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# No Granuloma and No Intracranial Hypotension

*To the Editor:*—The case reported by Dietrich and Smith[1] again demonstrates that performing steroid epidural injections under fluoroscopic guidance does not absolutely prevent perforation of the dura by the needle tip, because the needle is usually advanced before the next bolus of dye is injected. Measurements of skin to epidural space in magnetic resonance imaging films[2] showed that the posterior epidural space at C6–C7 averages 3 mm in adults; in the case in question, it was not visible in the magnetic resonance imaging in figure 1 or in the computerized tomography scan in figure 3. There are two possible explanations. One is shown in figures 1 and 2 demonstrating that the patient had Chiari I syndrome usually accompanied by a narrow posterior cervical epidural and intrathecal compartments. The other is the C6–C7 space, where a herniated nucleus pulposus is still present, displacing the dural sac posteriorly. There is no posterior epidural space in either figure 1 or figure 3, as noted before.[3]

As far as how the mass got there, if the steroid was injected epidurally, the substance loculated anteriorly where there was more room. Because the epidural space stops at the foramen magnum, it is likely that some of it went intrathecally through the previously made orifice, distributing through the subdural space above the clivus and other areas (figs. 1 and 2). However, 4 weeks is too soon to develop a granuloma, which was not seen at the time of surgery. Most likely, what the authors called *collections* is more likely the "depo" vehicle of triamcinolone preparation. Interestingly enough, when this type of steroid is deposited epidurally, the steroid fraction is absorbed within 2 days into the circulation; it does not cross the dura, as long as it remains intact. The depo vehicle may stay in the epidural compartment for 2–6 weeks. Three doses of 60 mg triamcinolone given within 1 month may be responsible for the accumulation of this substance in the anterior cervical epidural space and the smaller fractions shown intracranially (even after the drainage of the anterior epidural mass). The so-called intracranial hypotension was leakage of cerebrospinal fluid through the hole made at the time of the last epidural steroid injection.

The hanging drop method is not an appropriate technique in the absence of cervical epidural space, although it can be distended if a solution is injected from below. There is no solid evidence that depositing the steroid medication precisely in the intervertebral space where pathologic findings have been reported produces better results than if injected one or two spaces away or, for that reason, if steroids are deposited paravertebrally. Cervical epidural steroid injection can be performed safely and effectively at C7–T1, where there is consistently a wider epidural space that can be reached in more than 85% of the patients with a 11/2-in-long needle[2] without danger of perforating the dura.

Without doubt, a "lightening bolt" sensation with radicular distribution, while the physician is looking for the epidural space, means paraesthesia[4] on one of the intrathecal nerve roots, because there are not nerve roots in the posterior epidural space. If there is a "wet tap," the injection of steroids should be deleted because every steroid preparation available in the United States has preservatives and triamcinolone has polyethylene glycol and benzylic alcohol that may enter the subarachnoid space, initiating an inflammatory reaction in the arachnoid.[4,5] These are not urgent procedures, and the usual option of trying one space above is not applicable because the medication may pass through the previously made hole, as in this case. One hopes that the autologous blood and the fibrin, both well-known central nervous system irritants,[6] injected in the anterior epidural space will not produce arachnoiditis at the operative level. After all, it was neither a granuloma nor a case of primary intracranial hypotension.

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# Cervical Epidural Steroid Injection: Impact of Cervical Epidural Anatomy

*To the Editor:*—I read with interest the case report by Dietrich and Smith[1] describing a rare and potentially catastrophic complication of cervical epidural steroid injection. In their discussion, the authors comment on the technical aspects of cervical epidural steroid injection and also describe measures to minimize such complications. They suggest using the prone position, advancing the needle under continuous fluoroscopic guidance, and avoiding performing the injection at the level of a large protruding disc.

As for the prone position as a way to minimize the likelihood of such complication, there is no evidence presented supporting that notion. In fact, many practitioners continue to use the sitting position for cervical epidural steroid injection but with the forehead supported on a fixed object. Their suggestion of advancing the needle under continuous fluoroscopic guidance is impractical and involves significant radiation beam exposure to both the patient and the clinician performing the procedure. On the other hand, the epidural anatomy may explain the complication that the authors describe. In his article, Hogan[2] found that above the C7–T1 level, the posterior epidural space is almost nonexistent. That makes the use of the loss-of-resistance technique or the hanging drop technique more hazardous and difficult if performed above this level. Hogan warned against advancing the needle in areas of the spine where the anteroposterior depth of the posterior epidural space is diminished, predicting dural puncture. Furthermore, it is common practice to perform cervical epidural steroid injection at C7–T1 or below when the interlaminar approach is used. Hogan advocates the use of an epidural catheter when attempting a cervical

epidural steroid injection for treatment of pathology in the upper cervical spine. In this case, the dural puncture was not recognized, and possible intraneural injection in the spinal cord or the nerve root resulted in granuloma formation. That could explain the "lightening bolt" feeling that the patient experienced in the different aspects of her right arm. It has been also advocated to avoid entry at a spinal level where a large protruding disc is present. The authors addressed that issue adequately. Therefore, the choice of entry at C6–C7 could not be ruled out as the etiology of this unfortunate accident. If the entry had been at a lower level, this complication might have been avoided.

In conclusion, the meticulous study of the anatomy of the spine and its surrounding tissues is an essential first step before embarking into such a hazardous invasive procedure. The clinical concepts that were presented by Hogan[2] in his article are extremely valuable. Through this clinical report and others, we continue to learn and identify the hazardous potential of the many procedures we perform in the field of pain medicine.

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*In Reply:*—Dr. Aldrete wonders how the fusiform anterior epidural mass got there. We postulate that shortly after the first epidural steroid injection, a granulomatous response occurred with thickening of the dura; after the second block, the patient was becoming more symptomatic because of the increasing size of the mass. Superiorly, the inflammation from the mass extended through the foramen magnum, accounting for the postural component of the headaches, so-called axial loading. Inferiorly, the anatomy became distorted from the swelling and mass effect, predisposing to the "lightning bolt" paraesthesia and dural puncture during the third block. The procedure was not aborted, allowing triamcinolone and its preservative to gain access into the subarachnoid space with resultant arachnoiditis. The dural tear did not leak substantial amounts of cerebrospinal fluid until the overall swelling and mass effect of the granuloma lessened many months later. This led to "secondary" intracranial hypotension, which accounted for the incapacitating postural headaches. We suspect that the mass was caused by the preservative in the triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, Princeton, NJ) and not the steroid itself, but there is no way of knowing. The only way to know what the mass was composed of would be to obtain a biopsy, which would involve opening up the dura. This was not performed during surgery because of the risks involved. Injection of triamcinolone acetonide should have been aborted during the third cervical epidural steroid injection (CESI) block in our patient because of suspicion of wet tap due to the paresthesia with radicular irritation.

As far as the technical aspects of CESI, there is no clear consensus as to the superiority of one approach over another (*e.g.*, prone *vs.* sitting, use of fluoroscopy, transforaminal *vs.* interlaminar). In academic practices, the most common position used for CESI was prone (46%), followed by sitting (35%) and lateral decubitus (10%).[1] Only 39% of academic institutions reported use of fluoroscopy for CESI.[1] At our institution, the transforaminal approach is preferred (Mohan Kareti, M.D., Assistant Professor, Director of Pain Management, Department of Anesthesia, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio, verbal communication, May 2004). This approach can be used at nearly any level. The position for transforaminal injection is supine, with fluoroscopy on anterior-posterior and lateral views to confirm proper needle position. Aspiration is performed, and dye is injected to confirm epidural flow and to rule out intravascular (intraarterial), intrathecal, or soft tissue infiltration. For the interlaminar approach, injections are performed below C7, with the patient in the prone position.

The current patient's blocks were performed at an outside hospital, with the patient in the sitting position without head support, using a hanging drop method and intermittent fluoroscopy. Dr. Mchaourab reminds us that there is virtually no cervical posterior epidural space above C7.[2,3] Perhaps this unfortunate complication might have been avoided had the epidural been performed at a lower level. As mentioned by Dr. Aldrete, there is no solid evidence that depositing the steroid medication precisely at the level where pathologic findings have been reported produces better results than if injected one or two spaces away.

Although the patient did have low-lying cerebellar tonsils 7 months after CESI as part of her constellation of symptoms and signs of intracranial hypotension, she did not have a Chiari I malformation as suggested by Dr. Aldrete at the time of the initial CESIs. "Sinking" or "sagging" of the brain is a common finding in patients with intracranial hypotension and may mimic type I Chiari malformation.[4]

Fibrin glue, a mixture of fibrinogen, factor XIII, fibronectin, aprotinin, plasminogen, thrombin, and calcium, has a high tensile strength, tolerates moist environments, and forms a temporary biologic dural seal until healing occurs.[5] Fibrin glue is widely used in neurosurgery and otology to achieve watertight dural closure.[6] Regarding the long-term safety of fibrin glue, the patient is doing fine 17 months after surgery, the mass has regressed, the symptoms of intracranial hypotension have resolved, and the patient has returned to her former position as an attending anesthesiologist.

