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# Intrathecal and Epidural Somatostatin for Patients with Cancer

## Analgesic Effects and Postmortem Neuropathologic Investigations of Spinal Cord and Nerve Roots

Peter Mollenholt, M.D., Ph.D.,\* Narinder Rawal, M.D., Ph.D.,\* Torsten Gordh, Jr., M.D., Ph.D.,†  
Yngve Olsson, M.D., Ph.D.‡

**Background:** The antinociceptive effects of somatostatin (SST) after intrathecal administration in rats and dogs and analgesic effects after intrathecal or epidural administration in humans were described previously. In this study, we seek to determine the efficacy of SST in cancer pain management and its potential neurotoxicity.

**Methods:** Eight patients with intractable cancer pain were studied. Pain intensity was assessed by patients on a four-grade scale (severe, moderate, mild, none). Additional analgesic drug requirements before and concomitant with SST treatment were used to evaluate the pain relief and assessed on a four-grade scale (poor, fair, good, or excellent). Spinal cords of five patients were autopsied.

**Results:** The mean duration of SST treatment was 11.3 days. The mean daily dose was 1,252 µg (range 250–3,000 µg). In six patients the pain relief was rated "excellent" or "good" and in two patients it was assessed "poor" or "fair". None of the

patients demonstrated any evidence of neurologic deficit related to the SST treatment. At autopsy, two patients exhibited a moderate demyelination of some spinal dorsal roots and one patient also had a slight demyelination of the dorsal columns.

**Conclusions:** SST administered intrathecally and epidurally was an effective analgesic in patients with terminal cancer. Because the described neuropathologic changes could also be cancer-related or result from chemotherapy or radiation therapy we suggest that further judicious use of SST is justified in this category of patients, if their pain remains unrelieved despite large doses of opioid analgesics. (Key words: Anesthetic techniques: epidural; intrathecal. Pain: cancer. Peptides: somatostatin. Spinal cord: neurotoxicity.)

SOMATOSTATIN (SST) is a tetradecapeptide originally discovered by its ability to inhibit growth hormone release from the pituitary.<sup>1</sup> Though extensively distributed in most organs of vertebrates, SST displays specific and selective functions depending on its localization.<sup>2</sup> The existence of somatostatinergic, antinociceptive mechanisms in the spinal cord was first indirectly suggested by Terenius<sup>3</sup> in an *in vitro* study of the endogenous endorphin antagonist function of SST. The somatostatinergic system includes afferent axons terminating in dorsal horn,<sup>4</sup> spinal interneurons,<sup>5</sup> and descending and ascending pathways.<sup>6,7</sup> The presence of SST in the periaqueductal gray,<sup>8</sup> in substantia gelatinosa of the spinal cord, and in descending, pain-controlling systems from the brain stem<sup>9</sup> further suggests the existence of somatostatinergic pain inhibiting mechanisms. At a single-cell level, SST selectively depresses the nociceptive responses of dorsal horn neurons in an *in vivo* superfusion model.<sup>10</sup>

The analgesic potential of synthetic peptides like SST and its analogs,<sup>11</sup> dynorphin 1–13,<sup>12</sup> and salmon calcitonin<sup>13</sup> has been reported previously. Observations of neurotoxicity in experimental rat models after large

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\* Consultant in Anesthesiology, Department of Anesthesiology and Intensive Care, Örebro Medical Center Hospital.

† Consultant in Anesthesiology, Department of Anesthesiology, Uppsala University.

‡ Professor, Laboratory of Neuropathology, Institute of Pathology, Uppsala University.

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Address reprint requests to Dr. Mollenholt: Department of Anesthesiology, Oregon Health Sciences University, UHS-2, 3181 S.W. Sam Jackson Park Road, Portland, Oregon 97201-3098.

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intrathecal doses of these compounds<sup>14-17</sup> have hitherto precluded their widespread clinical use. However, it appears that rats are more sensitive to the toxic effects of the peptides than are other species, such as goats,<sup>18</sup> guinea pigs<sup>19</sup> and humans, because clinical postoperative pain trials with SST have proceeded apparently without incident.<sup>20</sup> The intrathecal and epidural administration of SST in humans became a subject of controversy on the issue of a potential neurotoxicity and ischemia of the spinal cord.<sup>21,22</sup> Furthermore, the statements on analgesic effects of epidural SST in postoperative pain have been challenged.<sup>23</sup>

The current clinical investigation was designed to extend our previous experimental work on dose-dependent antinociception, spinal vasomotor effects, and neurotoxicity of SST in rats<sup>24,25</sup> and guinea pigs.<sup>19</sup> The two aims of this study were to evaluate the analgesic effects of epidural or intrathecal SST in patients with terminal cancer whose pain relief was poor despite large doses of opioids and to study postmortem histopathologic changes in the spinal cord and nerve roots after a prolonged infusion of SST.

