

## Ropivacaine Neurotoxicity: A Stab in the Back?

*To the Editor:*—In a provocative case report, Ganapathy *et al.*<sup>1</sup> characterize immediate-onset localized low back pain with the transient neurologic symptom label—attributing that hallmark of putative local anesthetic neurotoxicity to the intrathecal administration of ropivacaine (Naropin®; AstraZeneca, Mississauga, Ontario, Canada). I beg to differ. Transient radiating radicular pain developed in the patient but did not become symptomatic until 3 days after ropivacaine injection, in the midst of an episode of severe postpuncture headache. The antecedent events in this case differ both temporally and qualitatively from the clinical transient radicular irritation triad of Schneider *et al.*<sup>2</sup>: radiating lumbosacral radicular pain at first appearing within hours after full sensory recovery, transient duration of the radicular pain lasting from hours to days, and a vexing absence of localizing “hard” neurologic signs.<sup>2,3</sup>

Conversely, in the case presented by Ganapathy *et al.*,<sup>1</sup> nonradiating lower back pain manifested almost instantly, persisted despite dense sensory blockade to T4, and remained little changed during recovery of normal sensation. It has been said that delayed onset and brief duration of classic transient radicular irritation are hallmarks of a mild neural (probably cauda equina) inflammatory reaction to irritant local anesthetic drug—comparable in quality and time course to a first-degree sunburn.<sup>4</sup> Crucial to differentiating this particular case from purely symptomatic transient radicular irritation are four distinctly hard neurologic findings: (1) numbness of the soles of both feet (whereas surgery was unilateral); (2) 3 weeks’ persistence of this troubling sign of neuraxial injury; (3) mild locomotor ataxia; and (4) asymmetry of ankle reflexes.

This case report lacks compelling evidence of ropivacaine neurotoxicity. Rather, immediate onset of nonsegmental central pain, persistence of this pain despite complete radicular sensory blockade, and subtle but persistent neurologic abnormalities all indicate a mechanical

rather than a pharmacologic neuraxial event—perhaps needle-contact surface trauma to the posterior columns. Trauma to the spinal cord proper is a more plausible consideration because only a centrally located generator could send pain impulses cephalad during spinal anesthesia; impulse traffic originating from spinal rootlets or other sites distal to the cord would have been halted by the neural blockade. Currently, there is no evidence for ropivacaine being a more aggressive myelotoxic local anesthetic than its benign pharmacologic cousins bupivacaine or mepivacaine.<sup>5,6</sup>

In brief, the clinical scenario presented by Ganapathy *et al.*<sup>1</sup> is consistent more with mechanical (needle) trauma to the spinal cord surface than with chemical (neurotoxic) irritation of cauda equina rootlets.

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*In Reply:*—Our response to the letter of Dr. de Jong has an anatomic basis. The spinal cord ends at the level of L1, and our spinal puncture was performed at L2-L3; therefore, it is extremely unlikely it was a “stab in the back” of the spinal cord. Secondly, a patient would perceive some kind of a paresthesia if one touched the spinal cord or any of the roots of cauda equina, which our patient did not report. Although it might be difficult to see such minute injuries, if we did inject into the spinal cord, the magnetic resonance image should show some minor changes at this level, and the magnetic resonance image showed no spinal cord abnormality. Finally, with many poorly defined

clinical syndromes, such as transient neurologic symptom, newer symptoms do get reported as the medical community becomes aware of the clinical condition. Therefore, as good clinicians performing spinal anesthesia on a regular basis, we differ with Dr. de Jong in regard to the clinical diagnosis.

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## Subarachnoid Sufentanil for Early Postoperative Pain Management in Orthopedic Patients: More Disadvantages Than Benefits?

*To the Editor:*—We read with great interest the article of Standl *et al.*<sup>1</sup> and would like to congratulate the authors for their well-conducted study. In part 1 of their investigation, they evaluated the effects of a single bolus of sufentanil, bupivacaine, or a combination of both administered through a spinal microcatheter on postoperative pain relief in patients after major orthopedic lower-limb surgery (n = 80). In

part 2, they studied the effects of repetitive (maximum of four) subarachnoidal sufentanil injections in a similar but much smaller group of patients (n = 10). We agree that the authors demonstrated that intrathecal sufentanil injections resulted in effective postoperative pain relief. However, we believe that risks and disadvantages associated with this technique outweigh the potential benefits.

Patients undergoing major orthopedic procedures of their lower limb, such as total knee or total hip replacement, deserve appropriate pain management not only during the immediate postoperative period but also for several days. With their technique, Standl *et al.*<sup>1</sup> provided analgesia only for the first 6–7 h after surgery in part 1 of their study and approximately 16 h in part 2. Unfortunately, pain after major lower-extremity joint replacement can be well-controlled while the patient is resting but is exacerbated when mobilization, using for example continuous passive motion, starts on the first postoperative day. Capdevilla *et al.*<sup>2</sup> demonstrated efficacy and safety of continuous infusion of local anesthetics *via* femoral catheters for pain management in patients after total knee replacement not only for the immediate postoperative period but also for the subsequent days of mobilization. Singelyn and Gouverneur<sup>3</sup> showed that the same technique offers appropriate analgesia after total hip replacements and is associated with minimal side effects.

The authors state that repetitive subarachnoid sufentanil injections (part 2 of the study) seem not to increase the risk of early respiratory depression. It is doubtful whether a study of only 10 patients justifies such a statement. However, 3 of 10 patients did show signs of respiratory depression after they received the first dose of intrathecal sufentanil. The concerns of the authors are best expressed by the fact that all 10 patients in part 2 of their investigation were admitted to the intensive care unit. Because no other explanation was offered, we conclude that this was done to monitor possible side effects related to the subarachnoid sufentanil injections. We believe that the need for increased surveillance in these patients represents a major disadvantage. An important attribute of effective postoperative pain management should be safety for the patient and not an increased risk with the need for continuous monitoring.

In conclusion, we believe that the value of subarachnoid sufentanil administered as repetitive injections *via* spinal microcatheters for postoperative pain management in patients after major orthopedic surgery to their lower extremity remains questionable. Epidural anes-

thesia has been the treatment of choice in these settings. However, since the introduction of low-molecular-weight heparin, epidural hematoma as a complication of this technique has been reported frequently.<sup>4</sup> Other methods of perioperative pain management, such as continuous infusion of local anesthetics *via* psoas,<sup>5</sup> sciatic,<sup>6</sup> or femoral catheters, have been shown to be safe, to provide excellent pain relief, and to improve outcome of patients undergoing major surgery of the lower extremities.<sup>2,3,7</sup> These methods have become the gold standard and should be used as a measurement when new techniques are evaluated.

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**In Reply:**—We read the letter of Gebhard *et al.* with great interest. Although we share some of the ideas stressed by the authors, we do not agree with several aspects of their statements.