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# The Eschmann Tracheal Tube Introducer Is Not Gum, Elastic, or a Bougie

*To the Editor:*—We read with interest the article by Brimacombe *et al.*[1] in which the authors demonstrated the superiority of the Eschmann introducer–guided technique of *ProSeal™* LMA (The Laryngeal Mask Company, Ltd., San Diego, CA) insertion over digital and introducer tool techniques. The authors are to be commended for their study, but we are concerned that the Eschmann endotracheal tube introducer was referred to as a *gum elastic bougie*. The gum elastic bougie is a urinary catheter that was originally used for dilation of urethral strictures. This catheter was used as an endotracheal tube introducer (to facilitate difficult tracheal intubation) by Sir Robert R. Macintosh[2] in 1949. Inspired by Macintosh's report, Venn[3] designed the currently used introducer in the early 1970s. He was then the anesthetic advisor to the British firm Eschmann Bros. & Walsh, Ltd. of Shoreham-by-Sea, West Sussex, United Kingdom, which accepted the design in March 1973.[3] The material of the newly designed introducer was different from that of a gum elastic bougie in that it had two layers: a core of tube woven from polyester threads and an outer resin layer. This provided more stiffness but maintained the flexibility and the slippery surface. Other differences were the length (the new introducer was 60 cm, which is much longer than the gum elastic bougie, thus facilitating endotracheal tube railroading over it) and the presence of a 35° curved tip, permitting it to be steered around obstacles.[4,5] The Eschmann endotracheal tube introducer went into production shortly after design acceptance in 1973, and all three design differences (material, length, and curved tip) have contributed throughout the years to the reported success with its use and widespread popularity.[6] As has been previously pointed out by Viswanathan *et al.*[4] in a review article, the Eschmann endotracheal tube introducer is not made of gum, is not elastic, and is not used as a bougie. Because of these differences between the two devices in design and function, we strongly recommend that the Eschmann endotracheal tube introducer should no longer be referred to as a *gum elastic bougie*.

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# Unassisted Gum Elastic Bougie–guided Insertion of the *ProSeal*™ Laryngeal Mask Airway

*To the Editor:*—We read with interest the article by Dr. Brimacombe *et al.*[1] regarding the new insertion technique of the *ProSeal™* laryngeal mask airway (PLMA; Laryngeal Mask Company North America, San Diego, CA). The authors describe a gum elastic bougie (GEB)–guided insertion technique and demonstrate that the new insertion technique is more frequently successful than the (manufacturer-recommended) digital or introducer tool techniques. The GEB-guided insertion technique—a Seldinger technique— optimizes the PLMA insertion attempt: The mask easily negotiates the palatopharyngeal interface without folding over and is directed into the esophagus. In addition, the drain tube is aligned with the esophagus, optimizing orogastric tube insertion.

A potential disadvantage of the GEB-guided technique is that an assistant is needed to stabilize the PLMA at the proximal end while the intubator feeds 5–10 cm of GEB in the esophagus.

We describe an unassisted GEB-guided insertion technique of the PLMA and comment on our clinical experience. We modified the original approach[1] to perform the unaided technique:

1. The PLMA was primed by inserting the GEB in the drain port such that 22 cm of the GEB was protruding from the distal end of the drain tube. This was realized by aligning the first GEB marking to the proximal end of the drain tube.
2. The GEB and PLMA were held as a unit with the dominant hand (fig. 1). The straight end of the GEB was inserted into the esophagus 5–10 cm under visualization during a gentle laryngoscopy.
3. After the removal of the laryngoscope, the PLMA was positioned at the mouth opening. Before advancing the PLMA, the GEB position was confirmed by inserting an extra 3–5 cm into the esophagus.
4. Using the standard digital technique, the PLMA was inserted over the GEB with the dominant hand while the GEB was stabilized with the nondominant hand.

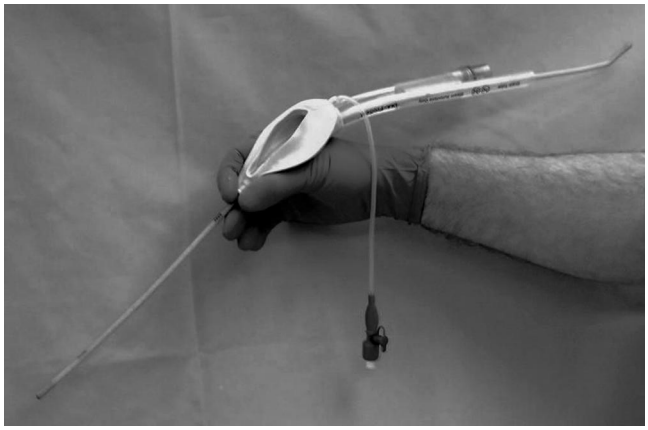

**Fig. 1. The dominant hand holds the *ProSeal*™ laryngeal mask and the distal gum elastic bougie as a unit.**

We used this technique in 10 successive male patients (American Society of Anesthesiologists physical status I or II; age, 20–80 yr)

scheduled to undergo orthopedic procedures for which intubation was not required. We inserted the PLMA in the first attempt and confirmed effective ventilation by the same criteria as Brimacombe *et al.*

A gentle laryngoscopy does not usually allow visualization of the esophagus. The insertion of the GEB behind the larynx is blind and defined by the ability to feed the desired length of GEB without resistance. In our group, we marked the straight end of the GEB at 5 and 10 cm with a sterile marker and confirmed under direct visualization that the GEB was inserted close to or at the 10-cm mark. Misplacement of the GEB occurred in one patient outside this group when less GEB length was protruding from the PLMA and less than 5 cm was inserted retrolaryngeal. In this case, the tip was inserted in a perilaryngeal elastic structure (pyriform sinus), and the malposition was diagnosed before PLMA insertion as a failure of the GEB to advance ("elastic resistance" in step 3). We consider this step necessary because oropharyngeal tissues recover to their original features after laryngoscopy and may pull the GEB out of the esophagus a couple of centimeters. From the initial straight shape during laryngoscopy and insertion, the GEB assumes a curved shape during PLMA insertion because it molds to solid oropharyngeal structures (hard palate, posterior pharynx).

A limitation of our technique is the fact that the nondominant hand may be used during PLMA insertion to extend the head or for a jaw lift. In these cases, the GEB cannot be stabilized without an assistant and may be further inserted in the esophagus with the PLMA. Our technique must be validated in a large group of patients.

The assisted and unassisted GEB-guided PLMA techniques may be used in critical situations when an unexpected difficult airway is encountered or an optimized first insertion attempt is preferred.[2] The GEB-guided PLMA technique has relevance as a teaching tool for the PLMA index finger technique because the smooth ride assured by the GEB should be reproduced with the standard insertion attempt.

The PLMA is a versatile device both in the operating room and outside the operating room. It was used as a rescue airway in an obstetric patient,[3] in a patient with lingual tonsillar hyperplasia,[4] in obese patients,[5] in the intensive care unit,[6] and in patients with manual in-line stabilization.[7] The GEB-guided PLMA techniques warrant further research regarding GEB esophageal insertion in a patient with full stomach, the interaction with cricoid pressure, and the impact of these techniques on the unstable cervical spine.

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# Bleeding, Dysphagia, Dysphonia, Dysarthria, Severe Sore Throat, and Possible Recurrent Laryngeal, Hypoglossal, and Lingual Nerve Injury Associated with Routine Laryngeal Mask Airway Management: Where Is the Vigilance?

*To the Editor:*—In the study entitled "Gum Elastic Bougie–guided Insertion of the *ProSeal™* Laryngeal Mask Airway is Superior to the Digital and Introducer Tool Techniques," Brimacombe *et al.*[1] reported an overall airway morbidity consisting of sore throat (14.6%), dysphagia (10.4%), and dysphonia (7.1%). The authors classified two sore throats, three dysphagias, and two dysphonias as severe at 18–24 h postoperatively. Any sore throat that did not produce "constant pain, independent of swallowing" was excluded from their data. The unusual nature of the reported morbidity associated with the *ProSeal™* laryngeal mask airway (PLMA; Laryngeal Mask Company North America, San Diego, CA) deserves attention for a multitude of reasons.

