

## The Neuropsychologic Deterioration Seen in the Placebo Group May Have Been a Result of Rigorous Exclusion Criteria

*To the Editor:*—In “Clinical Trial of the Neuroprotectant Clomethiazole in Coronary Artery Bypass Graft Surgery: A Randomized Controlled Trial,” by Kong *et al.*,<sup>1</sup> the authors assessed neuropsychologic deterioration following bypass surgery with cardiopulmonary bypass. They are to be congratulated for the rigorous design of their experiment and their willingness to report a “negative” result. Their topic is so important to our patients that model articles such as this, no matter what the result, are of the utmost significance.

The authors monitored embolic load during surgery using Doppler ultrasound of the common carotid or middle cerebral artery. Using this measure, they found no difference between the embolic loads in the study and the control groups, nor, as noted, was the neuropsychologic outcome different between the groups.

The authors comment, however, that, “the [neuropsychological] deterioration seen in the placebo group was less than anticipated at the planning stage. This may have been a result of the rigorous exclusion criteria. As a result, the study may have been underpowered.” In other words, both groups had an equivalent and better than expected outcome.

If embolic load during coronary surgery using cardiopulmonary bypass is related to surgical technique, then this unexpectedly good

outcome may be related to the presence of Doppler ultrasound monitoring. At least one article has suggested that surgeons, in the presence of a device that monitors emboli, improve their technique in an effort to avoid creating these emboli.<sup>2</sup> I would say that this explanation is at least as compelling as the idea that the study was underpowered and that Clomethiazole actually is protective.

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*In Reply:*—Dr. Gage raises the important problem of the possible impact of intraoperative monitoring on the behavior of surgical teams. He suggests that transcranial doppler monitoring may have led to improved surgical technique and thus may explain the less than anticipated neuropsychologic deterioration after coronary artery bypass surgery in our trial.<sup>1</sup> He references a study in carotid endarterectomy in which the surgeons were able to listen to the transcranial doppler recordings of microembolic signals.<sup>2</sup> In our pilot work we, too, used to make the records audible to the surgeon, but we found that this caused alarm and was distracting. Only a research fellow with headphones was aware of the transcranial Doppler signals in theatre in the reported study.

However, there is the more general possibility that any form of monitoring may motivate the surgeon in a less specific way. Cardiac surgeons, aware of the evidence of a deleterious role for cerebral microemboli during coronary artery bypass grafting, have had their attention drawn to those surgical manipulations most closely related to the release of embolic material. Knowing a patient will be monitored may lead to even greater care being taken at these times.

It is important to recall early research on the importance of the impact of observation on behavior. Studies first published in the 1930s of the Hawthorne plant of Western Electric manipulated various conditions (*e.g.*, light levels, rest breaks), and each change resulted in an increase in productivity.<sup>3</sup> Productivity also increased on return to the original conditions. The effect has been interpreted as the impact of

the feeling of being studied and is typically referred to as “the Hawthorne effect.” The impact of observation and study in surgery and its impact on surgical behavior in general, raise important issues in the design of studies and the generalization of research findings.

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## Neuroprotective and Antiepileptic Activities of Ketamine in Nerve Agent Poisoning

*To the Editor:*—We read with interest the review by Ben Abraham *et al.* providing guidelines for the care of victims of bioterrorism, in the October issue of ANESTHESIOLOGY.<sup>1</sup> This article is an important contribution at a time when using a nerve agent such as sarin, even in the civilian context, is increasingly likely.<sup>2</sup>

The authors stress the possibility of dangerous reactions occurring when ketamine is used in sulfur mustard casualties. However, this assessment based on unexplained results would require further investigations.<sup>3</sup> Despite this word of caution, we would like to emphasize the benefits of ketamine for nerve agent poisoning.

Ketamine has been safely used for more than 35 yr but was gradually banished from usual practice because of psychedelic side effects and was supplanted by new, easier to handle drugs. However, the potential neuroprotective effects linked to the blockade of *N*-methyl-D-aspartate (NMDA) glutamate receptors prompted a renewed interest in phencyclidine derivatives such as ketamine<sup>4</sup> and led to the discussion of one of the major contraindications of the molecule: brain damage.