Major orthopedic surgery may require prolonged postoperative analgesia. We were able to demonstrate the efficacy of repetitive subarachnoid sufentanil boluses for early postoperative pain relief *via* continuous microspinal catheters (continuous spinal anesthesia [CSA]) in our study.<sup>1</sup> Although the study protocol ended after the fourth injection of sufentanil, longer and presumably sufficient pain relief would have been obtained with this concept. As we stated, subarachnoid sufentanil can lead to short-term respiratory depression. As a consequence, close monitoring remains mandatory in this setting, and we recommend that patients be kept in an intensive or intermediate care unit as long as subarachnoid opioids are administered. Because most of our patients undergoing total knee or hip replacement or revision arthroplasty are older than 65 yr, cardiocirculatory and respiratory comorbidities often require prolonged and extended postoperative surveillance *per se*. In addition, CSA offers several benefits in comparison with alternative techniques, such as epidural anesthesia or peripheral nerve blocks, especially in elderly patients undergoing major lower-limb surgery.

In comparison with epidural anesthesia, CSA provides better cardiovascular stability and more reliable blocks.<sup>2</sup> In a study performed by Curatolo *et al.*,<sup>3</sup> 9% of 1,051 patients with epidural anesthesia experienced pain during surgery. Moreover, the risk of epidural hematoma is lower in spinal when compared with epidural anesthesia, although it is extremely low (less than 1:150,000) for both techniques.<sup>4</sup>

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Disadvantages of sciatic–femoral nerve blocks were demonstrated by Fanelli *et al.*<sup>5</sup> in patients undergoing lower-limb surgery. Despite a high success rate of 93% using a multiple puncture technique, only 71% of the patients would choose the same technique of regional anesthesia in the case of similar surgical interventions. In contrast, the success rate of CSA is nearly 100%, with a high acceptance by patients and surgeons.<sup>6</sup> In addition, surgeons' satisfaction with anesthetic techniques for joint replacement is mainly related to a complete muscle paralysis, which is more easily and perfectly achieved with spinal blocks rather than peripheral nerve blocks or epidurals. Both techniques, epidural anesthesia and combined sciatic–femoral nerve blocks, often require high cumulative doses of local anesthetics, thus increasing the risk of toxic side effects in compromised patients.

In terms of postoperative pain relief after major hip and knee surgery, we agree with Gebhard *et al.* that peripheral nerve blocks using catheter techniques provide adequate and even prolonged pain relief. However, the references cited by the authors seem to be most inappropriate to show safety and efficacy of these techniques because both references represent only case reports.<sup>7,8</sup>

In summary, repetitive subarachnoid sufentanil boluses provide excellent and immediate pain relief after major lower-limb surgery without impairing motor function. The calculable risk of side effects can be minimized by surveillance; therefore, CSA with sufentanil for postoperative analgesia seems to be preferable in patients with comorbidities who require postoperative monitoring for medical reasons.

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## Ophthalmic Blocks at the Medial Canthus

*To the Editor:*—We read with great interest the articles about ophthalmic blocks by Ripart *et al.*<sup>1-4</sup> The most recent article seems to establish that there is no restrictive intermuscular membrane impeding the flow of local anesthetic from extraconal to intraconal spaces with peribulbar blockade.<sup>1</sup> Three of the 10 dye injections in that study were performed with needle puncture at the medial canthus using the technique of Husted and were reported to produce filling of both extraconal and intraconal spaces.<sup>1,5</sup> However, one of the previous dye studies of Ripart *et al.*<sup>4</sup> reported that eight injections at the medial canthus using a similar technique all resulted in filling of the episcleral (sub-Tenon) spaces. Do the subtle differences in technique account for filling two different anatomic spaces, or is the pattern of anesthetic spread unpredictable with injection at the medial canthus?

We share the enthusiasm of Ripart *et al.*<sup>2</sup> for the medial canthal injection site, regardless of which anatomic space is involved. We have been using his technique with a slight modification for more than 3 yr in approximately 2,000 cataract patients. Like Husted, we perform needle puncture medial to the caruncle rather than lateral to help ensure against perforation by providing an extra few millimeters of separation between the needle and the globe.<sup>5</sup> We have had no instances of globe perforation, retrobulbar hemorrhage, or brainstem anesthesia. We have noted that chemosis as an indicator of episcleral anesthetic spread is only occasionally produced. In the past, we performed this block during deep propofol sedation to prevent patient reaction to the needle puncture despite use of topical anesthetic drops. Recently, we discovered that application of topical anesthetic directly to the medial canthal conjunctiva with a cotton swab for 1 min before puncture has virtually eliminated this initial discomfort and has lessened the need for sedation.

A minor problem we sometimes observe is sneezing, which, on occasion, necessitates interruption of the block because of patient

movement. We believe that this most likely represents irritation in some way to the ethmoidal nerves as they course through the medial orbit close to the needle tract.<sup>6</sup>

We have greatly appreciated the articles of Ripart *et al.*<sup>1-4</sup> and are glad the anesthesia community is becoming more aware of this excellent technique of regional ophthalmic anesthesia.

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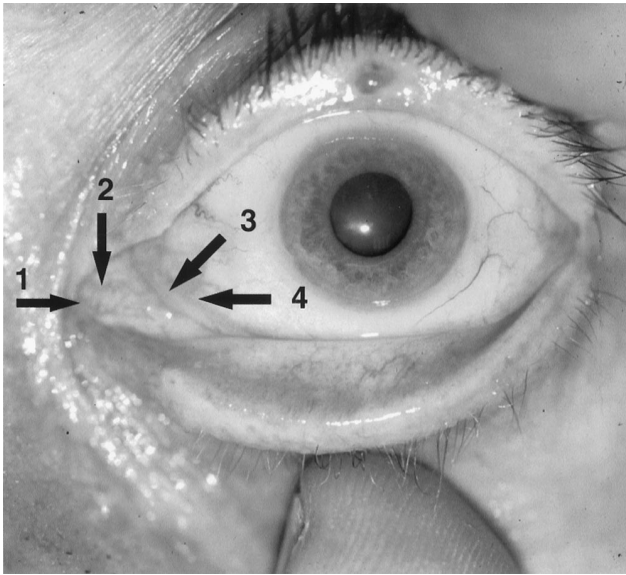
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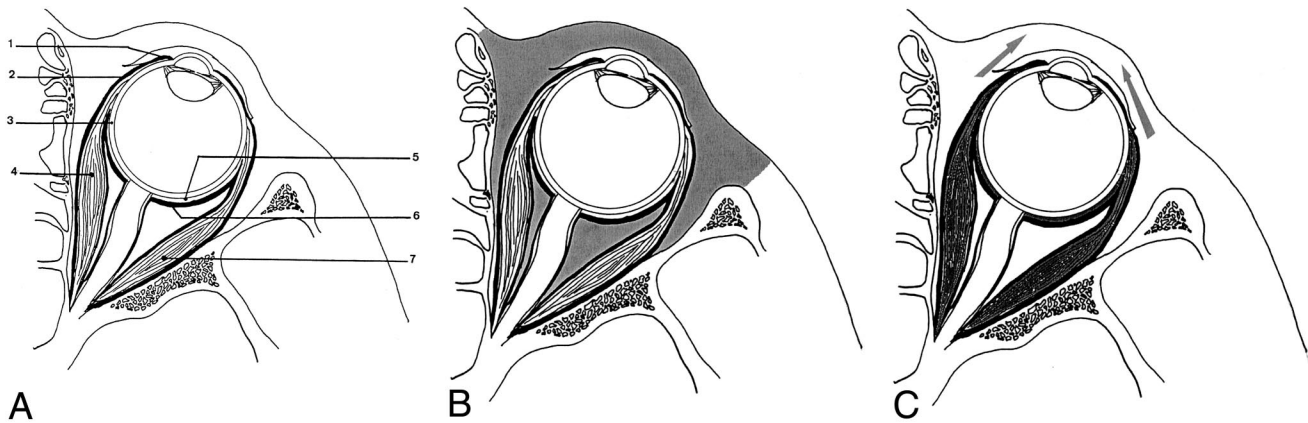
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*In Reply:*—We thank Dr. Lopatka *et al.* for their interest in our work and for their pertinent comments. The main concern is the difference between the technique described by Husted *et al.*<sup>1</sup> that Dr. Lopatka *et al.* seem to use and our technique.<sup>2-7</sup> They are very different. Husted uses a peribulbar (extraconal) injection. The local anesthetic is injected into the extraconal space, a part of the corpus adiposum of the orbit. This is a different route of injecting into the same space than when performing classic inferolateral peribulbar anesthesia. Using the technique of Husted, the needle is inserted medially to the caruncle, at the medial end of the lid aperture, near the junction between the lacrimal portion of the inferior and superior lids (fig. 1). Our technique is an episcleral (sub-Tenon) injection. The needle is inserted more laterally, tangentially to the globe, directly into the episcleral space (fig. 1). As