## Materials and Methods

Patients with terminal cancer and a life-expectancy of about 2–6 weeks who had intractable pain resulting from the malignant disease were selected by the referring physicians to be included in the study which was approved by the local Ethics Committee and the Swedish Drug Agency. Only patients whose pain relief was poor despite large doses of opioids were accepted. Patients with diabetes mellitus, neurologic deficits and those less than 30 yr of age were excluded. Informed consent was obtained from the patient or family. The experimental nature of the perispinal administration of SST was emphasized and the risk of toxicity explained.

The patients were asked to define (if possible) their sensation of pain as throbbing or aching (somatic pain) or burning (neuropathic pain). Pain intensity was then assessed by patients on a four-grade scale (severe, moderate, mild, none) before SST treatment and daily during the treatment. The SST dosages were adjusted in response to the patients' assessment of their pain. If the analgesia after SST administration was still inadequate (*i.e.*, "moderate" or "severe" pain persisted), the nurse was instructed to administer additional analgesics according to departmental routine (pain intensity "none" or "mild" being thus the departmental

treatment endpoint). The data on these analgesic drug requirements concomitant with SST treatment were compiled and subsequently used for additional assessment of pain relief on a scale poor, fair, good or excellent. Thus analgesia was graded "poor" when pain was unrelieved despite frequent administration of opioid analgesics; "fair" reflected pain which could be relieved by large doses of parenteral opioids (> 50 mg intravenous morphine daily); "good" represented pain relieved by oral morphine or low dose parenteral morphine (< 20 mg daily); and "excellent" was scored when the patient reported no pain after intrathecal or epidural SST.

To avoid bias we (P.M. and N.R.) made no attempt to influence or standardize the rescue opioid medication administered by the ward nurse. The daily activity before and after initiation of SST therapy was assessed by the nursing staff and recorded according to the protocol. Thus the physical activity was graded: confined to bed, mobile in bed, in wheelchair or able to walk. In parallel, the mental status was graded: confused, somnolent or lucid. Each patient served as his or her own control.

### *Preparation For Drug Administration*

Before SST administration the patients were transferred to the intensive care unit. The patients were randomized to two groups. Alternate patients were assigned for either epidural or intrathecal administration of SST. An intravenous infusion was started and EKG monitored continuously. Epidural or intrathecal block was performed in the usual manner using a 20-G Tuohy needle and a 22-G epidural catheter.

SST acetate (Ferring AB, Malmö, Sweden), available as a preservative-free lyophilic powder, was reconstituted immediately before injection. After reconstitution, SST is stable for 48 h. After a bolus dose of 250 µg SST (dissolved in 5 ml saline), a continuous infusion of 2 ml/h (5–60 µg/ml) was given through a portable pump (Deltec, Pharmacia). If pain relief was inadequate, the SST dose was increased in increments of 250 µg. The maximal daily dose was arbitrarily set at 3,000 µg.

After SST administration, blood pressure, pulse, and respiratory rate were monitored every 5 min for 30 min and every 15 min for an additional 2 h. The patients were returned to their wards after about 2.5 h of observation in the intensive care unit. The patients then were monitored according to ward routine. Neurologic examination was performed before the patients joined

**Table 1. Demographics and Catheter Locations**

Patient No.	Age (yr)	Sex	Primary Lesion	Type/Site of Pain	Site of Insertion
1	79	M	Liver carcinoma	Left shoulder and arm*	EP/T9-10
2	52	F	Breast carcinoma	Burning/chest	IT/L2-3
3	41	F	Kidney carcinoma	Aching/pelvis and right leg	EP/L3-4
4	38	F	Breast carcinoma	Aching/left shoulder, abdomen; burning/sacrum, right leg	IT/L3-4
5	71	M	Pulmonary carcinoma (small cell)	Aching/lumbar spine, ribs	EP/T12-L1
6	74	M	Melanoma	Burning/right arm, axilla; aching/coccyx	IT/L1-2
7	58	F	Breast carcinoma	Burning/right shoulder; aching/ back and pelvis	IT/L1-2
8	30	F	Retroperitoneal sarcoma	Aching/buring/pelvis, right leg, and back	EP/L1-2

EP = epidural; IT = intrathecal.