Because of cardiovascular and respiratory favorable properties, ketamine seems to be an anesthetic of choice for military surgery.<sup>5</sup> Better oxygen delivery and survival after ketamine anesthesia have been reported in experimental models of hemorrhage.<sup>6</sup> Reduced respiratory depression with higher  $P_{aO_2}$  values, when compared to halothane, makes it particularly safe for analgesia during surgical procedures far from the operating room.<sup>7</sup> During combat in a chemical warfare environment, the IV route would be difficult to consider and administration of ketamine by the intramuscular route would clearly be an advantage.

Of particular interest is the ketamine induced NMDA receptor-channel noncompetitive blocking, which most probably explains its neuroprotective and anticonvulsant properties. This makes ketamine particularly suitable for induction and maintenance of anesthesia in patients exposed to organophosphorous compounds.<sup>8</sup> Although ketamine has occasionally been reported to induce seizures, a larger body of evidence suggests that it actually displays anticonvulsant and neuroprotective properties.<sup>9</sup>

Not only the accumulation of acetylcholine but also excitatory amino acid neurotransmission is responsible for the nerve agent-induced *status epilepticus* and brain damage.<sup>10</sup> NMDA receptors, which are largely permeable to calcium, are particularly involved. A voltage-dependant magnesium block characterizes the NMDA channel. Depolarization, the final common pathway of multiple neuronal injuries, causes the magnesium block to be lifted, enabling calcium to enter the cell and induce the cascade of neuronal damage. Ketamine or Dizocilpine (MK-801) are noncompetitive antagonists that act inside the canal, at the phencyclidine site and demonstrate use-dependent, open-channel blockade. The first experimental results obtained with NMDA receptor antagonists in soman-poisoned animals demonstrate that only

the animals with *status epilepticus* exhibit neuronal damage, and the longer the convulsions, the worst the neurologic outcome. Limitation of seizures with these antagonists may thus prevent definite neurologic damage.<sup>11</sup> Because of an increasing difficulty in stopping nerve agents induced on-going seizures with time, it would be necessary to consider the use of ketamine as early as possible and multiple injections of anesthetic doses. The S(+) isomer, which is two to four times more potent than the R(−) isomer because of a superior pharmacological action on NMDA receptors, may exhibit better neuroprotective properties, although definitive results are still expected.<sup>12</sup>

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David C. Wartier, M.D., Ph.D., handled this exchange as Editor of the Review Article.

*In Reply:*—We read with interest the letter of Mion *et al.* regarding our review article. The issue that the authors raise, *i.e.*, our report of experimental data indicating a potential dangerous reaction to ketamine (prolonged apnea and respiratory distress) when animals were exposed to sulfur mustard, is theoretical, at least in part. As reviewers,

we could do no more than collect and present the specific experimental model and the related results at face value. The clinical aspects of the possible use of ketamine in nonconventionally intoxicated patients is problematic on several fronts. First, because ketamine potentially generates undesirable side effects *per se* that additively affect target-

organs of nerve agents (e.g., central nervous system: hallucinations; respiratory system: increased secretions), such potentiation may lead to unacceptable neurologic conditions. Second, ketamine has never been accepted clinically as a safe drug to control epileptic episodes, although its potential has been shown in animal models. Indeed, Mion *et al.*'s use of the word "may" is entirely appropriate in illustrating a potential but not contemporary use of ketamine as an antiseizure drug because of its NMDA-antagonistic properties. In the clinical setting, following the American, Israeli, and European protocols of antinerve agent protection, however, benzodiazepines are the *only* proven drugs to effectively control seizures while scopolamine, another weak NMDA-receptor antagonist, is the drug used to antagonize organophosphates' central effects. We indeed discussed in our review article the notion brought up by Mion *et al.* that "... ketamine [is] suitable for induction and maintenance of anesthesia in patients exposed to or-

ganophosphorous compounds."<sup>1</sup> Importantly, this reference used by the authors is inappropriate and extrapolative, because the article by Sheth *et al.* dealt with neither anesthesia nor organophosphorous compounds.

Finally, the concise explanation of the NMDA receptors-ketamine interactions in the central nervous system was appropriate, considering the scope of our review.

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## Possible Dangers of Discontinuing Statins Perioperatively

*To the Editor:*—I recently read with great interest the case report by Forestier *et al.*<sup>1</sup> "Severe Rhabdomyolysis after Laparoscopic Surgery for Adenocarcinoma of the Rectum in Two Patients Treated with Statins." With the rapidly increasing number of patients taking HMG Co-A reductase inhibitors (statins) for treatment of lipid disorders, I concur with the authors that peri-operative rhabdomyolysis might become a significant problem.