Practice Guidelines for Management of the Difficult Airway[2] established by a Task Force of the American Society of Anesthesiologists state that the anesthesiologist should follow and evaluate patients with signs and symptoms such as sore throat and difficulty swallowing because these symptoms could indicate bleeding, edema, or more serious complications such as perforation of the esophagus or trachea. The report also instructs the anesthesiologist to enter a written report in the medical chart and appropriately advise the patient. Dysphonia, which occurred in 17 of 240 patients in the study of Brimacombe *et al.*, is not listed as a complication of any of the other methods for managing a difficult airway,[2] nor is it listed as a complication of airway management in standard texts of anesthesiology.[3,4] Regarding the sign of dysphonia, is this the same form of morbidity that Howarth *et al.*[5] referred to as *dysarthria* (1%) in a previous PLMA report? *Dysarthria* describes imperfect articulation, whereas *dysphonia* is any impairment of voice. Clarification of this point is essential so that PLMA providers and patients will know what to expect postoperatively. Did any of the patients have a perforation, permanent dysphonia, or dysphagia? The reported morbidity associated with the PLMA becomes less acceptable when one considers that patients known or predicted to have a difficult airway, a mouth opening less than 2.5 cm, or a body mass index greater than 35 kg/m$^2$ or those at risk for aspiration were excluded from the study. Normally, a group of patients selected by these criteria would have minimal if any morbidity regardless of the method of airway management, *i.e.*, facial mask and airway or even orotracheal intubation. Complications of the frequency and magnitude reported require elucidation and moreover a solution if the technique is to achieve maximum utility in anesthesia practice. There are at least three factors to be considered. Mucosal abrasion as manifested by both visual and occult blood is an obvious factor that could be worsened by pressure ischemia resulting from cuff inflation to 60 cm $H_2O$. Silent regurgitation of gastric acid either during the procedure or in the perioperative period either alone or in conjunction with mucosal abrasions and impaired tissue perfusion could further complicate the

Med-Econ, Inc., Greenville, Ohio, provided document preparation.

process. Proper laryngeal mask airway selection (size) and placement along with periodic cuff deflation should be considered. Both cimetidine and metoclopramide, useful in patients with gastroesophageal reflux disease, might be effective in removing gastric acid from the triad of potential factors.

The role of the PLMA in managing the emergent airway is problematic. Based on the data of Brimacombe *et al.*, the overall insertion time and large SD (digital, 33 ± 19 s; IT, 37 ± 25 s; gum elastic bougie [GEB], 25 ± 14 s) suggests that although some PLMAs were quickly inserted, others were not (> 60 s), even when performed by an experienced provider in a highly selected patient population. The oropharyngeal leak pressures recorded (digital, 31 ± 8; IT, 30 ± 9; GEB, 31 ± 8) are of greater concern because the majority of emergency airway patients have noncompliant airways related to bronchospasm, laryngospasm, obesity, and obstructive airway disease and thus require high, sometimes sustained, peak airway pressures to achieve adequate ventilation. Therefore, replacing a facemask and airway with a leak pressure of greater than 40 with a PLMA with an oropharyngeal leak pressure of less than 25 could prove fatal. Here again, the authors should provide raw data; specifically how many patients had oropharyngeal leak pressures of less than 20–25? The SD of 8–9 suggests a significant number.

The authors, in referring to the GEB PLMA technique, state, "another potential advantage of the technique is that routine use of the laryngoscope may help maintain intubation skills and provide information about the ease of intubation." The GEB PLMA technique had other objective advantages over the blind insertion groups (digital and introducer tool). The incidence of visible blood was 2.5% in the GEB group and 4.4% in the combined groups in which blind insertion was used. This difference suggests that laryngoscopy (partial) reduces airway morbidity and is further supported by a lower incidence of morbidity 18–24 h postoperatively; the authors reported a combined (digital, introducer tool) airway morbidity of 33.5%, compared with 28% with the GEB method.

Table 1 summarizes the authors' results in 240 selected patients treated with the PLMA[1] compared with a group of unselected patients managed by facial mask and airway or orotracheal intubation. The authors caution that their results may not necessarily apply to less experienced personnel, further supporting the choice of facial mask and airway or orotracheal intubation over laryngeal mask airway. Why then would an anesthetist insert a GEB PLMA when a conventional endotracheal tube could be placed in less time, without an assistant? Additional benefits of orotracheal intubation include absolute airway control and relative freedom from morbidity—bleeding, dysphagia, dysphonia, dysarthria, severe sore throat, and nerve injury.[1,4,5]

**Table 1. Success Rate, Insertion Time, and Morbidity for PLMA*, FMA†, and Orotracheal Intubation†**

| | PLMA | FMA | Orotracheal Intubation |
|---|---|---|---|
| Success on first attempt | 90 | 100 | 96 |
| Insertion times, s | 27 | 4.0 | 16 |
| Overall, s | 33 | — | — |
| Failure rate | 1.25 | 0.5‡ | 0.02–0.05 |
| Visible blood | 3.75 | 0 | 0.5 |
| Dysphagia | 10.4 | 0 | 0 |
| Dysphonia | 7.1 | 0 | 0.05§ |
| Sore throat | 14.6 | 0.1 | 0.4 |
| Assistance required | Yes | 0 | Rare |

Data are expressed in percent, except for insertion times (seconds).

* From Brimacombe *et al.*[1] † Extrapolated from unpublished 1996–2001 quality assurance data in an unselected patient population. ‡ Adequate to maintain airway > 30 min. § Hoarseness.

FMA = facial mask and airway; PLMA = *ProSeal*™ laryngeal mask airway.

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*In Reply:*—Dr. Reier's aggressively titled letter demonstrates a lack of understanding of the aims of our study,[1] the laryngeal mask concept, and the *ProSeal™* laryngeal mask airway (PLMA; Laryngeal Mask Company, Henley-on-Thames, United Kingdom) literature and exposes a deep-rooted, unfounded belief that the endotracheal tube (ETT) and facemask are the undisputed accepted standards for modern airway management. We will respond to each of his many points in turn.

First, Dr. Reier is incorrect in stating that sore throats were excluded if they did not cause constant pain, because most patients with a nonconstant sore throat had pain on swallowing or speaking and were therefore included in these morbidity categories.

Second, the use of terminology such as *dysarthria* and *dysphonia* is somewhat confusing because there are a variety of conflicting definitions used by researchers. It is essential that these terms are therefore defined when used. We defined dysphonia as difficulty/pain on speaking. Further analysis of our data reveals that all patients with dysphonia had pain on speaking, and none had any impairment of vocal function. Patients with airway morbidity symptoms were all followed up, and none of these symptoms persisted beyond 72 h.

Third, Dr. Reier suggests that patients with normal airways have minimal airway morbidity when treated with the facemask and ETT. Airway morbidity is indeed low for the facemask (although postoperative jaw pain is more common than the *LMA-Classic*™ [Laryngeal Mask Company, Henley-on-Thames, United Kingdom][2]), but this is certainly not the case for the ETT. An analysis of studies comparing the *LMA-Classic*™ and laryngoscope-guided tracheal intubation reveals that the incidence of sore throat is much higher for laryngoscope-guided tracheal intubation (39% *vs.* 17%; $P < 0.00001$; table 1). An article[3] and accompanying editorial[4] in the August 2003 issue of ANESTHESIOLOGY highlight the dangers of routine tracheal intubation. The incidence of airway morbidity is similar for the PLMA and *LMA-Classic*™.[5]

Fourth, Dr. Reier considers that the etiology of airway morbidity with the PLMA was related to mucosal injury (abrasions during insertion and ischemia after insertion) and to regurgitation of gastric acid. Dr. Reier is clearly unaware of a study demonstrating that the PLMA exerts pressures against the surrounding mucosa that are lower than perfusion pressure[6] and that the PLMA protects the patient from regurgitation when correctly positioned.[7] By default, the most likely cause of airway morbidity with the PLMA is trauma during insertion.

**Table 1. Studies Comparing the Incidence of Sore Throat for the *LMA-Classic*™ and Laryngoscope-guided Tracheal Intubation**

| Study | n | Sore Throat, % LMA | Sore Throat, % LGTI |
|---|---|---|---|
| Adults | | | |
| Alexander and Leach[17] | ~108 | 7 | 10 |
| Akhtar *et al.*[18] | 15 | 0 | 33 |
| Tabo[19] | 30 | 43 | 83 |
| Wulf *et al.*[20] | ~98 | 10 | 28 |
| Joshi *et al.*[21] | ~190 | 13 | 24 |
| Arndt *et al.*[22] | 100 | 37 | 60 |
| Saeki *et al.*[23] | 20 | 15 | 50 |
| Oczenski *et al.*[24] | 25 | 12 | 16 |
| Rieger *et al.*[25] | ~101 | 17 | 19 |
| Higgins *et al.*[26] | ~888 | 17 | 46 |
| Children | | | |
| Klockgether-Radke *et al.*[27] | 50 | 12 | 20 |
| Splinter *et al.*[28] | ~56 | 13 | 5 |
| Overall | ~1,681 | 17 | 39 |
| Statistics | 17% (314/1,886) *vs.* 39% (602/1,528) $\chi = 223$, $P < 0.00001$ | | |

LGTI = laryngoscope-guided tracheal intubation; LMA = laryngeal mask airway.