\* Data on type of pain not available (patient confused).

the study, immediately after SST administration and twice weekly afterward. The examination included assessment of sensation by pinprick test distally and proximally on each extremity and bilaterally over the chest and abdomen. The gross strength was evaluated in flexors and extensors. Weakness or loss of reflexes was noted if present. The ward nurses were instructed to contact one of the authors (P.M. or N.R.) if there was any new clinical evidence of neurologic deficit (muscular weakness or numbness of skin) or respiratory depression. Respiratory depression was defined as respiratory rate  $\leq 10$ /min.

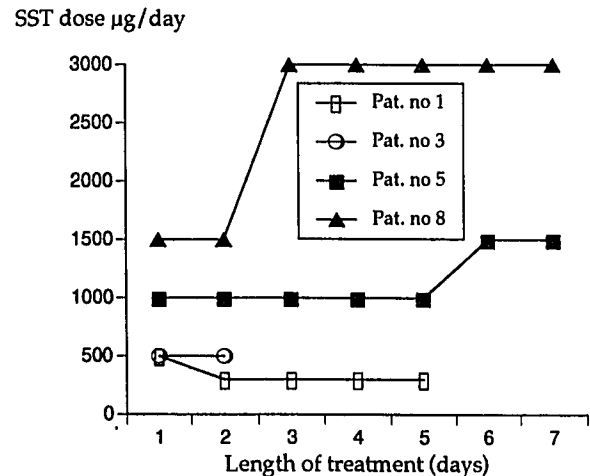
#### Histopathologic Analysis

At autopsy, the spinal cords were excised and immersed into a neutral buffered 3.7% formaldehyde solution. Samples from the cervical, thoracic and lumbar segments of each spinal cord were embedded in paraffin; sectioned; and stained with hematoxylin, eosin, and Luxol fast blue. The pathologist was unaware of the kind of treatment until the study had been completed.

#### Results

Eight patients (three males and five females), aged 30-79 (mean 55.3) yr were treated during the study period (table 1). The types and sites of primary lesion and of pain are shown in table 1. Patients 1-7 had pain associated with cancer and skeletal metastases. Patient 8 had pain localized to pelvis and back and believed

to be caused by sarcomatous invasion of the lumbar spine and sacrum. Patient 2 had primarily neuropathic pain, and patients 3 and 5 had primarily somatic pain. Patients 4 and 6-8 had both somatic and neuropathic pain. The mean duration of treatment was 11.3 (range 2-30) days; it was  $5.2 \pm 2.3$  days in the epidural group and  $17.5 \pm 11.9$  days in the intrathecal group. All patients received a bolus dose of 250  $\mu\text{g}$  followed by varying doses of SST given as continuous infusion. The mean daily dose irrespective of the route of administration was 1,252 (range 250-3,000)  $\mu\text{g}$ . It was 1,366 (range 300-3,000)  $\mu\text{g}$  in the epidural group (fig. 1) and 1,217 (range 250-2,000)  $\mu\text{g}$  in the intrathecal



**Fig. 1.** Time plot of epidural somatostatin dose requirements during study.

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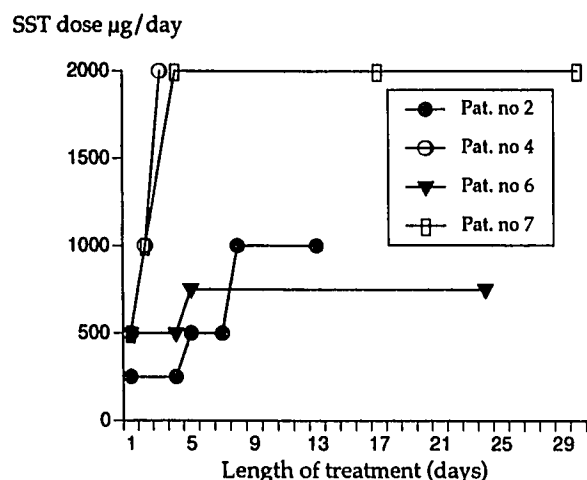


Fig. 2. Time plot of intrathecal somatostatin dose requirements during study.

group (fig. 2). In patients 1–4, 6, and 7, the pain relief after SST treatment was rated “excellent” or “good” (table 2). The onset of analgesia was noted within 5–10 min. after administration of intrathecal or epidural bolus dose.