However, I would like to air a note of caution in regards to the authors final statement: "Considering that these drugs are used for long-term prevention, stopping the drug for a few weeks before surgery would not significantly decrease the cardiovascular protection." In the March issue of *Circulation*, Heeschen *et al.*<sup>2</sup> addressed this very topic in their study, "Withdrawal of statins increases event rates in patients with acute coronary syndromes." These authors investigated the effects of statin therapy in 1616 patients who had coronary artery disease and acute chest pain. They found that the patients who had their statin therapy discontinued on hospital admission for whatever reason actually did worse than the group who continued to receive their statins. The increased event rate was independent of cholesterol levels, and the only predictors of patient outcome were in fact troponin T elevation, electrocardiographic wave changes, and continuation of statin therapy.

With this study in mind, I would argue against Forestier's recommendation that statin therapy be withdrawn for a few weeks before surgery. This topic obviously needs more investigation before any recommendations can be made. The incidence of perioperative myopathy and rhabdomyolysis needs to be ascertained by a review with a larger cohort than 2. The next question raised then is: What is the incidence of rhabdomyolysis for the individual drugs within the statin class? Also, these patients

taking the statins are at least at a mildly increased risk of perioperative cardiac events and potentially are at a major risk if in fact they have a lipid disorder and known coronary artery disease. Discontinuing the statins in these high-risk patients might actually be a major disservice to them if in fact they suffer a perioperative ischemic event and are without their statin therapy. The risk of rhabdomyolysis in patients on statins who have no known coronary disease might outweigh the risk of discontinuing the statins. When does the risk of perioperative rhabdomyolysis decrease—immediately postoperatively or days to weeks later, and when should the statin be restarted? These are all questions that must be answered before any recommendations regarding continuation/discontinuation of statin therapy in the perioperative setting can be firmly issued.

I would like to thank Forrester *et al.* for raising this issue and for warning us about the risks of this increasingly popular class of drugs.

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*In Reply:*—Dr. Kreisler's comment concerning the risk of statin withdrawal is thought provoking. However, the study referred to concerns patients who were admitted for acute aggravated angina or acute coronary syndromes. These are patients with severe coronary heart disease, who may not be representative of the vast majority of statin users undergoing elective surgery in the absence of an acute coronary syndrome. If indeed stopping statins causes patients to run a risk of a serious coronary event, this is very worrisome, because most users are for primary prevention<sup>1</sup> without major coronary artery disease, and most stop the drug spontaneously within about 6 months. In that case, stopping (and therefore starting) statins may become a major factor in the risk of coronary events. Maybe it would be better in these patients not to stop, or alternatively not to start the drugs.

Anesthesiology, V 98, No 6, Jun 2003

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## Acute Normovolemic Hemodilution: The Subgroup of Patients Likely To Benefit Remains Uncertain

*To the Editor:*—Matot *et al.* reported a significant reduction in exposure to allogeneic blood transfusion by acute normovolemic hemodilution (ANH) in adult patients undergoing elective liver resection.<sup>1</sup> They also concluded that ANH could be routinely considered for this surgical procedure.<sup>1</sup> As discussed in this article and reviewed elsewhere, it is possible that biased experimental designs were, in part, responsible for the previously reported efficacy of ANH.<sup>2</sup> ANH has also been argued to profit to a restricted subgroup of patients difficult to identify.<sup>2</sup> In this respect, we believe that Matot *et al.* conclusions warrant some comments. Indeed, it has long been accepted that there is a considerable risk of massive bleeding during elective liver resection.<sup>3</sup> However, improvements in surgical techniques, technology, and preoperative assessment, in conjunction with a better understanding of the functional anatomy of the liver, have dramatically reduced the risk of bleeding during elective liver resection.<sup>4,5,6</sup> Moreover, situations likely to cause intraoperative bleeding can be anticipated,<sup>4</sup> such as preexisting adhesions resulting from previous surgery, organ removal, cava or portal vein resection, or recanalization.<sup>4</sup> The tolerance of lower intraoperative hemoglobin concentrations, together with the limitation of intraoperative fluid administration, has contributed to the decrease in intraoperative transfusion requirement in elective liver resection.<sup>1,4,7</sup> Indeed, a 30% transfusion rate has been reported in series of nonselected patients undergoing elective liver resection.<sup>4</sup> Selected patients, including ASA 1, Child A cirrhotic patients, underwent major liver resection without blood transfusion.<sup>5</sup> Consequently, the 40% transfusion rate recorded by Matot *et al.* in the control group is higher than is currently routinely expected in specialized centers, thus suggesting that a selected population carrying an increased bleeding risk was operated on in this institution.