An important finding in our study was that trauma was less common with the gum elastic bougie–guided technique.[1]

Fifth, Dr. Reier considers that the PLMA has no role in the emergent airway because it is too slow to insert and has an inadequate seal to deal with noncompliant lungs. He also claims, without citing evidence, that the majority of emergent airway patients have noncompliant lungs. We consider that 25–34 s—which was the average time from picking up the PLMA to successfully inserting it into the pharynx, establishing correct positioning, and establishing effective ventilation—is rapid enough for the emergent airway. The PLMA has a seal that is 10 cm $H_2O$ higher than that of the *LMA-Classic*™,[8] which is more than adequate to ventilate even morbidly obese patients[9] and those undergoing laparoscopic surgery.[10] A recent study showed that digital insertion of the PLMA has a success rate similar to that of the *LMA-Classic*™.[11] The *LMA-Classic*™ has been recommended by the American Society of Anesthesiologists for the emergent airway since 1993.[12] Unlike the ETT, the LMA does not trigger bronchospasm,[13] so higher tidal volumes are possible for a given peak pressure for the LMA than for the ETT.

Sixth, Dr. Reier suggests that swapping a facemask with an oropharyngeal leak pressure of greater than 40 cm $H_2O$ for a PLMA with an oropharyngeal leak pressure of less than 25 cm $H_2O$ could prove fatal in the emergent airway. We never suggested making such an exchange in our article. However, to ventilate a patient with a facemask at airway pressures of greater than 40 cm $H_2O$ would inevitably lead to massive gastric dilatation (gastric insufflation begins with peak airway pressures of around 20 cm $H_2O$[7,14]) unless cricoid pressure is simultaneous applied,[14] in which case insertion of a PLMA and passage of a gastric tube might reduce morbidity and mortality.

Seventh, Dr. Reier presents previously unpublished, non–peer-reviewed data suggesting that the facemask and ETT are superior to the PLMA in terms of success on the first attempt, insertion time, failure rate, visible blood, airway morbidity, and the need for an assistant. It is beyond the scope of this reply to debate all these points; suffice it to say that most of the data presented by Dr. Reier are totally at odds with the plentiful, peer-reviewed published data. For example, the incidence of sore throat for laryngoscope-guided tracheal intubation is more like 40% rather than 0.4% (table 1), and the incidence of sore throat with the facemask is more like 4%[2,15] than 0.1%. Also, such interstudy comparisons are difficult to interpret scientifically. Meaningful comparisons between the performance of the PLMA *versus* the ETT and the facemask will have to await the results of properly conducted clinical trials. The benefits of the *LMA-Classic*™ over the facemask and ETT, however, have been well established.[16]

Finally, Dr. Reier states than the PLMA has a failure rate of 1.25% and always requires an assistant. In fact, there were no overall failures, because the other techniques succeeded if the primary technique failed. Matioc and Arndt demonstrate how that technique can be easily conducted without an assistant.

Matioc and Arndt's excellent technique for gum elastic bougie–guided insertion of the PLMA without an assistant extends its range of use to resuscitation and other single-operator situations. We would like to add that the gum elastic bougie–guided technique has an extremely high success rate. The author and colleagues have used it in more than 6,000 patients, with a first-time insertion failure rate of 0.07% (n = 4; failure to position the PLMA in the pharynx), and a first-time ventilation failure rate of 0.5% (n = 28; failure to ventilate once in the pharynx). The etiology of first-time insertion failure was limited mouth opening (n = 3) and unexpected pharyngeal pathology (n = 1). The etiology of first-time ventilatory failure was laryngospasm (which was treated with propofol or muscle relaxation), mechanical compression of the vocal cords (which was treated by applying jaw thrust or removing air from the cuff), infolding of the cuff (which was treated by removing air from the cuff or use of a smaller size), or epiglottic down-folding (which was treated by jaw thrust and reinsertion with maintained laryngoscopy). The overall ventilation failure rate for the technique was 0.08%. There have been no cases of esophageal or pharyngeal injury.

We thank Dr. El-Orbany *et al.* for pointing out our incorrect use of the term *gum elastic bougie*. We were aware of the terminology issue when we wrote the article but decided to use *gum elastic bougie* because we considered it the most commonly used and best-understood term. We would like to point out that the Eschmann endotracheal tube introducer/gum elastic bougie is not ideal for use with the PLMA because the distal portion does not have an atraumatic tip. The development of an atraumatic esophageal guide for use with the PLMA and other extraglottic airway devices is currently under way.

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Anesthesiology 2004; 101:1244 

# Is There Any Reason to Withhold $\alpha_2$ Agonists from Patients with Coronary Disease during Surgery?

*To the Editor:*—London *et al.*[1] and Kertai *et al.*[2] are to be commended for their review on $\beta$ blockers and outcome. As an alternative to $\beta$ blockers, after introduction of $\alpha_2$ agonists in human anesthesia,[3] several large-scale trials or meta-analyses suggested that $\alpha_2$ agonists decrease myocardial ischemia/infarction or mortality after cardiovascular surgery.[4–6] Another meta-analysis reported that $\beta$ blockers decreased cardiac death from 3.9% to 0.8% and that $\alpha_2$ agonists decreased cardiac death from 2.3% to 1.1%.[7] By contrast, another point of view suggests that $\beta$ blockers and $\alpha_2$ agonists cannot carry a relative risk reduction higher than 25%.[8] Authors suggested that $\alpha_2$ agonists are an alternative when asthma/hyperreactive airway,[1,2,7] atrioventricular block,[1,2,7] or decompensated systolic failure[7] are present. In fact, $\alpha_2$ agonists reduce bronchoconstriction in human[9] and dog[10] models, and clonidine increases stroke index in patients with cardiac failure who have a New York Heart Association classification of III or IV[11,12]: The sicker the patient is, the larger the systolic performance seems to increase.[13,14] A recent editorial[15] stated that the "53% reduction in overall mortality [due to $\alpha_2$ agonists is] actually . . . more impressive that was has been found in the pooled $\beta$-blocker studies." Given the fewer contraindications of $\alpha_2$ agonists as compared with $\beta$ blockers, we surmise that clinicians could consider $\alpha_2$ agonists as *first-line* drugs. Given the recent availability of intravenous $\alpha_2$ agonists on the North American market, administration of $\alpha_2$ agonists is simple: oral or intravenous or down the nasogastric tube or rectally. Appropriate reduction in anesthetic doses and volume loading in coronary/hypertensive patients presenting for major cardiovascular surgery[3] or major noncardiac surgery have been delineated. As suggested,[7,15] $\alpha_2$ agonists and $\beta$ blockers should be directly compared. Conversely, they may be combined to achieve maximal favorable effects.

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Anesthesiology 2004; 101:1245 

*In Reply:*—The overall tenor in the letter of Quintin and Ghignone in response to our article,[1] "Perioperative β-Adrenergic Receptor Blockade," advocates the use of $\alpha_2$ agonists as first-line drugs for cardioprotection in perioperative medicine. In this respect, we wish to stress some practical clinical points.

In contrast to the author's recommendation, $\alpha_2$ agonists should not be used to replace β-adrenergic antagonists in patients with high-degree heart blocks, simply because, in addition to their attenuation of catecholamine release, $\alpha_2$ agonists induce bradycardia by vagomimetic effects.[2,3]

Furthermore, $\alpha_2$ agonists have controversial effects in congestive heart failure. As reviewed recently,[4] uncontrolled inhibition of sympathetic tone may have deleterious consequences.

There is often confusion regarding the cellular protective mechanisms underlying $\alpha_2$ agonists and β-adrenergic antagonists. This is reflected by reference 8 cited by the authors in their letter. In principle, although both treatments decrease sympathetic outflow, β-adrenergic antagonists predominantly affect the end organ (reviewed in Zaugg *et al.*[2] and Zaugg and Schaub[4]).

The usefulness of β-adrenergic antagonists in perioperative medicine relies on a limited number of studies with small sample sizes.[1] However, there is a substantive base of large clinical studies in the cardiology literature strongly supporting their use. This does not exist for $\alpha_2$ agonists.

There is limited literature on the use of combinations of antiadrenergic therapies for cardioprotection (simultaneous treatment and not sequential). A useful discussion of this idea has recently been published in Zaugg *et al.*[2] The combination of β-adrenergic antagonists with $\alpha_2$ agonists may result in unexpected pharmacologic surprises, *i.e.*, clonidine plus sotalol may increase blood pressure. There is currently no evidence to combine antiadrenergic treatments except for regional anesthesia plus β-adrenergic antagonists or $\alpha_2$ agonists (mostly intrathecally administered).