we stated in our first article<sup>2</sup> when we began using this technique, we were convinced that it was another peribulbar approach, similar to the technique of Husted. However, after intensive anatomic works,<sup>6,7</sup> we found that the two spaces of injections are different. Peribulbar injection results in a spread of the local anesthetic into the whole corpus adiposum of the orbit, including the intraconal space in which are located all the sensory and motor nerves that must be blocked to ensure good akinesia and analgesia of the eyeball<sup>8</sup> (fig. 2B). This spread is sometimes uncertain or incomplete, explaining some partial failures of peribulbar anesthesia. Injecting into the episcleral space forces the spread of the local anesthetic circularly around the scleral portion of the globe, thus encountering the ciliary nerves just before they enter the sclera and accounting for a good sensory block (fig. 2C). There is



**Fig. 1.** Site of introducing the needle. 1 = Site of introducing the needle for the technique of Husted; 2 = caruncle; 3 = semilunar fold of the conjunctiva; 4 = site of introducing the needle for our technique.



**Fig. 2.** (A) Semischematic view of a horizontal section of the orbit. 1 = Common insertion of bulbar conjunctiva and Tenon capsule on the eyeball, near the sclerocorneal limbus; 2 = anterior facial sheath of the eyeball (the Tenon capsule); 3 = sclera; 4 = medial rectus muscle; 5 = episcleral space (sub-Tenon); 6 = posterior facial sheath of the eyeball; 7 = lateral rectus muscle. Note the continuity between the Tenon capsule and the sheaths of the rectus muscles. (B) Same view as A, with figured spread of a local anesthetic injected into the peribulbar space, with subsequent spread into the muscular cone. Because the space for spreading is the adipose tissue of the orbit, including small septas network, this spread may be incomplete or heterogeneous, thus accounting for imperfect blocks. (C) Same view as A, with figured spread of a local anesthetic injected into the episcleral (sub-Tenon) space. Note the spreading into the whole episcleral space and into the sheaths of the rectus muscles, thus accounting for good akinesia. Because the episcleral space is adherence-free and septum-free, this spread is more constant, thus accounting for more constant akinesia. Additionally, because the anterior Tenon is not tightly sealed, part of the local anesthetic flows to the lids, accounting for akinesia of the orbicularis muscle.

a continuity between the fascial sheath of the eyeball (the Tenon capsule) and the sheaths of the recti muscles. Thus, injecting into the episcleral space also guides the spread of the local anesthetic into the sheaths of the recti muscles, where it encounters the terminal motor nerves, accounting for a good akinesia of the globe. Because the fascial sheath of the eyeball fuses anteriorly with the bulbar conjunctiva, episcleral injection results in subconjunctival infiltration (chemosis). Finally, the excess local anesthetic flows into the lid, thus preventing blinking. This difference between the techniques explains the greater efficacy of our technique as compared with classic peribulbar injection.<sup>5</sup> However, there is a small difference in the position of the needle between the technique of Husted and our technique. A small misplacement of the needle during an intended Husted approach may

result in episcleral injection, and conversely, Dr. Lopatka outlines that an intended peribulbar anesthesia occasionally produces chemosis, which is the indicator of episcleral injection.

The work of Vohra and Good<sup>9</sup> has outlined the interest of the medial canthus for preventing inadvertent globe perforation. One of the main risk factors of perforation is myopic staphyloma, which is frequently located posteriorly to the globe (with an increased risk of retrobulbar injection) or inferiorly (with an increased risk of inferolateral peribulbar injection) but very infrequently on the medial part of the globe. Theoretically, this should be an argument in favor of the safety of medial canthus approaches. However, introducing a needle into the orbit has its own hazards. Safety of eye blocks depends mainly on skill, experience, and strong anatomic knowledge.

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## Does Early Preload Adaptation Exist in Patients with Septic Shock?

*To the Editor:*—We congratulate Vieillard-Baron *et al.*<sup>1</sup> for the article entitled “Early Preload Adaptation in Septic Shock? A Transesophageal Echocardiographic Study.” The authors of this study were unable to confirm the concept of early preload adaptation by left ventricular dilatation in septic shock as described by Parrillo *et al.*<sup>2,3</sup> Vieillard-Baron *et al.*<sup>1</sup> conclude that systolic function was the unique determinant of stroke index in septic shock. We have two comments regarding this study.

First, the conclusion is based on the validity of an accurate measurement of left ventricular end-diastolic volume by transesophageal echocardiography in patients with septic shock. Indeed, to our knowledge, the relation between the true left ventricular end-diastolic volume and the left ventricular end-diastolic volume and areas measured using transesophageal echocardiography has not been analyzed in patients with septic shock. Therefore, we are not sure about the validity of these results, and it cannot be excluded that transesophageal echocardiography techniques possibly underestimate left ventricular end-diastolic volume in this study.