Anesthesiology 2003; 98:1519

*In Reply:*—I take this opportunity to thank Drs. Lentschener and Ozier for their comments and showing keen interest in our recent article.<sup>1</sup> It is true that the number of liver resections without transfusion has increased substantially in recent years. However, as reported by Gozzetti *et al.*<sup>2</sup> and Rees *et al.*,<sup>3</sup> despite the improvement in surgical and anesthetic technique, 41% and 38% of liver resections (minor and major) required transfusion, respectively. In addition, only 19.6% of major hepatectomies were performed without intraoperative blood transfusion.<sup>2</sup> Although in the present study we included ASA 1 or 2 patients, the study included only patients scheduled to major hepatic resections. Moreover, a third of the patients had previous surgery, and on four occasions, the vena cava was involved. Therefore, I believe that the 36% transfusion rate found in the present study is not unacceptable. I agree with Lentschener and Ozier that acute normovolemic hemodilution is not expected to lower the need for blood transfusion in all patients undergoing liver resection. However, as suggested in the present study, it may benefit patients undergoing major hepatic resec-

tion. In conclusion, we believe that the findings of Matot *et al.* recorded in patients undergoing elective liver resection still substantiate previous concerns regarding ANH.<sup>2</sup> ANH is strongly suggested to reduce transfusion requirement in elective liver resection. Nevertheless, the subgroup of patients likely to have a benefit from ANH remains a poser.

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tions. It seems that future work in this area should focus on Child B patients, as suggested by Lentschener and Ozier.

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## Is Attenuation of Extracellular Dopamine Increase in the Nucleus Accumbens the Major Mechanism by which Dexmedetomidine Increases the Cocaine Seizure Threshold in Rats?

*To the Editor:*—I am very impressed with the recent article by Whittington *et al.*, which demonstrated that dexmedetomidine increased the cocaine-induced seizure threshold *via* the attenuation of the cocaine-induced increase in extracellular dopamine concentration in the rat nucleus accumbens.<sup>1</sup> It is true that the increase in extracellular dopamine concentration in the nucleus accumbens may be closely related to the cocaine-induced seizure activity because cocaine inhibits dopamine transporters, but recent studies have suggested that  $\sigma$  receptors, which are endoplasmic reticulum protein and directly activated by cocaine, are more likely involved in the cocaine-induced seizure activity than the dopamine transporters.<sup>2</sup> On the other hand, we have recently demonstrated that ketamine, which has anticonvulsant and also proconvulsant properties, markedly increases dopamine release in the nucleus accumbens.<sup>3</sup> Ketamine affected the  $\sigma$  receptors<sup>4</sup> and ketamine-induced c-fos protein expression in the posterior cingulate and retrosplenial cortices, which might be a reliable indicator of ketamine-induced psychotomimetic activity, was mediated at least partly *via* the  $\sigma$  receptors.<sup>5</sup> Therefore, I wonder whether the cocaine-induced increase in extracellular dopamine concentration in the nucleus accumbens is the major mechanism by which cocaine induces seizures and furthermore the  $\sigma$  receptors may be involved in the inhibitory effects of dexmedetomidine on the cocaine-induced seizures.

Anesthesiology 2003; 98:1520

*In Reply:*—We would like to thank the editor for allowing us the opportunity to reply to Dr. Nakao's interesting correspondence.

We do realize that other mechanisms may play a role in mediating cocaine-induced seizure activity. Indeed, the existence of different mechanisms may be the reason that these seizures are often clinically refractory to anticonvulsant monotherapy.<sup>1</sup> In our study, we focused on the dopaminergic system, because the plasmalemmal dopamine transporter is still thought to be the classic mechanism through which many of the psychomotor effects of cocaine are produced.<sup>2</sup> Moreover, we also concentrated on the role of mesolimbic dopamine, because our previous work suggested that dexmedetomidine effectively decreases dopamine in the nucleus accumbens.<sup>3</sup> Although our findings support the hypothesis that accumbal dopamine has a significant effect on cocaine-induced seizure activity, in no way do they suggest that this is the sole mechanism by which these seizures are mediated.