All patients required escalating doses of SST (figs. 1 and 2). In patient 5 the analgesic response was graded

“poor” and in patient 8 it was “fair” (table 2). The behavioral variables of analgesic response are summarized in table 3. Patients 1–3 and 6 increased their physical activity and except for patients 2 and 5, the mental status of the patients improved.

Patients 2, 7, and 8 received radiation therapy in the spinal cord area. In two of these patients (2 and 8), however, radiation therapy was stopped about 2 weeks before SST treatment. Patient 7 received radiation therapy concomitantly with SST treatment. In addition, patients 2 and 7 were treated with chemotherapy before and concomitant with intrathecal SST administration. In patient 8 chemotherapy was stopped before starting epidural infusion of SST (table 4).

#### Technical Problems and Complications

There was no evidence of neurologic deficit or respiratory depression attributable to SST administration in any patient. Patient 2 became agitated and tremulous during the first night of SST treatment and was treated with repeated doses of 5 mg subcutaneous morphine (total 20 mg) (table 2) for possible morphine withdrawal symptoms. Approximately 48 h after initiation of SST administration the same patient experienced a burning pain sensation in her legs. SST infusion was

Table 2. Analgesic Requirements before and after Epidural or Intrathecal Somatostatin Treatment

Patient No.	Daily Analgesic Dose before SST Treatment	Daily Concomitant Analgesic Dose during SST Treatment	Response to Treatment
1	Ketobemidone,* 60 mg orally Ketobemidone, 20 mg im Paracetamole, 3 g orally	None	Excellent
2	Morphine, 500 mg iv	Morphine, 20 mg sc†	Good
3	Ketobemidone, 80 mg iv Methadone, 30 mg orally	None	Excellent
4	Morphine, 300 mg iv	Morphine, 20 mg sc‡	Good
5	Morphine, 40–60 mg sc Morphine, 160 mg orally Paracetamole, 6 g orally	Unaltered	Poor
6	Morphine, 60 mg orally Paracetamole, 4 g orally	Morphine, 0–20 mg orally Paracetamole, 1 g rectally	Good
7	Morphine, 10–30 mg sc Morphine, 600 mg orally Paracetamole, 3 g orally	Morphine, 180 mg orally Paracetamole, 3 g orally	Good
8	Morphine, 1500 mg orally Ketobemidone, 100 mg rectally	Morphine, 60 mg iv§	Fair

SST = somatostatin.

\* Ketobemidone is a synthetic opioid that is equipotent with morphine.

† This dose of morphine was used to treat withdrawal symptoms and not for pain relief.

‡ Intravenous morphine, 300 mg daily after removal of a dislodged intrathecal catheter.

§ Intravenous morphine, 200–1200 mg daily after the unintentional removal of the epidural catheter.

**Table 3. Patient Activity before and after Epidural or Intrathecal Somatostatin Treatment**

	Patient No.							
	1	2	3	4	5	6	7	8
Physical activity								
Confined to bed	X	X	X					
Mobile in bed	○*	○	○			X		⊗
In wheelchair							⊗	
Able to walk				⊗	⊗	○†		
Mental status								
Confused	X							
Somnolent			X	X		X	X	X
Lucid	○	⊗	○	○	⊗	○	○	○

X = activity before somatostatin (SST) treatment; ○ = activity during SST treatment.

\* Enabled to use left arm during SST treatment.

† Enabled to use right arm during SST treatment.

stopped and the intrathecal catheter withdrawn. However, intravenous morphine 500 mg daily failed to control her chest pain, and a second intrathecal catheter was inserted the following day. The analgesic response to intrathecal SST in this patient was good and there were no further complications. Patient 6 had nausea, headache, and vertigo during the last 4 or 5 days of the SST treatment. The intrathecal catheter was removed because infection was suggested. However, aerobic and anaerobic culture of CSF and blood showed no evidence of bacterial growth. In patient 4, the analgesic effect of intrathecal SST began to decrease after 24 h. After 3 days it was no longer possible to aspirate the CSF. The catheter was removed because of possible dislodgment. In patient 8, placement of epidural catheter was technically difficult and administration of even

small volumes of saline (< 5 ml) were painful. However, SST treatment could be continued by slow infusion rates. A tumor encroachment on the spinal canal was subsequently noted at autopsy.