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Anesthesiology 2004; 101:1245–6 

*In Reply:*—We appreciate the interest and valuable comments of Drs. Quintin and Ghignone in our Editorial View published in the January issue of ANESTHESIOLOGY.[1] Along with β blockers, $\alpha_2$ agonists may offer significant protection against cardiac morbidity and mortality in patients undergoing major noncardiac surgery.[2–5] $\alpha_2$ Agonists have also been proposed as an alternative cardioprotective treatment strategy in high-risk surgical patients who have relative or absolute contraindication to β-blocker use.[6] To support their view, Drs. Quintin and Ghignone refer to large-scale clinical trials and several meta-analyses performed in recent years. However, the only large-scale study available to date is that of Oliver *et al.*,[5] which showed no overall effect of mivazerol (an intravenous $\alpha_2$ agonist) on the prespecified combined endpoint of myocardial infarction and cardiac death in the whole study population of 2,854 patients. Only a *post hoc* analysis showed that in a subgroup of 904 patients with known coronary artery disease who underwent major vascular surgery, mivazerol was associated with a significantly lower incidence of the combined endpoint. The meta-analyses cited also show similar findings that perioperative benefits may depend largely on the patients at risk and the surgical procedure involved, with the largest benefit observed in patients undergoing major vascular surgery.[2–4] These findings and Drs. Quintin and Ghignone's[7] own experience prompted them to surmise that clinicians could consider $\alpha_2$ agonists as first-line drugs. However, the previous meta-analysis that concluded that clonidine reduced perioperative ischemia[4] was underpowered (358 noncardiac surgical patients in two studies), and effects were only reported on ischemia.[3] Furthermore, the results of the two more recent meta-analyses[2,3] are mainly driven by the results of the large-scale mivazerol trial.

In summary, we agree with the statement of Drs. Quintin and Ghignone that future studies directly comparing $\alpha_2$ agonists and β blockers are needed. Until then, high-risk patients undergoing major noncardiac surgery should be given β blockers that not only reduce perioperative cardiac morbidity but also improve long-term outcome in patients with coronary artery disease, congestive heart failure, and hypertension.[8–11] In case of contraindication to β blockers, an $\alpha_2$ agonist should be considered as a possible alternative to reduce perioperative cardiac complications.[12]

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Anesthesiology 2004; 101:1246–7 

# In Defense of *In Vitro* Findings

*To the Editor:*—The article by Taniguchi *et al.*[1] was informative and provocative. However, we take issue with their contention that the data published by Gissen *et al.*[2] have little, if any, relevance to the clinical situation.

Only one of us (D. H. L.) is a coauthor of that earlier study, but we both agree with all of the criticisms of Taniguchi *et al.* of our methodology. However, the intent of Gissen *et al.* was to do exactly what Taniguchi *et al.* criticized us for doing—overwhelming neurons with potentially injurious agents. We did that to simulate a catastrophic situation that would occur clinically, namely the accidental intrathecal injection of an amount of low-pH chloroprocaine that contained sodium bisulfite intended for epidural delivery.

Taniguchi *et al.* made six criticisms of the study of Gissen *et al.* It is true that (1) "experiments were conducted on isolated segments of nerve that lack a cell body, a blood supply, and normal physiologic defenses" and (2) "the model is, by nature, unstable, and conduction will deteriorate and fail without intervention within a few days." Nonetheless, it is also true that it was experiments with a similar *in vitro* preparation (the isolated frog sartorius-sciatic nerve) that provided the initial data that resulted in today's clinical use of muscle relaxants in anesthesia practice. Both therapeutic and toxicologic events that occur *in vivo* can often be simulated by drug exposure of isolated tissues *in vitro*. For this reason alone, the authors should not be so quick to condemn the data of Gissen *et al.*

Nevertheless, even the four remaining criticisms that Taniguchi *et al.* argue do not detract from the value of the study of Gissen *et al.*:

3. "Conduction failure (as used by Gissen) is an imperfect endpoint." Inasmuch as most of the clinical sequelae from exposing nerve tissue to high concentrations of intrathecal local anesthetics, *inter alia*, are neurologic deficits, they most likely arise from conduction failure, so this seems a logical physiologic endpoint to measure.
4. "It is difficult to know relevant concentrations in an *in vitro* system devoid of normal physiologic processes." This is true, but does not preclude an investigation. The concentration of putatively toxic substances in the system used by Gissen *et al.* was assumed to be equal to the concentration-injected intrathecally that likely caused the cauda equina syndrome. Although it is true that the isolated vagus nerve in a physiologic solution is not in the same environment as, for example, nerve roots passing through the cerebrospinal fluid near blood vessels and other drug adsorbing tissues, we do not know the extent to which the "normal physiologic" processes *in vivo* are compromised by the toxic actions of the deleterious substances.
5. "Nerves are exposed to a bath containing undiluted bisulfite . . . an exposure that is not likely to occur *in vivo*, in which . . . cerebrospinal fluid buffers are present."
6. "The composition of the *in vitro* bath remains relatively constant over time because it lacks redistribution or any appreciable uptake."

Both statements 5 and 6 rest on an assumed mixing pattern of the injected solution over time. When a large volume of concentrated drug intended for the epidural space is accidentally injected intrathecally, over a short time, a relatively high drug (or adjuvant) concentration may be present around the spinal roots for minutes. Little hydrodynamic mixing occurs after the initial bolus injection,[3,4] and the diffusion of substances that controls their dilution occurs on the same time scale as their penetration into nerve tissue, the likely site for toxic actions. Even if these conditions exist for only several minutes, that is potentially long enough to cause cauda equina syndrome. In fact, another study has shown that as little as 3 min exposure to 5% lidocaine can cause irreversible nerve conduction failure.[5] Furthermore, that is exactly what Taniguchi's coauthor believed happened when excessive amounts of 5% lidocaine caused cauda equina syndrome (conduction failure) during continuous spinal anesthesia.[6,7]

Just as Taniguchi *et al.* criticizes the methodology of Gissen *et al.* for not being "clinical or physiologic," a recent editorial[8] raised similar concerns about the methodology of Taniguchi *et al.* Just how clinical and physiologic is the continuous 2-h intrathecal infusion that Taniguchi *et al.* used? What clinical (and physiologic) scenario does that represent? It represents a nonideal way of studying a rare complication[8] and in that sense it is similar to the approach of Gissen *et al.*

In fact, this particular situation is one example of the larger strategic question: How do we account for the causes of the occasional adverse clinical events that are clearly not the fault of the physician's technique but occur frequently enough to suggest causative linkages with drugs, adjuvants, or devices? There can be no prospective approaches, and retrospective studies all suffer from the pitfall of low numbers of events and heterogeneous patient populations with differing demographics and anatomical variabilities that are invisible to physical examination. Carefully conducted animal studies with models closest to the clinical circumstance provide the opportunity to simulate the clinical sequelae and thereby validate the approach, but these experimental effects are often difficult to explain mechanistically. *In vivo* recordings of neuronal activity for the long times over which toxic effects may develop is extraordinarily expensive and unlikely to find funding from the National Institutes of Health, the pharmaceutical industry, or professional societies. The next best approach to reach a mechanistic explanation is to study simpler systems, such as the isolated nerve *in vitro*. We suggest to those who use behavioral phenomenology to study the toxicity of intrathecal agents that their knowledge would be well advanced by electrophysiologic investigations of the nerves exposed to drug, either *in vivo* or *in vitro*, and we would be glad to advise them on how to conduct such studies.

Although not scientific, it is nevertheless noteworthy that after the publication of the article of Gissen *et al.* and the removal of sodium bisulfite by manufacturers from the epidural chloroprocaine formulation, there have been no reports of chloroprocaine-induced cauda equina syndrome. There are probably several reasons for this observation, such as the now routine slow and incremental epidural injections. Therefore, although this is not proof of the safety of chloroprocaine *per se*, it is inconsistent with the conclusion of Taniguchi *et al.* that "clinical deficits associated with unintentional intrathecal injections of chloroprocaine likely resulted from a direct effect of the anesthetic, not the preservative." Before making this claim, should Taniguchi first simulate in rats the same clinical conditions[9–11] (*i.e.*, the intrathecal

injection of massive amounts of chloroprocaine, bisulfite, or both) that prompted Gissen *et al.* to do their study?

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# Chloroprocaine or Sulfite Toxicity?

*To the Editor:*—Whether sulfite contained in drug formulations exerts detrimental effects remains unresolved, even after many years of its use as a pharmaceutical preservative. That sulfite can be toxic is confirmed by a number of animal studies, although many have conflicting results. Furthermore, babies born with deficiencies of sulfite oxidase, the mitochondrial enzyme that oxidizes sulfite to nontoxic sulfate, have a range of serious abnormalities that do not allow long-term survival.[1] However, sulfite is an endogenous substance generated as a result of the catabolism of sulfur-containing amino acids.[2] Sulfite concentrations seem to be an important factor in its toxicity.