We agree with Dr. Nakao's relevant comments that  $\sigma$  receptors are also mechanistically involved in cocaine-induced seizures; however, as for the involvement of  $\sigma$  receptors in mediating the anticonvulsant effects of dexmedetomidine, we are currently unaware of any evidence

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in the literature demonstrating that dexmedetomidine has a significant effect at  $\sigma$  receptors. Given this, it is unlikely that the demonstrated anticonvulsant effects of dexmedetomidine involve these receptors.

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## Gabapentin: The First Preemptive Anti-Hyperalgesic for Opioid Withdrawal Hyperalgesia?

*To the Editor:*—It was with great interest that we read the study of Dirks *et al.*, who found a substantial reduction in postoperative morphine consumption over 4 h after remifentanyl-based anesthesia for

radical mastectomy by preoperative application of a single dose of 1200 mg oral gabapentin.<sup>1</sup> The authors suggested either a potential effect of gabapentin on acute pain or the potential modulation of

Anesthesiology, V 98, No 6, Jun 2003

intraoperative induction of opioid tolerance. In an accompanying editorial, Gilron pointed out the vast analgesic potency of gabapentin in humans.<sup>2</sup>

However, in a human inflammatory pain model, 1200 mg gabapentin reduced neither the primary hyperalgesia to heat nor the secondary hyperalgesia to pinprick.<sup>3</sup> In the human heat-capsaicin model, 1200 mg gabapentin reduced the secondary hyperalgesia to pinprick but did not affect the primary hyperalgesia response.<sup>4</sup> Hence, in accordance with studies in chronic pain,<sup>5,6</sup> gabapentin provides antihyperalgesic but not antinociceptive properties. Postoperative pain, however, is predominantly nociceptive in origin.

Dirks *et al.* performed high-dose remifentanyl-based anesthesia using 0.4 µg/kg/min. It is well known that opioids may induce hyperalgesia.<sup>7</sup> In particular the transition from short-acting opioids may be accompanied by hyperalgesia.<sup>8</sup> Because remifentanyl does not induce acute opioid tolerance,<sup>9</sup> an increase in postoperative morphine consumption after high-dose remifentanyl-based anesthesia may be explained by the development of opioid withdrawal hyperalgesia.<sup>10</sup>

Dirks *et al.* studied only the immediate postoperative stage for a period of 4 h. Any information about the postoperative morphine consumption over the first 24 h is lacking. Taken together they may, therefore, have studied remifentanyl withdrawal induced hyperalgesia after mastectomy. Thus we suggest that gabapentin may not be a "broad-spectrum" analgesic for postoperative pain therapy, but rather the first effective antihyperalgesic drug for the preemptive treatment of transient hyperalgesia after short-acting opioid-based anesthesia. Further studies are needed to test this fascinating aspect of gabapentin.

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*In Reply:*—The above letter responds to the provocative question of whether gabapentin is a "broad spectrum" analgesic<sup>1</sup> and appropriately points out that things are not quite so simple.

Gustorff *et al.* postulate that the effects of gabapentin reported by Dirks *et al.*<sup>2</sup> are not due to antinociception but, rather, to the suppression of hyperalgesia caused by withdrawal from intraoperative opioids. This is a reasonable hypothesis; however, it should be noted that Fassoulaki *et al.* recently observed similar reductions in pain and opioid consumption with gabapentin in patients who received *no* intraoperative opioids.<sup>3</sup> Therefore, gabapentin's effects cannot be solely due to suppression of opioid withdrawal hyperalgesia.