#### *Histopathologic Findings*

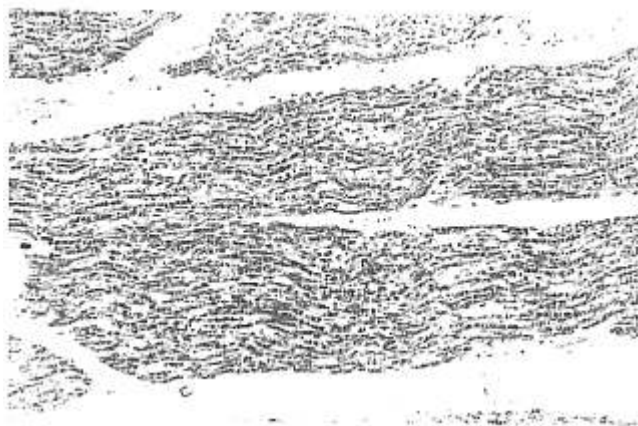
Postmortem observations of neuropathologic changes in the spinal cord after continuous SST infusion were made in five patients. No abnormalities were present in patients 1–3. Patient 7 exhibited lumbar and thoracic meningeal carcinomatosis and moderate degeneration of some dorsal roots within the cauda equina (fig. 3). The spinal cord was otherwise normal. Patient 8 had a sarcomatous tumor expanding into the lumbar spinal canal. She exhibited a slight degeneration of dorsal columns of cer-

**Table 4. Metastatic Site at Autopsy, Premortem Radiation/Chemotherapy, and Histopathologic Findings**

Patient No.	Tumor Invasion Site	Radiation Therapy (field)	Chemotherapy	Dorsal Root Degeneration	Dorsal Column Degeneration
1	Thoracic and lumbar vertebrae	15 Gy (left axilla)	None	—	—
2	Thoracic and lumbar vertebrae, dura mater	35 Gy (spine)	CMF, FML Adriamycin	—	—
3	Thoracic and lumbar vertebrae	36 Gy (pelvis)	None	—	—
7	Thoracic and lumbar vertebrae,	30 Gy (spine)	MMM, FML Farmorubicin	+	—
8	Lumbar vertebrae, dura mater	54 Gy (lumbar spine)	Methotrexate Dacarbazine Adriamycin	+	+

Patients 1, 3, and 8 received epidural somatostatin, whereas Patients 2 and 7 received intrathecal SST.

CMF = cyclophosphamide, methotrexate, fluorouracil; FML = fluorouracil, methotrexate, leucovorin; MMM = methotrexate, mitomycin, mitoxantron.



**Fig. 3.** High-power magnification of a longitudinal section through a dorsal spinal nerve root of patient 7. There is a slight loss of myelinated fibers and a moderate fragmentation of other fibers. Otherwise this root is normal in appearance. (Luxol fast blue stain.)

vical, thoracic and lumbar spinal cord (fig. 4). There was also a moderate degeneration of the lumbar dorsal roots with loss of myelinated fibers. A few mononuclear inflammatory cells were also present.

### Discussion

This study reports the analgesic action of epidural and intrathecal SST in a limited number of patients with terminal cancer. In the absence of clinical neurologic deficits the finding of spinal cord lesions in two patients emphasizes two issues pertinent to the spinal administration of synthetic peptides in patients with cancer: (1) the justifiability of clinical application of compounds that are potentially toxic in some and innocuous in other animal species and (2) the causes of neurodegenerative lesions in patients with advanced malignancy within the spinal canal.

On entering the study, many of the patients were oversedated and confused because of the large doses of opioids they had been receiving. Consequently, it was difficult to accurately assess the subjective pain experience before and after SST treatment. Also, the assessing nurses were not blinded as to the therapies that the patients were receiving. These evaluations could thus have been biased by their expectations. Nevertheless, SST treatment was associated with a discernible behavioral improvement (table 3). Furthermore, SST treatment was associated with a substantial reduction of daily opioid requirements indicating the analgesic action of the peptide (table 2).