Taniguchi *et al.*[3] studied intrathecal neurotoxicity of chloroprocaine, sodium bisulfite, and bisulfite-containing chloroprocaine at the concentrations of each administered in a sulfite-containing chloroprocaine formulation. They showed that in the rat, neurotoxicity, as measured by tail-flick latency and by histologic evaluation, was higher with chloroprocaine alone than with chloroprocaine combined with bisulfite. In explaining their lack of sulfite toxicity, the authors indicated that there may be species differences in sulfite oxidase expression. This is a particularly salient point for rats because these animals have sulfite oxidase concentrations 10–20 times higher than those in humans.[4] Large differences among animals is also exemplified by the finding that sulfite plasma half-lives were reported to be 1–2 min in rats, 3–4 min in rabbits, and 10 min in rhesus monkeys after intravenous sulfite administration.[5] Therefore, the rat may not be a good model for evaluating the potential sulfite component of chloroprocaine toxicity.

The results of Taniguchi *et al.*[3] are also of interest in that they demonstrate an apparent protective role of sulfite in the model used. This raises the question of whether endogenous sulfite should only be considered a metabolic waste product or whether it may serve a useful purpose as an endogenous antioxidant and reductant. In rats, endogenous plasma sulfite was shown to increase when the animals were challenged with endotoxin.[6] The wide range of sulfite effects, *e.g.*, allergic responses, sulfite oxidase deficiency syndrome, *in vivo* and *in vitro* toxicities, and now an apparent protective effect from chloroprocaine, underscores the unique nature of this compound. Interpretation of sulfite toxicity studies should be done cautiously and in the context of possible multiple effects derived from the complex chemistry of this sulfur-containing compound.

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*In Reply:*—We appreciate the comments of Drs. Lambert and Strichartz. Their letter raises a number of valid points regarding the utility and value of *in vitro* experimentation. However, they seem to confuse utility with clinical relevance, trivializing the distinction between isolated fragments of nerve and more complex physiologic systems, and underestimating the disparity between absolute concentrations determined *in vitro* and relevant concentrations in an intact animal.

The purpose of our study was to determine the relative neurotoxicity of intrathecally administered chloroprocaine and bisulfite. Although other investigators had previously evaluated these compounds, their comparative toxicity had never been established. Our results demonstrated that chloroprocaine was potentially neurotoxic when administered at a clinically relevant concentration, whereas bisulfite seemed to be neuroprotective, a rather surprising finding given the view held by many that bisulfite, not chloroprocaine, was responsible for the early clinical injuries associated with Nesacaine-CE. This prevailing view was based on a number of studies but principally the work of Gissen *et al.*[1] Using an isolated

nerve model, they reported that exposure to chloroprocaine with bisulfite at a pH of 3 produced irreversible conduction failure, whereas the same solution at a pH of 7.3 resulted in recovery; irreversible block also occurred with exposure to bisulfite without chloroprocaine, but only at a low pH. Our discussion of possible sources for these conflicting data included factors unique to the model of Gissen *et al.* that present limitations when extrapolating from these *in vitro* studies to intact mammalian systems.

It is puzzling that Drs. Lambert and Strichartz take our discussion of the limitations of the experiments of Gissen *et al.* (with which they completely agree) to represent a global condemnation of *in vitro* experimentation. We do not—nor would any reasonable person—dispute the critical role of *in vitro* experimentation in scientific inquiry and drug development. Indeed, that muscle relaxants were first tested *in vitro* grossly understates the utility of such experiments—it would be fair to say that without *in vitro* studies, few drugs would exist. We have personally used a variety of *in vitro* models in our explorations of anesthetic neurotoxicity. In addition to studies of conduction failure in isolated nerve, we have investigated the role of intracellular calcium using dorsal root ganglia cell culture,[2] an *in vitro* system perhaps more remotely linked to clinical practice. Moreover, included in the reference list of Drs. Lambert and Strichartz is an article containing studies we performed in a plastic tube simulating the subarachnoid space.[3] Nonetheless, although *in vitro* experimentation requires no defense, the limitations imposed by the unique characteristics of these models must be considered.

Drs. Lambert and Strichartz defend the use of conduction failure by Gissen *et al.* as a surrogate outcome based on the fact that clinical deficits likely arise from irreversible conduction loss. We agree that this is a logical physiologic endpoint. However, although clinical deficits may arise from conduction failure, the corollary is not necessarily true, at least not for studies conducted on nerve fragments—there are many things capable of producing conduction loss in this unstable *in vitro* system that would not impact an intact animal. Extrapolation must therefore be made cautiously, a point apparently recognized by Drs. Lambert and Strichartz as they have previously commented: "It is possible that the acute irreversible loss of conduction occurs by different mechanisms than those yielding slower developing prolonged conduction deficits."[4]

They state that lack of knowledge regarding the relevant concentration *in vitro* "does not preclude" investigation. We agree. However, it does place constraints on the data that again must be considered when extrapolating to intact physiologic systems. This point can be readily appreciated by examining the anesthetic concentrations required to produce conduction block in their isolated sciatic nerve preparation.[4] In this *in vitro* model, tetracaine is 100 times more potent than lidocaine and 18 times more potent than bupivcaine.[4] In contrast, despite marked differences in methodology, potency ratios determined *in vivo* closely parallel clinical practice.[5,6]

Drs. Lambert and Strichartz question the use of infusion in our model, asking what clinical (and physiologic) scenario this represents. This model was developed to investigate anesthetic neurotoxicity after a series of reports of clinical injury associated with continuous spinal anesthesia.[7,8] Substantial clinical[7] and experimental[3] evidence suggested that maldistribution was an important etiologic factor in injury, *i.e.*, maldistribution resulted in high anesthetic concentrations within a restricted area of the subarachnoid space, unmasking the potential toxicity of the anesthetic agents. Accordingly, to investigate factors that may affect such injuries, we developed a model in which a restricted sacral distribution is deliberately produced, in part, by administering drug by infusion.[9,10] In its exposure of neural elements to very high, albeit regional, concentrations of anesthetic solutions, our model parallels the clinical injuries that occurred with Nesacaine-CE. Maldistribution provides other advantages as well. The limited spread avoids hemodynamic changes, and unpublished data from our laboratory demonstrate that blood pressure is virtually unaffected with this method of administration. In addition, because deficits are limited caudally, animals require only minimal care, and they can be maintained for prolonged periods after injury without generating concern for their welfare. This in turn permits extensive functional and histologic studies. Nonetheless, the point raised by Drs. Lambert and Strichartz is valid—the extent to which our model differs from the early cases in which large bolus doses of Nesacaine-CE were administered intrathecally is a limitation that must be considered, at least with respect to these particular clinical injuries.

Dr. Baker's letter raises some critical points that reinforce a seventh limitation of the data of Gissen *et al.* that were not included in the comments of Drs. Lambert and Strichartz and that apply to our data as well. It was the postulate of Gissen *et al.* that bisulfite induced injury through liberation of sulfur dioxide, a reaction favored by low pH.[1] However, as Gissen *et al.* note, the normal body economy is well protected by enzymatic conversion of sulfites to less toxic sulfates. But it is possible that enzyme activity was severely depressed in these *in vitro* experiments, given that they were conducted at room temperature on segments of disrupted nerve exposed to a pH equivalent to that of the test solution. With respect to the latter point, despite the comments of Drs. Lambert and Strichartz regarding subarachnoid distribution, it is highly unlikely that even large volumes of solution administered intrathecally would be completely undiluted or that pH would be completely unaffected by cerebral spinal fluid and cellular buffers. Therefore, there are a number of factors that may make the model of Gissen *et al.* uniquely vulnerable to bisulfite toxicity. In contrast, our model may be relatively insensitive because of higher concentrations of sulfite oxidase in rats compared with humans.[11] Clearly, much more information is needed to adequately appreciate the clinical toxicity and the neuroprotective potential of such compounds.

In short, the strengths, limitations, and unique characteristics of the various experimental models must be considered when interpreting the data they generate, and our comments regarding the data of Gissen *et al.* served to highlight the unique aspects of their model that could potentially generate results at variance to clinical reality. These comments can be summed up well by a passage from Drs. Lambert and Strichartz' published investigation of anesthetic toxicity in isolated nerve: "However, caution should be used in quantitatively extending these toxic effects to mammalian nerves *in vivo*."[4]

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# Questioning the Mechanism of Nerve Injury

*To the Editor:*—We were struck by the title "Possible Mechanism of Irreversible Nerve Injury Caused by Local Anesthetics" that appeared recently in ANESTHESIOLOGY.[1] Kitagawa *et al.*[1] showed that "local anesthetics used clinically can form molecular aggregations at high concentrations, resulting in the appearance of detergent properties in these agents." They concluded, "The mechanisms of irreversible neurologic injury induced by high concentrated local anesthetic seem likely to result from the detergent nature of local anesthetics."