Second, interestingly, the initial study of Parker *et al.*<sup>2</sup> describes two groups of patients with quite different left ventricular volumes. In the subgroup with a lower systemic vascular resistance index (SVRI;  $1,127 \pm 159 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ ), mean left ventricular volume index was normal ( $81 \pm 9 \text{ ml/m}^2$ ), whereas the other group showed left ventricular dilatation and a higher SVRI ( $1,559 \pm 168 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ ). Calculating SVRI for the patients studied by Vieillard-Baron *et al.*<sup>1</sup> on the basis of the hemodynamic data provided (systolic arterial pressure = 90-110 mmHg; mean arterial pressure  $\approx 60$  mmHg; central venous pressure = 13 mmHg; cardiac index =  $3.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ), we

obtained an SVRI of  $1,175 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ . This value is comparable to the low SVRI group reported by Parker *et al.*<sup>2</sup> but more interestingly, in both studies, these groups have a normal left ventricular volume index. This comparison also suggests that there is not really a contradiction between the data of the two clinical investigations. Both Parker *et al.*<sup>2</sup> and Vieillard-Baron *et al.*<sup>1</sup> report a normal mean left ventricular volume in patients with septic shock and decreased afterload.<sup>4</sup>

In conclusion, we believe that further studies should be performed to define more precisely the concept of early preload adaptation by the left ventricle in septic shock.

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*In Reply:*—I read with interest the comments by Bendjelid and Suter regarding our article entitled “Early Preload Adaptation in Septic Shock? A Transesophageal Echocardiographic Study.”<sup>1</sup>

As we stated in this study, measurements by transesophageal echocardiography underestimated end-diastolic left ventricular volume. Comparing this method with the conventional transesophageal echocardiographic approach, we have observed an average underestimation of 12%. Therefore, even with this underestimation, left ventricular end-diastolic volume was in the normal range in the septic patients in our study. This finding was corroborated by a simultaneously normal value for left ventricular end-diastolic area in the short axis.

Retrospective calculation performed by Bendjelid and Suter showed a low systemic vascular resistance index in the patients in our study. This finding is expected in sepsis. However, they should have performed this calculation for the three subgroups described in the study, not only for the whole group. Particularly, in hypokinetic (and nondilated) patients, the average systemic vascular resistance index calculated by their formula was  $2,089 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ , rendering their argumentation irrelevant.

Finally, Bendjelid and Suter concluded that the patients in our study were similar to the subgroup of nondilated patients of Parker *et al.*<sup>2</sup> I do not agree with this assumption because a major difference exists. In the report of Parker *et al.*<sup>2</sup> recovery was conditioned by the ability of the left ventricle to acutely dilate, and nondilated patients had a 100% mortality rate. Fortunately, it was not the case in our report, in which crude mortality was 40%.

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## Seeking an Integrated Model of Anesthetic Action

*To the Editor:*—The recent special articles by Eger *et al.*<sup>1</sup> and Eckenhoff and Johansson,<sup>2</sup> although different in many specifics, are collectively important for their recognition that, ultimately, elucidating the mechanism of general anesthetic action requires understanding well beyond the binding of these drugs to one or more receptors and the subsequent modulation of that receptor's activity. Each group of authors has offered simple models of what might occur when multiple receptors are bound by molecules with anesthetic properties. As each has amply demonstrated, such models are easy to critique but difficult to supplant. How do we begin the task of building more realistic models, and what might they reveal of general anesthetic mechanisms?

It is clear that general anesthetics bind and modulate the activity of multiple receptors and receptor classes, in which binding to the voltage-gated receptors primarily affects the membrane properties of individual neurons, and binding to the ligand-gated receptors primarily affects the interaction of these neurons. Therefore, a plausible model of anesthetic action must show how these effects at one or more receptors could map to the general anesthetic state. Unfortunately, at the current time, this is not a well-specified endpoint. Certainly, the induction of neural quiescence would lead to an anesthetic state, but this represents an anesthetic state far deeper than the established activity of the brain and spinal cord during general anesthesia would suggest. Electroencephalographic studies during administration of the volatile anesthetics or ethanol<sup>3</sup> consumption exhibit an increasing level of organization, implying a greater degree of synchronous activity. Although this concept of anesthetic action seems to implicate the ligand-gated channels responsible for neural interaction, the situation is more complex. Theorists recognize at least two generic patterns of neural spike activity with distinct topologic signatures, one of which is more likely to lead to synchronous activity when incorporated into a network.<sup>4</sup> Importantly, as demonstrated in simple examples of biophysical neuron models, one type of behavior can often be readily transformed into the other with simple parameter changes as could conceivably occur as a consequence of anesthetic interaction with the voltage-gated ion channels.<sup>4</sup> Another membrane factor that could conceivably affect cell-to-cell coupling is the pattern of spike activity, in which suppression of bursting behavior, even if the average number of spikes remains relatively constant, could prevent depolarization of the postsynaptic neuron.

One persistent argument in the anesthetic mechanisms literature<sup>5</sup> is that the receptors responsible for precipitating the anesthetic state when appropriately occupied should have a concentration-effect relation that parallels that of the *in vivo* system. Attention is generally paid to the slope and midpoint of such curves. Experience with theoretical and computational neural models indicates that there is no reason to expect that these slopes should be at all the same. For example, at the single neuron level, consider the Morris-Lecar barnacle muscle fiber model.<sup>6</sup> Persistent spike activity can be terminated in an abrupt fashion as the conductance of the  $Ca^{++}$  channel is continuously decreased (A. G., unpublished computer simulation of Morris-Lecar model, 2000). At the other extreme are models involving multiple neurons, such as the theoretical solution<sup>7</sup> of a now classic problem from the circadian rhythm literature, which demonstrates that there is a specific threshold for neural coupling, below which synchronous activity cannot occur. This could occur either through modulation of synaptic interactions (ligand-gated receptors) or through small decrements in the activity or pattern of activity of the individual neurons (voltage-gated receptors), either of which would lead to decreased coupling with members of the network. Each of these examples suggests more of a threshold type (bifurcation or phase transition) of *in vivo* behavior as anesthetic modulation of receptor activity takes place, and that less-than-perfect threshold behavior is the consequence

of biologic variability in the population. Already, this concept of a phase transition has been the basis for one large-scale model of general anesthetic action.<sup>8</sup>

Regarding the midpoint of the concentration-effect relation of *in vitro* preparations, it has been argued that clinically relevant concentrations should lie close to this midpoint, and consequently, anesthetic modulation of the voltage-gated channels may not be responsible for the anesthetic state.<sup>5</sup> By recognizing the possibility of threshold behavior and linearizing about the midpoint of a hypothetical concentration-effect curve, Eger *et al.*<sup>1</sup> hypothesize that clinically relevant concentrations should lie within a factor of 3 of the midpoint to reach thresholds in the range of 0.1–0.9. For the example of the Morris-Lecar model presented here, persistent neural spike activity ceased with only an 11% decrease in  $Ca^{++}$  conductance. In a modification of the Morris-Lecar model to introduce bursting,<sup>4</sup> burst duration decreases in a graded fashion as  $Ca^{++}$  conductance is decreased so that the burst duration is more than halved when  $Ca^{++}$  is reduced by 20% (A. G., unpublished computer simulation of modified Morris-Lecar model, 2000). Similar but more complex behavior is seen for more elaborate single cell models, such as that of the hippocampal CA-3 neuron<sup>9</sup> (A. G., unpublished computer simulation of Pinsky-Rinzel CA-3 neuron model, 2000), although conclusions based on these more elaborate models will depend on the ability to introduce anesthetic modulation of all the ion channels accurately.