Nevertheless, this raises questions central to understanding the modulation of pain by gabapentin. While Gustorff *et al.* correctly indicate that postoperative pain is predominantly nociceptive, they fail to emphasize the importance of spinal sensitization,<sup>4</sup> which contributes to hyperalgesia and allodynia and which may be suppressed by gabapentin. Indeed, although gabapentin has little antinociceptive effect in the uninjured organism, it has been shown, in the absence of opioids, to reduce pain responses after surgical tissue injury.<sup>5</sup>

The latter comments by Gustorff *et al.* illustrate the complexities of interpreting gabapentin's effect when administered with opioids. Ethical conduct of most postoperative trials requires the provision of rescue analgesia, often in the form of patient-controlled analgesia with morphine, which necessitates the integration of pain measures with morphine consumption as co-relevant outcome measures.<sup>6</sup> Although trials have been equivocal thus far,<sup>7,8</sup> the possibility that mechanisms of opioid tolerance<sup>9</sup> contribute to postoperative hyperalgesia and increased opioid requirements may confound results of analgesic trials. Therefore, gabapentin trials involving concomitant morphine administration must be interpreted in light of a possible interaction between these drugs. In this regard, we have observed in the rat that gabapentin

Anesthesiology, V 98, No 6, Jun 2003

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prevents the development of morphine tolerance and partially reverses established tolerance indicating that such an interaction indeed exists.<sup>10</sup> Thus, although follow-up studies will further characterize the role of gabapentin in postoperative pain, even more sophisticated strategies are needed to distinguish between its specific pharmacological effects (e.g., analgesia, antihyperalgesia, antiallodynia and reversal of opioid tolerance).

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## Systemic Effects of Epidural Medications

*To the Editor:*—I read with great interest the report by Carli *et al.*<sup>1</sup> in which improvement in bowel motility, pain relief and other quality-of-life issues following bowel surgery were attributed to the use of intraoperative epidural anesthesia and post operative epidural analgesia. Bupivacaine when administered in the epidural space is systemically absorbed resulting in serum blood levels. Giving a “maximum of 15–20 ml in the epidural space”<sup>1</sup> of bupivacaine 0.5% and waiting for the appearance of bilateral sensory block will also result in a serum level of the local anesthetic before incision. As the control group did not receive a comparable dose of an intravenous amide anesthetic before surgery it is inappropriate to conclude that the bupivacaine works through an epidural mechanism. In a recent study, Groudine *et al.*<sup>2</sup> administered intraoperative intravenous lidocaine to patients undergoing radical retropubic prostatectomy and demonstrated many of the benefits Carli *et al.*<sup>1</sup> observed in their patients (faster return of bowel function and diminished pain) in addition to a shorter hospital stay without the need to administer the drug epidurally. Menigaux *et al.*<sup>3</sup> demonstrated that the analgesia observed with sufentanil was dependent on plasma concentration and not route of administration (more epidural sufentanil had to be given to get the same analgesia seen with a lower intravenous dose).

The above letter was sent to the authors of the referenced report. The authors did not feel that a response was required. —Michael M. Todd, Editor-in-Chief

Amide anesthetics have potent antiinflammatory activity,<sup>4</sup> and this activity may play a significant role in minimizing the duration of ileus and postoperative pain. Carli *et al.*<sup>1</sup> have clearly shown a benefit to giving patients an amide local anesthetic perioperatively. However, no convincing evidence was presented that this drug must be given by the epidural route to be effective.

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## Need for Additional Control in Studies of Epidural Outcome

*To the Editor:*—The recent study of Carli *et al.*<sup>1</sup> provides valuable evidence that enhanced postoperative analgesia with an epidural catheter can improve outcome in terms of quality of life. A mock epidural catheter in the control group might have added further assurance that nonblinding did not lead to differential treatment or expectations between the study groups, but the authors did an excellent job of standardizing postoperative care to minimize this effect.

However, recent advances in the study of pain treatments suggest that an additional control should be present in studies on the efficacy of epidural compared to intravenous analgesia. The group receiving intravenous analgesia should also receive low dose intravenous or subcutaneous local anesthetic, to produce plasma levels comparable to those in the epidural group. Local anesthetic at plasma levels achieved with nontoxic intravenous administration or prolonged epidural administration has been shown to have analgesic properties in animal models both *in vitro*<sup>2,3</sup> and *in vivo*,<sup>2</sup> and in humans.<sup>4,5</sup> Of particular relevance to the issue of whether “diminishing postoperative pain may decrease the incidence of long-term chronic pain”<sup>6</sup> is the efficacy of intravenous local anesthetic in treating neuropathic pain models.<sup>2,5</sup>