In 1994, we published results of *in vitro* experiments regarding the irreversible conduction block associated with high concentrations of local anesthetics.[2] In that publication, we examined the changes in the compound resting potential (CRP) of the isolated frog sciatic nerve. The CRP, like the compound action potential (CAP), is an average of membrane potentials of all the fibers in the nerve bundle. The CRP became less negative (by 18 ± 2 mV, n = 3) when 5% lidocaine was placed in the drug exposure pool. The kinetics of this apparent depolarization consisted of a rapid phase of 5–10 mV in amplitude, occurring in less than 10 s, and a slow phase of 10–15 mV amplitude, taking 10–15 min to reach steady state. The CAP amplitude decreased to zero within 40 s of exposure to 5% lidocaine. On replacement of lidocaine by amphibian Ringer's solution, this apparent depolarization reversed with a corresponding rapid and slow phase, and the CRP was restored to within 2–4 mV of its predrug value after a 2-h washout, although the CAP did not reappear. A similar depolarization of 24 ± 4 mV, consisting of rapid and slow phases, resulted when the nerve was exposed to 200 mM choline chloride dissolved in Ringer's solution. In the choline chloride Ringer's solution, however, the action potential amplitude only decreased by 58.8 ± 6.4% (n = 4) and recovered to within 3.2 ± 0.8% of the initial value after a 50-min wash in Ringer's solution. It is likely that the rapid apparent depolarization is actually an ionic solution artifact resulting from the interaction of the silver–silver chloride electrode in the test pool with the increased [$Cl^-$] present in both 5% (185 mM) lidocaine hydrochloride and 200 mM choline chloride. The mechanism of the slow phase is unclear, but both phases of this depolarization seem to result from differences in the ionic composition and not tonicity, because exposure of two nerves to Ringer's solution containing 400 mM dextrose (7.2%, equally hypertonic to the lidocaine) changed the CRP by less than 0.4 mV, accompanied by small reductions of the CAP (11% and 18%) that remained after 2 h of washing in Ringer's solution. In contrast, if the nerve was intentionally lysed by 5% sodium lauryl sulfate (an ionic detergent) in Ringer's solution, the CRP disappeared within 3 min (a permanent depolarization of 30–40 mV),[3] accompanied by an irretrievable loss of the action potential.

At first glance, the mechanism proposed by Kitagawa *et al.* seems plausible. However, our data suggest that lysis of the nerve cell membrane resulting from a detergent action is not the mechanism for irreversible nerve injury that we observed in an isolated nerve preparation. It seems more likely that the local anesthetic injury that we observed resulted from a "wrecking" of the sodium conductance system (lack of CAP generation) in the face of preserved membrane structure, ionic gradients, and CRP.

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*In Reply:*—We thank Lambert *et al.* for their interest in our article[1] and stimulating comments. We would like to take the opportunity to address the issues raised by their insights.

Lambert *et al.* suggest that the mechanism of local anesthetic neurotoxicity is unrelated to membrane disruption caused by the detergent nature of highly concentrated local anesthetics, instead resulting from breakdown of the sodium conductance system (*i.e.*, absence of compound action potential generation) despite the presence of an intact membrane structure and normal ionic gradients and compound resting potential. The basis for their contention is that, although both compound action potential and compound resting potential in excised sciatic nerves of the bullfrog disappear permanently after bathing in sodium lauryl sulfate (typical detergent) solution,[2] compound resting potential recovers without compound action potential recovery after bathing in 5% lidocaine solution for 15 min, as noted in their earlier electrophysiologic study.[3]

However, the study cited as grounds for their question about our conclusions seems to have an inherent limitation in that the period for bathing the specimen in 5% lidocaine is 15 min. Kanai *et al.*[4] reported a similar study using a single crayfish axon and demonstrated that although resting potential recovers after bathing in 80 mM lidocaine solution for 15 min, resting potential permanently disappears after bathing for 30 min. They suggested that highly concentrated lidocaine causes membrane disruption and indicated in that time-dependent study that sufficient exposure (≥ 30 min) was needed for membrane disruption to be induced by lidocaine. Ready *et al.*[5] also demonstrated successfully that lidocaine at a concentration of 4% or higher induces histopathologic changes in spinal nerves during a dose-dependent study of a spinal anesthesia model in rabbits. The fact that highly concentrated lidocaine causes membrane disruption is thus not in doubt.

We advocated in our article that the mechanism of membrane disruption induced by highly concentrated local anesthetics would result from the detergent nature of these agents.[1] From the perspective of results from various investigators, including Lambert *et al.*, we speculate that an intermediate step may exist in the membrane disruption dynamics induced by 5% lidocaine, with resting membrane potential maintained despite permanent inhibition of action potential. The electrophysiologic phenomena described by Lambert *et al.* may represent an early phase in the sequence of neurotoxic dynamics induced by 5% lidocaine.

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# Movement of the Cauda Equina during the Lateral Decubitus Position with Fully Flexed Leg

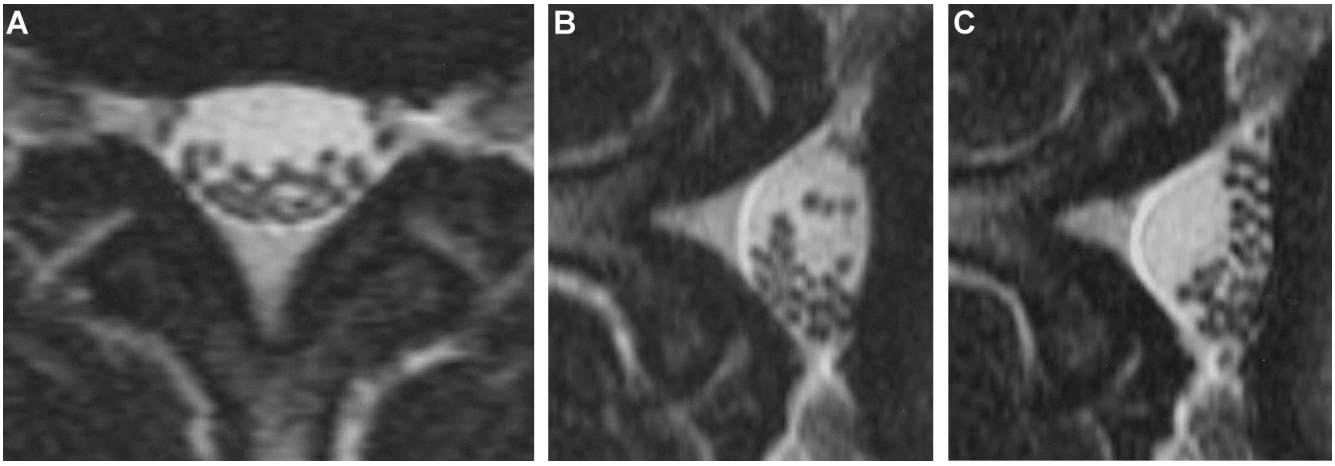


**Fig. 1. Axial view of the cauda equina. Magnetic resonance images (T2 weighted, spin echo, TR 2,000/TE 100 ms) at the L3–L4 level in the same subject were obtained in the supine position (*A*), the left lateral decubitus position without fully flexed leg (*B*), and the left lateral decubitus position with fully flexed leg (*C*). L = left; R = right; TE = echo time; TR = repetition time.**

*To the Editor:*—Spinal anesthesia is performed in the lateral decubitus, sitting, or prone-jackknife position. The lateral decubitus position is the most common position for performance of spinal anesthesia because it allows patients to be more comfortable. We previously demonstrated that the cauda equina was dynamically shifted to the left side of subarachnoid space when patients were in the left lateral decubitus position. To perform spinal anesthesia, however, patients are usually placed in the lateral decubitus position, with the knees drawn up to the stomach, the leg fully flexed, and the neck flexed (fully flexed leg) to curve the back outward. However, there have thus far been no reports on the structural change of the cauda equina in the lateral decubitus position with fully flexed leg. We examined the influences of a fully flexed leg in the lateral decubitus position on structural change of the cauda equina using magnetic resonance imaging. Three healthy volunteers (age, 36 ± 11 yr; height, 160 ± 2 cm; weight, 55 ± 2 kg) were studied with magnetic resonance imaging, and their positions were changed as follows: the supine position, the lateral decubitus position without fully flexed leg, and the lateral decubitus position with fully flexed leg. An interesting movement of the cauda equina was observed by changing position to fully flexed leg in the lateral decubitus position. Figures 1A, B, and C show axial images of magnetic resonance in the supine position, the lateral decubitus position without fully flexed leg, and the lateral decubitus position with fully flexed leg, respectively. As in our previous study,[1] the nerve roots of the cauda equina moved to the left side of the subarachnoid space with gravity in the left lateral decubitus position without fully flexed leg (fig. 1B). Furthermore, the fully flexed leg position moved the roots of the cauda equina to the ventral site and created a free space in the dorsal subarachnoid space (fig. 1C). This phenomenon was observed in all volunteers.

Previously, we have considered that the fully flexed leg position can be used to widen the interlaminal space. However, the lateral decubitus position with fully flexed leg also creates a free space in the dorsal subarachnoid space. Although we do not know whether these changes in the position of the cauda equina have any relevance to the risk of nerve injury during spinal anesthesia, this information should be useful to perform spinal anesthesia.