Thus far, the exchange between Eger *et al.*<sup>1</sup> and Eckenhoff and Johansson<sup>2</sup> has highlighted only the acute aspects of the induction of general anesthesia. However, it is now recognized that synaptic reorganization is ongoing in the central nervous system on a continuous basis, shaped by the prevailing pattern of presynaptic and postsynaptic activity. Moreover, there is a growing appreciation, at least in simple systems, that conductances of voltage-gated receptors can be differentially regulated to preserve a given activity pattern.<sup>10</sup> Thus, induction of general anesthesia for a period of time could lead to fundamental alterations in central nervous system function. Receptors whose activity is modulated by anesthetics may or may not be essential for induction of the general anesthetic state but could play a role in how the nervous system responds to this state. Whether interactions like these could be the basis for some of the longer-term effects of general anesthesia<sup>11</sup> remains speculative.

In summary, although we have come a long way, a full appreciation for the mechanism of general anesthetic action and its consequences will in all probability require a systems level approach emphasizing the collective interactions of multiple neurons in which the activity of one or more receptors has been modulated by an anesthetic and perhaps other drugs that are known to contribute to the anesthetic state. In addition to helping to solve the puzzle of anesthetic action and pave the way to more rational drug design and use, such approaches, through the need to address broad integrative aspects of central nervous system function, could have implications well beyond our specialty. The only thing that may be safe to say at this point is that this is an exciting area in which we could experience a few surprises.

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## What Are "Relevant" Concentrations?

*To the Editor:*—We are indeed delighted that we struck a nerve (and not an inhibitory one!) in such a distinguished group of investigators. We are also encouraged that there is so much agreement between our special articles.<sup>1,2</sup> For example, Eger *et al.*<sup>2</sup> conclude, as did we, that binding isotherms for a molecular target may be significantly shifted from the response isotherms for the same target, whether *in vitro* or *in vivo*. Thus, dissociation constants for an anesthetic-target interaction may be very different than EC<sub>50</sub> values for the function of that target. This should not be contentious because it is already well-documented.<sup>3,4</sup>

We also agree that when multiple targets contribute to an effect, the EC<sub>50</sub> of this concentration-effect relation is shifted to the left of that of any of the individual components (their fig. 3, our fig. 1), even with the overly simplistic integrative paradigm of additivity. We both conclude that the steep slopes of concentration-effect curves represent low population variability, although we differ in the interpretation of this observation. It is possible that some anesthetic targets are so important to organism survival that their conservation is ensured, and in turn, their sites and responses to anesthetics are likewise well-preserved. However, we believe that this remarkably conserved response (across the whole animal kingdom) to inhaled anesthetics arises from multiple interacting targets—the normal heterogeneity in any one of which will only have a small effect on the final integrated behavioral response. This interpretation is consistent with knockout and inhibitor experiments to date: the effects on inhaled anesthetic potency is consistently small and incomplete. However, because our current understanding of the integrated behavior of complex neuronal circuits remains in its infancy, critical testing of these ideas will have to await the appropriate studies and modeling methodology.

Therefore, despite agreement, or at least no argument, with many points in our article that render sensitivity a criterion of questionable validity, Eger *et al.*<sup>2</sup> chose to focus on whether the slope of the minimum alveolar concentration (MAC) response yields insight into the number of anesthetic targets and their sensitivity. This is where we disagree. As noted, the mechanism of low variability is not yet clear, so is it safe to draw conclusions from a simple, untested mathematical model that attempts to link the MAC slope *quantitatively* to underlying targets? Eger *et al.*<sup>2</sup> do acknowledge that "Nonlinearities, including thresholds, amplification, and feedback, exist in biologic systems and may obscure the true association between sensitivity of the receptor target and sensitivity of the organism to anesthetics." However, they then dismiss this "important caveat" by assuming "... a linear relation between anesthetic interaction with the receptor target and the anesthetic response of the whole organism." Therefore, their conclusions should be viewed with considerable skepticism because of the admitted invalidity of a major underlying assumption. Even if one accepts this assumption, there are further assumptions that are arbitrary. For example, the conclusion that receptor EC<sub>50</sub> values "... are not expected to differ from clinically relevant concentrations by more than

a factor of 3" is based largely on an assumption supported only by intuition: "We suggest that T [threshold] lies within 0.1-0.9." If their intuition is off by only a little (T is, for example, 0.05-0.95) or if the Hill number is closer to 1 (there is little evidence of cooperative anesthetic binding to any target), the separation of receptor EC<sub>50</sub> from population EC<sub>50</sub> exceeds 10-fold, in accordance with our article. Therefore, it is essential for the reader to recall that a model rests on its underlying assumptions, and if they are faulty, any subsequent "analysis" is simply a mathematical exercise. Here, we are presented with a model containing an admittedly invalid assumption, and another that is arbitrary. Therefore, it would seem scientifically prudent to reclassify their conclusions as hopeful speculations.

Eger *et al.*<sup>2</sup> will counter that we, too, used an invalid assumption (equal, additive effects of multiple targets) in our Special Article,<sup>1</sup> but we used it as a lower limit of complexity to show that shifts in EC<sub>50</sub> can occur even with the simplest model of integration. We would welcome a credible argument that more complex, nonlinear models of integration reduce the likelihood and magnitude of shift in EC<sub>50</sub>.

Some have interpreted our initial Special Article to promote the use of any anesthetic concentration in *in vitro* research. This is not the case. We, too, believe that the likelihood of a target being an important contributor diminishes with increasing EC<sub>50</sub>. However, we believe it is premature and scientifically naïve to exclude the possibility of a target contributing to anesthesia based on this criterion alone. Both articles clearly show that once one accepts that more than one target contributes to anesthetic action, the relation between organism and molecular EC<sub>50</sub> values will diverge (as noted in our article, divergence is common, even with a single target). The magnitude and direction of divergence is not yet predictable. Models are important tools but must be tested by experiment and not by intuition.

What concentrations should be used in *in vitro* studies? Again, we advocate the construction of complete concentration-effect relations to reliably determine the sensitivity of a system. This occasionally requires very high concentrations to find the maximum response of a system. Confining ourselves to examining only "clinical concentrations" in *in vitro* studies limits the information derived, may be misleading, and cannot be regarded as rigorous science. We concede that some consistently measurable response should be evident at clinical concentrations for an *in vitro* system to be judged relevant. However, it is well-known that *in vitro* conditions can alter and, in some cases, eliminate or reverse responses to drugs, so even this concession must be viewed cautiously.