However, as the treatment continued, seven patients required increasing doses of intrathecal and epidural SST. These dosages were roughly equal to or less than the dosages described previously in two studies of patients with terminal cancer (240–6,000  $\mu\text{g}$  daily).<sup>26,27</sup> It is unclear if the increasing dose requirement reflects tachyphylaxis<sup>28</sup> or the development of tolerance similar to the experimental desensitization to barrel rotation after repeated intracerebroventricular doses of SST in rats.<sup>17</sup> It should be pointed out that both the epidural and intrathecal SST doses had to be increased substantially. Interestingly, the mean daily epidural SST dose exceeded the intrathecal dose by only 149  $\mu\text{g}$  (11%). The equianalgesic ratio between intrathecal and epidural dose of morphine is believed to be in the range of 1:10–1:15.<sup>29</sup> In our study this difference was not apparent when epidural and intrathecal SST was administered. Thus a bolus injection of 250  $\mu\text{g}$  SST provided effective and prompt analgesia by both routes of administration. Because in an *in vivo* canine model the permeability of epidural SST into the intrathecal space was reported to be very low (0.02%)<sup>30</sup> one should expect the high epidural *versus* intrathecal dose ratio considering the thickness of the human dura<sup>31</sup> and the high molecular weight of SST (molecular weight 1,636 Da). However, such inferences may be misleading. Thus in human epidural morphine pharmacokinetic studies Sjöström *et al.*<sup>32</sup> estimated the fraction of an epidural bolus penetrating into the subarachnoid space to be 3.6%. Durant and Yaksh<sup>33</sup> estimated this fraction in dog to be 0.31%. As with opioids<sup>34</sup> and peptides<sup>35</sup> the pharmacokinetics of epidural SST are probably in-



**Fig. 4.** Low-power magnification of a transverse section of the spinal cord of patient 8. There is reduced staining of the medial parts of the dorsal columns. (Luxol fast blue stain.)

fluenced by the vascular transport *via* the arachnoid granulations and epidural venous plexuses. Because the fraction of the dose of exogenous peptide that ultimately reaches the receptor site in the dorsal horn of the spinal cord in humans is not known, the dose requirements for epidural and intrathecal SST remain to be defined.

In addition to the matter of potency and efficacy, the reports on "nonresponders" to the SST treatment focus on the issue of indications for intrathecal or epidural use of this peptide. Indeed, in the treatment of postoperative pain, the percentage of SST "nonresponsiveness" was as high as 35%.<sup>36</sup> Furthermore, SST appears less effective in patients with cancer who have superimposed acute or postoperative pain. It is interesting to note that in patient 6, SST provided good analgesia for melanoma-related pain in his right arm and axilla. However, when the patient fractured his coccyx after a fall SST was ineffective for coccygeal pain. A similar phenomenon was noted in patient 5 after rib fracture. Also, intrathecal or epidural SST did not provide effective analgesia in patient 4, who complained of postoperative pain after palliative oophorectomy (table 5). In these situations epidural or intrathecal SST appears inferior to intraspinal opioids. These findings are in keeping with those of a previous investigation.<sup>25</sup> The efficacy of SST in relieving somatic *versus* neuropathic pain remains unclear. Both patient 2 (who had a neuropathic, burning chest pain) and patient 3 (who had a severe, aching, somatic pain in her pelvis and right leg) experienced relief. Patients 7 and 8, who had meningeal carcinomatosis and previous palliative radiation therapy for carcinomatous neuropathy,<sup>37</sup> could

not separate the pain components on the basis of response to treatment.

To our knowledge, spinal cord histopathologic studies have not been performed after the intrathecal or epidural administration of SST in humans. In the course of this study, five patients or their families consented to a postmortem examination (table 4). Patients 7 and 8 exhibited a moderate degeneration of some dorsal roots. Patient 8 also had a slight degeneration of the dorsal columns. This latter lesion included cervical, thoracic, and lumbar spinal cord without any gradient of intensity toward the lumbar segment. In contrast to the posterior column demyelination in patient 8, the experimental neurotoxic lesions in SST-treated rats affected primarily the motoneurons stained with calcitonin gene-related peptide, a marker for motoneurons and primary afferent neurons. Furthermore, this effect of SST varied considerably depending on the distance from the injection site. Thus already at the midthoracic level, the rat spinal cord appeared normal.<sup>38</sup>