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The above letter was sent to the authors of the referenced report. The authors did not feel that a response was required. —Michael M. Todd, Editor-in-Chief

The mechanism(s) of this effect remains to be elucidated, but occurs at levels too low to block sodium channels, and may involve effects on neuronal calcium homeostasis<sup>3,7</sup> and frequency of sodium channel response to stimuli.<sup>2</sup> Low-dose local anesthetics also have significant antiinflammatory effects,<sup>8</sup> and the levels of acute phase inflammatory proteins may affect subjective acute postoperative physical well being.<sup>9</sup>

This comment is not specific to Carli *et al.*<sup>1</sup> Unfortunately, most if not all clinical studies of epidural anesthesia on outcome have neglected this control, even those that have rigorously included an epidural catheter in subjects not receiving epidural analgesia to blind the study; *e.g.*, Norris *et al.*<sup>10</sup>

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## Can't Blame Bupivacaine

*To the Editor:*—Arndt and Downey<sup>1</sup> vividly convey a physician's dismay when motor, sensory, and bladder function are agonizingly slow to return after uneventful spinal block. The delayed recovery pattern described here is not unlike that seen when a potent vasoconstrictor such as neosynephrine is added to the local anesthetic solution to prolong deliberately the duration of sensory blockade. Because the patient remained painfree, pharmacologic or mechanical cauda equinopathy,<sup>2</sup> fortunately, could be ruled out decisively in the differential diagnosis.

Although the authors postulate low spinal fluid volume as a contributing factor, that might be a rather slender straw to cling to in a healthy 20-yr-old young woman with freely aspirable spinal fluid.<sup>3</sup> Instead (because a vasoconstrictor wasn't used), the addition of fentanyl to intensify and prolong bupivacaine block did achieve its intended purpose—albeit as a statistical outlier well beyond the expected norm of  $4 \pm 2$  h.<sup>1</sup> All told, this correspondent finds no compelling evidence to

single out bupivacaine as the sole culprit for the protracted spinal analgesia.<sup>4</sup> That is to say, the letter's title "Exceptionally Prolonged Anesthesia after a Small Dose of Intrathecal Bupivacaine" falls short. Rather, the title should have read "Prolonged Analgesia after Intrathecal Bupivacaine plus Fentanyl."

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## Postoperative Sore Throat: Due to Intubation or Reflux Disease?

*To the Editor:*—It is not uncommon for patients to complain of a "sore throat" after surgery that requires intubation. Despite variations in the degree of difficulty of intubation, there seems to be no correlation between attempts or duration of intubation and the degree (if any) of sore throat. In most instances, the patient makes the complaint immediately after surgery.

On occasion, however, the patient makes no comment until a few days after surgery. Despite the delay in onset of symptoms, this pharyngitis is still often blamed on the intubation process. However, there are other causes of inflammation that should be considered, chief among them gastroesophageal reflux disease (GERD).

We are report one such case in a patient with a history of reflux disease. A 58-yr-old man underwent excision of a renal tumor. The intubation and surgery were uneventful. On the fourth postoperative day, he complained of a severe sore throat, which persisted for many weeks. Initially, this was thought to be related to intubation. An otolaryngologist was consulted and a detailed examination was performed. This examination revealed no injuries related to intubation; however, it did show inflammation of the pharynx consistent with the changes seen in GERD. An endoscopy performed by gastroenterology also revealed an acute exacerbation of reflux

disease. Once the patient was adequately treated, these symptoms disappeared in approximately 6 weeks.

GERD is being diagnosed with greater frequency today, and patients may be on oral antireflux medication preoperatively, such as Prilosec or nexium. These drugs are quite often discontinued in the immediate postoperative period. In addition, ileus is common postoperatively because of bowel manipulation intraoperatively, administration of intraoperative and postoperative narcotics, interstitial edema (third spacing), or a combination of these factors. Lack of ambulation further promotes ileus. Patients also tend to spend more time in the recumbent position. Repeated attempts to clear the throat because of the irritation will merely increase it.

GERD is now recognized as being fairly common in the general population, and more and more patients arriving for surgery give a history of some degree of GERD, whether being medically treated or not. As this is now recognized, and given the multitude of factors postoperatively that promote GERD, the anesthesiologist should consider this disease when visiting a patient with late-onset pharyngitis after surgery.