Eger *et al.*<sup>2</sup> did not take the bait from our article and discuss the relevance of the MAC response to anesthesia and to *in vitro* targets. As we stated, anesthesia (as defined by the MAC response) is a quantal event and not a continuous, saturable response. Is it valid to quantitatively relate a continuous *in vitro* variable to this quantal, yes-or-no behavioral response? Perhaps, but only if the underlying mechanism of such a "threshold" is understood. That it is far from understood is

exemplified by quotes from a recent article<sup>5</sup> in which two of the recent articles' authors are coauthors: "These results illustrate the difficulties in attributing behavioral responses to drug-receptor interactions . . .," and ". . . immobilization and hypnosis produced by volatile anesthetics are complex phenomenon mediated by multiple receptor populations." This is exactly the argument underlying our original article.<sup>1</sup>

We remain convinced that sensitivity of *in vitro* preparations cannot be rigorously used as a yardstick for relevance to *in vivo* effects. When constructing their Special Article, Professor Eger informed us that it was an attempt at consensus, normally a desirable corporate goal. However, consensus is a poor strategy for generating knowledge because it inhibits the creative approaches and ideas that move us forward. In the words of Walter Lippman, "Where all men think alike, no one thinks very much." However, we do need to agree that continued debate and thinking in this area are necessary to foster new questions, further research, and ultimately greater insight into the mystery of how general anesthetics exert their clinical effects.

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*In Reply:*—Our article<sup>1</sup> dealt with mechanisms underlying the immobility produced by inhaled anesthetics. We analyzed the possible connections between the population concentration-effect relations applied in the determination of MAC (the minimum alveolar concentration required to eliminate movement in 50% of patients in response to a noxious stimulus) and the receptor concentration-effect relations that might underlie MAC.

From simple, mathematically consistent models, we concluded that an additive effect of several receptors could not explain either the steepness of the population concentration-effect relation underlying MAC or the position of that relation relative to the concentration-effect relations for receptors mediating anesthesia. Assuming a finite variability in individual responses to anesthesia, our analysis concluded that the steepness of the concentration-effect relation underlying MAC results from effects on only one or a few receptors and that the anesthetic concentration depressing or exciting such receptors cannot radically differ from MAC. Eckenhoff and Johansson<sup>2</sup> disagree with the assumptions underlying the proposed model and, therefore, any conclusions resulting from it. However, if one accepts those assumptions, our analysis and conclusions are sound. They differ diametrically from the analysis and conclusions originally offered by Eckenhoff and Johansson,<sup>2</sup> a simpler analysis flawed by truncating the sum of several dose-response curves and improperly fitting curves to the resulting data. Eckenhoff and Johansson<sup>2</sup> found that the combined effects of several receptors could produce the steep population-effect curves found for MAC determinations (Hill coefficients of 6-20), whereas we found that the combined effects of several receptors produced a maximum Hill coefficient of 1.5.

Gottschalk, Eckenhoff, and Johansson argue that our simplistic models may not mirror the complex results that flow from an organ such as the brain, or the spinal cord—which mediates MAC. Perhaps this is true, but our simplistic models lead to conclusions that square with the comment of Eckenhoff and Johansson that "we, too, believe that the likelihood of a target being an important contributor diminishes with increasing EC<sub>50</sub>." Eckenhoff and Johansson argue that our use of simple models that assume linearity or additivity "invalidates" those models because nonlinearities *may* govern the relations that we have analyzed. However, neither they nor we know that nonlinearities govern the relations between multiple receptors sites. Therefore, it seems premature to dismiss the simple models and presumptuous to use the

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term invalidate. Similarly, in our article, we provided more than "intuition" in defining the probable limits to the threshold. Whether more complex models will lead to different conclusions awaits further efforts.

Eckenhoff and Johansson argue that the "remarkably conserved response (across the whole animal kingdom) to inhaled anesthetics arises from multiple interacting targets—the normal heterogeneity in any one of which will only have a small effect on the final integrated behavioral response. This interpretation is consistent with knockout and inhibitor experiments to date: the effects on inhaled anesthetic potency is consistently small and incomplete." We agree that many knockout experiments provide small or no effects,<sup>3</sup> but, in contrast to Eckenhoff and Johansson, we propose the simpler view that no or little effect means no or little effect. The comment regarding inhibitor experiments is incorrect. Some of these produce profound effects on anesthetic requirement,<sup>4,5</sup> and inhibitor studies that do not affect MAC indicate that the inhibited receptor does not mediate MAC. Therefore, not every receptor affected by anesthetics must mediate anesthesia.

The notion that a single receptor might govern a given effect of inhaled anesthetics is consistent with findings for many injected anesthetics. Only one receptor seems to underlie the effects of anesthetics such as propofol, etomidate, and ketamine ( $\gamma$ -aminobutyric acid type A receptor for propofol and etomidate; *N*-methyl-D-aspartate for ketamine), and the concentrations materially affecting each receptor lie within the range producing clinical effects. That is, a single target is probably responsible for the action of these agents. The fact that inhaled anesthetics affect diverse receptors makes it tempting to argue (as do Eckenhoff and Johansson) that each contributes to the anesthesia they produce. Indeed, an effect on a given receptor may only apply to a specific action (e.g., immobility or amnesia). However, such a conclusion may be as incorrect as it would be for the actions of propofol, an anesthetic that can cause amnesia and immobility during noxious stimulation, all through enhancement of the response of the  $\gamma$ -aminobutyric acid type A receptor to  $\gamma$ -aminobutyric acid. And the population dose-effect relation defining the propofol EC<sub>50</sub> for immobility has a Hill coefficient<sup>6</sup> of 6 or 7, a value similar to that for inhaled anesthetics.

All of us agree that a population threshold explains the steepness of the *in vivo* concentration-effect curves for MAC and, further, that individual variability (and measurement error) explains, at least in part, why *in vivo* concentration-effect curves are not infinitely steep. We believe all agree that receptors with EC<sub>50</sub> values that deviate from the population EC<sub>50</sub> value are less likely to be mediators of the *in vivo* effect, but we may disagree on the extent of the deviation required to dismiss a given receptor as relevant.

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Our position continues to be that relevant concentrations for studies of anesthetic effects on the receptors (or interneuronal pathways) that mediate anesthesia (MAC) probably do not differ markedly from concentrations required to produce anesthesia, and that only one or a few receptors mediate the anesthetic effect underlying MAC.

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## Should Imaging Studies Be Routinely Performed Prior to Epidural Steroid Injections?

*To the Editor:*—Epidural lipomatosis (EL) is a rare disorder that results from overgrowth of normal epidural fat. It is often associated with exogenous intake of steroids and is most commonly isolated to the thoracic spine. We present a unique case of steroid-induced thoracic, lumbar, and sacral EL. It is important to recognize that EL, among other disorders, can present in a similar clinical fashion as herniated disc disease but requires a different approach for its management. We also raise the question of when an imaging study should be obtained before an invasive intervention.

A 43-yr-old, 84-kg man with a long-standing history of steroid-dependent asthma presented with new onset lower back pain of 3 months' duration. Symptoms were first noticed after a hospital stay for an asthma attack, during which he received corticosteroids therapy. He described aching pain in the lower back, with lancinating pain radiating down the legs in a radicular pattern. Symptoms were exacerbated by back flexion and were relieved by warm baths and lying flat. During physical examination, he had tenderness upon palpation of the lumbar paraspinal muscles, as well as pain with back flexion and extension. Bilateral straight leg raise was negative at 70°. Motor power of the lower extremities was within normal limits. Magnetic resonance imaging of the spine revealed extensive EL from the lower thoracic spine through S1, causing moderate to severe deformity and constriction of the thecal sac from L3 to S1 (fig. 1).