Two alternative hypotheses may explain our neuropathologic findings in two of five patients. First, the observed spinal cord lesions may be attributable to neurotoxic effects of SST. Under experimental conditions, large (40–100- $\mu$ g) intrathecal doses of SST resulted in vasoconstriction, neuronal degeneration, and necrosis in the rat spinal cord.<sup>15,16,39</sup> The ischemia was believed to be related to direct spinal interaction of SST with coexisting adrenergic transmitters such as norepinephrine and  $\gamma$ -aminobutyric acid.<sup>5</sup> Disruption of the vascular tone maintained by other peptides, such as substance P, which is distributed in parallel with SST, has been suggested,<sup>25</sup> as has vasoconstriction

**Table 5. Pain Intensity before and after Epidural or Intrathecal Somatostatin Treatment**

Patient No.	Degree of Pain before SST Treatment	Degree of Pain during SST Treatment	Reason for Stopping SST Treatment
1	Severe	None	Death
2	Severe	Mild	Death
3	Severe	None	Death
4	Severe	Initially none, later mild*	Premature dislodgement of catheter
5	Moderate/severe	Moderate†	Poor response
6	Severe	Mild‡	Headache and vertigo§
7	Severe	Mild	Death
8	Severe	Mild to moderate	Catheter removed (unintentionally)

SST = somatostatin.

\* Recent oophorectomy.

† Recent, multiple rib fractures.

‡ Concomitant coccygeal fracture.

§ Catheter removed due to unsubstantiated suspicion of intrathecal infection.

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caused by enhancement of the intermediolateral column cell function and sympathetic stimulation.<sup>14</sup> In the current investigation, the neuropathologic lesions were observed in the patients exposed to the largest total doses of the peptide, which is significant because the neurodegenerative effects of SST in rats after intrathecal administration are dose dependent.<sup>38</sup> However, none of our patients showed any evidence of neurologic deficit after the SST treatment. It should be borne in mind that the functional capacity of the nervous system may to a certain extent compensate for neuronal lesions. There are examples of illnesses in which the widespread neuronal degeneration may be detected histologically in the absence of neurologic deficits.<sup>40</sup>

In the second hypothesis, the posterior column degeneration and damage to the lumbar dorsal roots in these two patients represent the effects of a combination of malignant disease and iatrogenic factors. Indeed, if the spinal cord and dorsal roots had been compressed by meningeal carcinomatosis (patient 7) or direct tumor expansion (patient 8), posterior column and dorsal root demyelination could result. Thus direct effects of tumor encroachment of the spinal canal, distant effects of cancer, such as paraneoplastic myelopathy and neuropathy,<sup>41-43</sup> neurotoxic chemotherapy, and radiation therapy<sup>44,45</sup> all are likely to cause such widespread, diffuse neurodegenerative changes in the spinal cord (table 4). Consequently, it is difficult to determine if the histopathologic changes in our study may be attributed to neurotoxic effects of SST or any of the above-mentioned factors. We note that our histopathologic findings are quite similar to those reported by Coombs *et al.*<sup>46</sup> after chronic administration of intrathecal morphine for management of intractable cancer pain. In two of seven patients, posterior column degeneration that had not been observed clinically was noted. One of these patients had received previous radiation therapy toward the spinal cord. The authors concluded that the histopathologic changes (posterior column degeneration) were most likely caused by the malignant disease.<sup>46</sup>

In conclusion, SST administered intrathecally and epidurally was an effective analgesic in patients with terminal cancer. Superimposed acute pain caused by recent fractures or postoperative pain appeared to be less responsive to SST treatment. The epidural administration of SST was as effective as intrathecal administration. Although there was no clinical evidence of SST-related neurologic deficits some neuropathologic

changes were noted postmortem in two of five patients. These two patients also received the highest doses of SST. Considering that the therapeutic index of intrathecal and epidural SST cannot be established on the basis of this investigation it is difficult to advocate or discourage further clinical use of this experimental substance. However, because the lesions described in this study may well have been caused by the malignant disease process, chemotherapy, or radiation therapy, we suggest that the judicious epidural or intrathecal administration of SST appears justified in selected patients with terminal cancer in whom pain remains unrelieved despite large doses of opioid analgesics.

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