no basis to justify the spinal application of SST in humans.

D. M. GAUMANN, M.D.
Resident in Critical Care Service
Department of Anesthesiology

T. L. YAKSH, Ph.D.
Professor of Pharmacology
Laboratory of Neurosurgical Research
Mayo Clinic
Rochester, Minnesota 55905

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