Before magnetic resonance imaging, the patient received a lumbar epidural steroid injection by another institution for suspected disc herniation, which gave him no relief. Based on the imaging findings, we referred the patient to physiotherapy and recommended tapering his steroid intake, if clinically feasible.

Epidural lipomatosis is a rare manifestation of Cushing syndrome. The abnormal fat deposition is reportedly induced by endogenous or exogenous steroids.<sup>1</sup> In two publications, EL has been attributed to epidural steroid injection.<sup>2,3</sup> The clinical presentation of EL includes back pain that can be associated with radicular symptoms. The causal effect between EL and radiculopathy is generally well-accepted.<sup>4</sup>

This patient's magnetic resonance imaging showed a unique picture of extensive EL affecting the thoracic, lumbar, and sacral spine. This diagnosis was missed by a physician who performed an epidural steroid injection based on clinical presentation, an intervention that



**Fig. 1. Magnetic resonance image sagittal view of the lower thoracic and lumbosacral spine, showing the extent of lipomatosis (indicated by arrows).**

could have exacerbated his disease.<sup>2,3</sup> We believe the diagnosis of EL can often be missed if the appropriate imaging studies are not performed because of its rare incidence and because of a clinical presentation similar to that of herniated disc disease. There is a wealth of information that could be obtained from imaging the spine, such as detecting anatomic abnormalities or gross deformities like spinal stenosis, as well as other spinal cord disorders. The information obtained may influence the invasive management plan, at times eliminating it, at

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other times modifying it. Does that imply that we should order magnetic resonance imaging for every patient referred with back pain and radiculopathy, knowing the financial burden of such an expensive test? One can argue that the cost of a single neurologic injury can offset the cost of many imaging studies. However, to justify the routine use of such an expensive test, one needs to compute the prevalence of many disorders of the spine, such as EL, spine tumors, certain spinal cord diseases, and others—a task that is yet to be performed. For example, the incidence of EL among patients receiving chronic steroid therapy has been found to be high (90%) in one review of 21 cases (19 of 21).<sup>1</sup> Although it is yet to be determined whether routine imaging must precede invasive management of lower back pain, this case suggests that magnetic resonance imaging should be considered before treatment in patients whose history or physical examination results are consistent with excessive corticosteroid concentrations.

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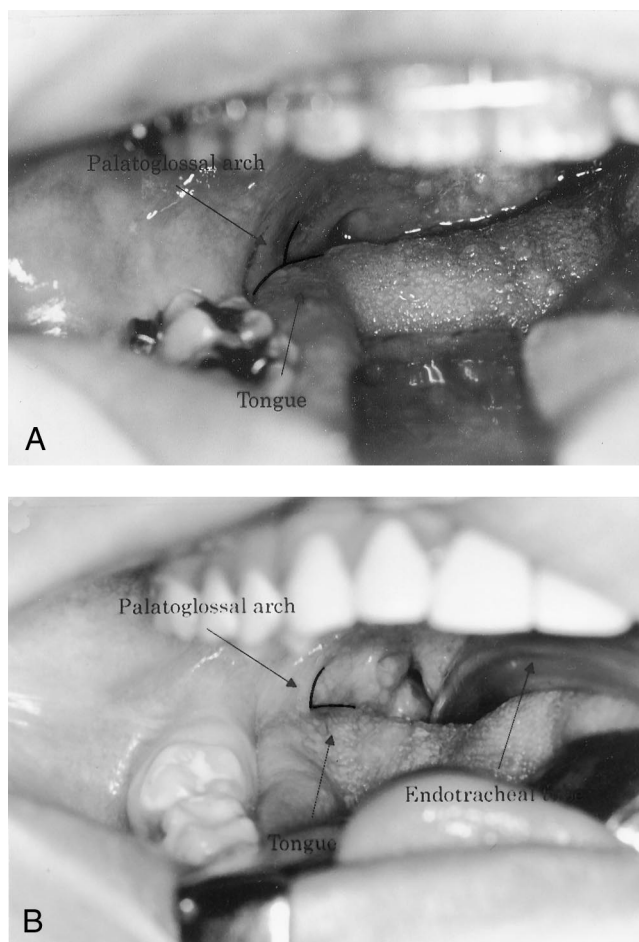
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## Difficult Laryngoscopy Due to the Abnormal Palatoglossal Arch

*To the Editor:*—The palatoglossal arch curves downward and forward from the soft palate to the tongue and forms the lateral part of the isthmus faucium with the palatopharyngeal arch. We experienced difficult laryngoscopy in a patient with an anatomically abnormal palatoglossal arch.

A 15-yr-old boy with mental retardation caused by glycogen-storage disease with frequent hypoglycemic episodes was scheduled for dental treatment during general anesthesia. Premedication consisted of scopolamine and pentazocine. Anesthesia was induced with intravenous midazolam and inhalation of nitrous oxide, oxygen, and sevoflurane. Vecuronium was administered intravenously to facilitate endotracheal intubation. A Macintosh blade was inserted into his mouth and advanced between the right molars and the right side of the tongue. The tongue was about to be displaced to the left to visualize the larynx when the laryngoscopist noticed that it was impossible to displace the base of the tongue with the Macintosh blade. She observed the anatomic relation between the tongue and the pharynx to clarify the reason why the tongue could not be displaced and laryngoscopy was difficult. Her observation of the base of the tongue revealed that the right palatoglossal arch was attached to the dorsal part of the tongue, not to the lateral part (fig. 1).

The palatoglossal arch contains the palatoglossus muscle, which originates in the oral surface of the palatine aponeurosis, extends forward, downward, and laterally in front of the palatine tonsil, and enters the lateral part of the tongue, passing deeply and transversely through the tongue with intrinsic transverse muscle fibers.<sup>1</sup> The muscle elevates the posterior part of the tongue and pulls down the soft palate, thus constricting the isthmus of fauces and closing off the oral cavity from the oropharynx.<sup>2</sup> During ordinary laryngoscopy with the Macintosh blade, the blade was advanced along the right lingual edge toward the right molars and the base of the tongue, then into the pharynx, while the tongue is displaced to the left. However, in this patient, a laryngoscopist could not displace the tongue to the left while advancing the blade along the right lingual edge because the right palatoglossal arch was attached to the dorsal part of the tongue. This anatomic abnormality prevented the displacement of the tongue to the left, which lead to difficult laryngoscopy using the Macintosh blade. The laryngoscopist tried a different method of laryngoscopy without displacement of the tongue to the left. She inserted the Macintosh blade into the open mouth and advanced it forward along the center of the dorsum of the tongue and pushed the base of the tongue upward



**Fig. 1. (A)** The palatoglossal arch attached to the lateral part of the tongue in a normal patient. **(B)** The palatoglossal arch attached to the dorsal part of the tongue in the current patient. This anatomic abnormality prevented the displacement of the base of the tongue to the left during ordinary laryngoscopy with the Macintosh blade.