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## Can Choice of Vasopressor Therapy Affect Rostral Spread of Spinal Anaesthetic?

*To the Editor:*—In our routine practice, we have observed an apparent association between choice of vasopressor used during spinal anesthesia for cesarean section and rostral spread of spinal blockade to cold sensation. We are not aware of such an association having been reported previously.

For cesarean section, we routinely use a needle through needle combined spinal epidural technique at L3/4. Two ml of plain spinal bupivacaine 0.5%, combined with 20 µg of fentanyl, is given in the sitting position, and 10 ml of epidural saline is given *via* the Tuohy needle, before the epidural catheter is passed. The patient is then placed in the supine position with left lateral tilt. This produces effective spinal anesthesia for most patients without the need to top up the epidural, but approximately 25% of patients develop cervical level neural blockade to cold sensation. However, we have observed that when we use an infusion of phenylephrine to prevent hypotension, the incidence of cervical level neural blockade to cold sensation seems to be lower than when we use a combination of phenylephrine and ephedrine (in a ratio of 100 µg:3 mg, respectively).

This unexpected observation has led us to retrospectively analyze the results from a recently published, randomized, double-blind study from our hospital.<sup>1</sup> In that study we compared phenylephrine (100 µg/ml) (phenylephrine group), ephedrine (3 mg/ml) (ephedrine group), and a combination of phenylephrine (50 µg/ml) with ephedrine (1.5 mg/ml) (combination group), given by infusion during spinal anesthesia for elective cesarean section in low-risk, term pregnancies. Four spinal anesthetic techniques were used in the study, and randomization to group was stratified for each anesthetic technique. Technique 1: 2.5 ml of spinal hyperbaric 0.5% bupivacaine with 20 µg of fentanyl, given in the sitting position. Technique 2: 2 ml of spinal levobupivacaine 0.5% with 20 µg of fentanyl, and 10 ml of epidural saline, given in the sitting position. Technique 3: 2 ml of spinal levobupivacaine 0.5% with 20 µg of fentanyl, given in the left lateral position. Technique 4: 2.5 ml of spinal levobupivacaine 0.5% with 10 µg of fentanyl, given in the left lateral position. Spinal anesthetics were performed at L3/4 and patients were then placed supine with left lateral tilt. Table 1 shows the number of patients with cervical level neural blockade to cold sensation for each vasopressor group. Neural blockade to cold sensation was assessed using ethyl chloride spray and was recorded at the time of skin incision. There was no difference in the spinal-skin incision interval for the vasopressor groups. All patients with cervical level neural blockade to cold sensation had good hand grasp strength, and none had respiratory difficulty.

The incidence of cervical level neural blockade to cold sensation was lowest in the phenylephrine group and highest in the ephedrine

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**Table 1. Cervical Level Neural Blockade to Cold Sensation with Spinal Anesthesia**

	Phenylephrine	Ephedrine	Combination	P Value
Spinal technique 1	n = 24	n = 23	n = 23	
Cervical blockade	0	6	2	P = 0.02
Spinal technique 2	n = 13	n = 14	n = 14	
Cervical blockade	0	7	3	P = 0.01
Spinal technique 3	n = 7	n = 8	n = 8	
Cervical blockade	0	0	1	
Spinal technique 4	n = 4	n = 5	n = 4	
Cervical blockade	0	1	0	
All patients:	n = 48	n = 50	n = 49	
C2	0	5	1	
C3	0	1	0	
C6	0	0	1	
C8	0	8	4	P = 0.0003

Number of patients with cervical level neural blockade to cold sensation for each spinal anesthetic technique, and upper cervical level blockade to cold sensation for all patients, by group. Data expressed as numbers (Kruskal-Wallis).

group. For 6 of the 14-ephedrine group patients with cervical level neural blockade to cold sensation the level was above C4. These observations suggest that choice of vasopressor may affect rostral spread of spinal anesthetic. Increased epidural volume can enhance spread of spinal anesthetic.<sup>2</sup> Perhaps phenylephrine causes greater epidural vein constriction than ephedrine. This may decrease enhancement of spread of spinal anesthetic by engorged epidural veins of pregnancy. However, our observations are based on retrospective data analysis. The hypothesis that choice of vasopressor therapy can affect the spread of spinal anesthetic and, if so, the mechanism and its clinical significance, needs to be examined in well-designed prospective studies.

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