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without displacing it to the left. This maneuver made arytenoid visualization possible. The palatopharyngeal arch, which was located behind the palatoglossal arch, was normal, and there was no abnormality in the relation between these arches. In general, the so-called Mallampati test is available to predict difficult laryngoscopy.<sup>3</sup> However, preoperative intraoral examination was difficult in this patient because of mental retardation. Based on our experience, we propose that the abnormal palatoglossal arch should be described as one of the anatomic factors that make laryngoscopy difficult to perform.

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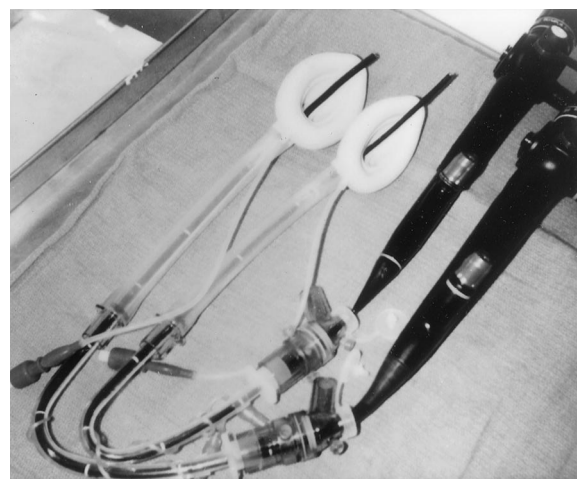
## A New Technique of Fiberoptic Intubation through a Standard LMA™

*To the Editor:*—The purpose of passing a nasal RAE tracheal tube (NRT) (Mallinkrodt, St. Louis, MO) over a fiberoptic bronchoscope (FOB) to fiberoptically intubate through a standard *Laryngeal Mask Airway™* (LMA™) (Laryngeal Mask Co., Henley on Thames, Oxon, UK) (fig. 1) is to gain a 5- to 6-cm greater depth of tracheal intubation compared with a standard endotracheal tube.<sup>1,2</sup> A standard endotracheal tube, when fully inserted through an appropriately sized standard LMA™, enters the trachea by a mere 1-2 cm.<sup>1-3</sup>

Figure 1 shows a 7.0-mm-ID NRT inside a No. 5 LMA™ (upper left assembly) and a 6.0-mm-ID NRT inside a No. 4 LMA™ (lower right assembly). In both assemblies, the distal tip of the NRT is positioned 1 cm proximal to the aperture bars, which then allows one to fiberoptically and sequentially identify the aperture bars, laryngeal structures, and the trachea. The NRT is also positioned within the shaft of the LMA™ with the Murphy eye at the 12 o'clock position to facilitate passage of the tip of the NRT through the middle compartment of the aperture bars and then the vocal cords (over the FOB). With this spatial arrangement of the NRT inside the LMA™ and assuming a distance from aperture bar to vocal cord of 4.0 cm,<sup>3</sup> fully passing an Olympus BF type P40 FOB (Melville, NY) through a 7.0-mm-ID NRT and passing an Olympus BF type 3C FOB through a 6.0-mm-ID NRT results in the FOB entering the trachea by only 2 and 4 cm, respectively. Indeed, in a few patients (5-10%) with the 7.0-mm-ID NRT, No. 5 LMA™, and the larger FOB combination, I have been unable to reach the trachea with the FOB by 0.5-1.0 cm; in these instances, the NRT must be advanced at the same time as the FOB is advanced. However, simultaneous NRT and FOB movement significantly complicates the procedure and disturbs the FOB view. The purpose of this letter to the editor is to point out that by simply cutting off the proximal 2 cm of the NRT, one gains a 2-cm greater depth of tracheal entry by the FOB, while maintaining adequate depth of tracheal intubation by the NRT, *i.e.*, satisfactory clinical performance by both the FOB and the NRT.

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**Fig. 1.** Photograph showing the assembly of equipment (fiberoptic bronchoscope, bronchoscopy elbow, nasal RAE tube, and LMA™) used for fiberoptic intubation of the trachea with a nasal RAE tube passed through an LMA™. The upper left assembly consists of a 53.5-cm-long, 5.0-mm-OD Olympus BF type P40 fiberoptic bronchoscope; a 37-cm-long, 7.0-mm-ID nasal RAE tube; and a No. 5 LMA™. The lower right assembly consists of a 54.5-cm-long, 4.0-mm-OD Olympus BF type 3C fiberoptic bronchoscope; a 35-cm-long, 6.0-mm-ID nasal RAE tube; and a No. 4 LMA™.

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## Claude Bernard, the Spinal Cord, and Anesthesia

*To the Editor:*—It is well-established that the spinal cord is the predominant site where general anesthetics act to abolish movement in response to painful stimulation.<sup>1-4</sup> What is perhaps less well-known is that Claude Bernard<sup>5</sup> (1813-1878) had already shown that the spinal cord can be anesthetized independently of the brain.

Bernard used frogs to demonstrate that chloroform acts on the spinal cord<sup>6</sup> (an English translation by B. R. Fink is available from the Wood Library-Museum of Anesthesiology, Park Ridge, IL).<sup>6</sup> Anesthetic effect was measured as the suppression of reflex limb withdrawal after pinching. The frogs were placed head-down in a vessel filled with a dilute (1:200 in water) solution of chloroform. They were held in place by a rubber membrane. The head and forelimbs of the animal were thus immersed in the anesthetic solution while the hind legs and abdomen remained exposed to air. After a few minutes, the hind legs became anesthetized (as did the forelimbs) as a result of absorption of chloroform through the skin and distribution by blood circulation. Bernard repeated the experiment with a frog whose spinal cord had been cut just below the forelimbs. The hind legs, which at the beginning briskly retracted with pinching, became anesthetized, as seen with a normal frog. Because there was no communication between the brain and the hind legs, Bernard concluded that chloroform is capable of suppressing withdrawal of the pinched limb by acting on the spinal cord alone. (A direct anesthetic effect on nerves had already been ruled out.)

Bernard also showed that anesthetic action on the brain influences the spinal cord. For his demonstration, he ligated the descending thoracic aorta of a frog. After confirming that that pinching of the hind legs still caused withdrawal, he placed the frog head-down in the chloroform solution. The withdrawal reflex was then abolished. He

attributed this suppression to an effect of the brain on the spinal cord because the aortic ligature prevented the chloroform from reaching the lower cord.

The foregoing information does not mean that there was no need for the ingenious work of Rampil and Antognini.<sup>1,3,4</sup> Experiments with amphibians cannot be blindly applied to mammals. Bernard chose a concentration of chloroform much higher than the ED<sub>50</sub> (a 1:200 dilution corresponds to 62 mm, whereas the ED<sub>50</sub> is of the order of 1 mm)<sup>7</sup> and did not compare the relative sensitivities of the brain and spinal cord. Finally, he only looked at reflex limb withdrawal to assess anesthetic effect, whereas the recent studies examined gross purposeful movements.<sup>8</sup>

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