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# A Modified Rapid Sequence Induction Using the *ProSeal*™ Laryngeal Mask Airway and an Eschmann Tracheal Tube Introducer or Gum Elastic Bougie

*To the Editor:*—One of the most problematic difficult airway management situations is the patient with a known difficult airway who is at risk of aspiration but who is unsuitable for awake tracheal intubation. We describe a new approach to this situation that involves the use of the *ProSeal™* laryngeal mask airway (PLMA; Laryngeal Mask Company North America, San Diego, CA) and a reusable Eschmann endotracheal tube introducer or gum elastic bougie (GEB).

A 62-yr-old, 94-kg man with chronic obstructive pulmonary disease presented for an urgent laparotomy for a suspected perforated appendix. He had a well-documented history of failed laryngoscope-guided tracheal intubation (on two occasions due to poor laryngeal view) but successful facemask ventilation and laryngeal mask airway insertion. The patient insisted on airway management only after induction of anesthesia due to a previous bad experience with awake tracheal intubation. A decision was made to place a GEB using laryngoscope guidance either in the trachea using the bent end first (if any glottic structures could be seen) or in the esophagus using the straight end first (if no glottic structures could be seen) to facilitate insertion of an endotracheal tube or PLMA,[1] respectively. After 10 min of preoxygenation (time taken for end-tidal oxygen to be greater than 90%), the patient was induced with 0.5 mg alfentanil and 180 mg propofol, cricoid pressure was applied by a trained assistant, and 100 mg suxamethonium was administered. As predicted, neither the glottis nor the epiglottis could be seen, despite optimal laryngoscopic conditions. The GEB was therefore advanced with its straight end first along the right posterior pharyngeal wall toward the pyriform fossa. Cricoid pressure was released briefly (< 5 s) so that the GEB could be advanced through the hypopharynx into the proximal 10 cm of the esophagus.[2] The lack of the characteristic tactile sensation from the tracheal rings and the lack of resistance when inserted to length confirmed esophageal placement. A size 5 PLMA was then railroaded along its drain tube into the pharynx, and cricoid pressure was rereleased to allow the distal cuff to enter the hypopharynx. The cuff was immediately inflated with 20 ml air. The PLMA was fixed into position, the GEB was removed, and a gastric tube was inserted *via* the drain tube of the PLMA. Six hundred milliliters of bile-stained fluid was suctioned from the stomach. Ventilation was easy with tidal volumes greater than 1,000 ml without an oropharyngeal or esophageal leak and peak airway pressures of 25–30 cm $H_2O$. Oropharyngeal leak pressure was greater than 40 cm $H_2O$. Anesthesia management was otherwise uneventful, and there were no postoperative pulmonary complications.

In principle, this novel approach to difficult airway management should have a very high success rate because the failure rate for passage of a GEB into either the trachea or the esophagus should be very low, and the success rate for railroading an endotracheal tube or PLMA along it should be very high. If there is doubt about whether the GEB is in the trachea or esophagus, the PLMA should be railroaded first because esophageal placement is much more likely. If this does not provide an effective airway, it is likely that the GEB is in the trachea, and the PLMA should be removed and the endotracheal tube should be railroaded into position. In the unlikely event that both of these options fail, an alternative airway management strategy is required.

Although fiberoptic-guided intubation using a guide wire and airway exchange catheter is feasible using the PLMA,[3] we elected to complete the case with the PLMA. There is a moderate body of evidence (a cadaver study[4] and several anecdotal reports[5–13]) suggesting that a correctly placed PLMA provides protection against regurgitation. One group reported no episodes of regurgitation in 300 patients, as determined by litmus testing of the bowl after removal.[14] The efficacy of seal of the distal cuff against the hypopharynx, as determined in fresh cadavers,[4] is 40–80 cm $H_2O$—more than enough to protect against passive regurgitation.[15] In addition, the process of exchanging the PLMA for a endotracheal tube may put the patient at risk of aspiration, and success is not guaranteed.

The safety of placing a GEB into the esophagus has not been established; however, there is some evidence that it is probably safe when conducted under direct vision and force is avoided, and there can be little doubt that it is justified in the failed intubation scenario. A recent study reported no occult blood on the GEB in 80 of 80 patients,[16] and we have used the technique on more than 6,000 occasions without any evidence of minor or major esophageal injury. Furthermore, GEBs are frequently misplaced into the esophagus with the bent end first (probably more likely to cause injury than with the straight end first) during failed intubation, but esophageal injury is rarely reported.[17] It is worth noting that the American Society of Anesthesiologists already recommends the use of the esophageal tracheal Combitube (Kendall Sheridan Catheter Corporation, Argyl, New York),[18] which is known to cause esophageal injury,[19–21] as an option in failed tracheal intubation. The development of an atraumatic esophageal guide for use with the PLMA and other extraglottic airway devices is currently under way and should make this approach even safer.

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# GlideScope®-assisted Fiberoptic Intubation: A New Airway Teaching Method

*To the Editor:*—It is well known that "practice makes perfect" when learning fiberoptic intubation (FOI). Although subjecting patients with normal airways to awake FOI for mere teaching purposes is usually inappropriate, it is common to have residents obtain FOI experience in patients with normal airways during general anesthesia. However, conducting FOI in this setting has time pressures that are not present with awake intubation, because special concerns of oxygenation, ventilation, and awakening exist. Complicating this situation is the fact that frequently only the operator can see what is happening, such that the supervisor can only offer limited assistance.

The purpose of this letter is to describe a new technique for FOI using the GlideScope® video laryngoscope (Vitaid Airway Management*, Williamsville, NY). After anesthetic induction, a GlideScope® is introduced in the usual manner,[1,2] followed by introduction of the fiberoptic bronchoscope (FOB). While the resident manipulates the FOB into position, the supervisor monitors the GlideScope® display to see where the tip of the FOB is located. (The resident looks only through the FOB and does not look at the GlideScope® display.) The supervisor then provides verbal feedback to the resident as to the location of the tip of the FOB. When the FOB has entered well into the trachea, the endotracheal tube is passed over the FOB into the glottis. Here, use of the GlideScope® can again be helpful because, should the endotracheal tube get caught on the arytenoids[3] or other laryngeal structures, it becomes evident on the GlideScope® display, and appropriate corrective action (such as twisting the endotracheal tube) can easily be taken.

It should also be pointed out that during general anesthesia, the lumen of the pharynx and the larynx usually becomes smaller as a result of reduced muscle tone. Insertion of the GlideScope® lifts the tongue and the jaw to open up these structures and facilitates the identification of anatomical landmarks by the user of the FOB.

Finally, it should be emphasized that this technique would be expected to be useful for other purposes, as in situations where FOI is difficult even for experienced operators, as may occur, for example, in the case of an airway soiled by blood.

Based on using this technique in eight anesthetized patients to date, I have found it to be particularly valuable, especially in averting lengthy detours to peripheral structures such as the piriform fossae. It was also my experience that this technique offers a "macro view" that is helpful even when a video bronchoscope is available. Although it is my clinical impression that FOI using this technique can be accomplished in a shorter period and accelerates resident learning, formal studies are needed to test these impressions.

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# An Alternative to Transtracheal Injection for Fiberoptic Intubation in Awake Patients: A Novel Noninvasive Technique Using a Standard Multiorifice Epidural Catheter through the Bronchoscope Suction Port

*To the Editor:*—Anesthetizing the airway caudal to the vocal cords (in preparation for awake fiberoptic tracheal intubation) may present a clinical challenge because patients may not tolerate a transtracheal procedure or identification of landmarks may prove difficult. Another technique is to insert a bronchoscope through the vocal cords and then spray local anesthetic through the "work port." However, the latter technique may evoke patient discomfort because the bronchoscope tends to encroach on tracheal mucosa, thereby noxiously stimulating the internal branch of the recurrent laryngeal nerve. Alternatively, we describe a unique method of atraumatically anesthetizing the lower airway using equipment that is readily accessible in most operating rooms.

*Via* the suction port of a small adult (3.8 mm OD) bronchoscope (Olympus PortaView® LF-GP Fiberscope, Melville, NY), we insert a 20-gauge nylon closed-end multiorifice epidural catheter (model 11771-01; Portex, Keene, NH) until the tip of the catheter begins to emerge from the distal tip of the bronchoscope (fig. 1). A local anesthesia–containing syringe is affixed to the bronchoscope (fig. 1), thereby freeing both hands for bronchoscope operation. After oropharyngeal topical application of local anesthetic, the bronchoscope is inserted until the tip lies immediately superior to the vocal cords. Thereafter, the epidural catheter is advanced (fig. 2) into the trachea under direct visualization, and local anesthesia is sprayed during catheter advancement. When anesthesia has been achieved, the bronchoscope is inserted into the trachea, and the endotracheal tube is advanced.

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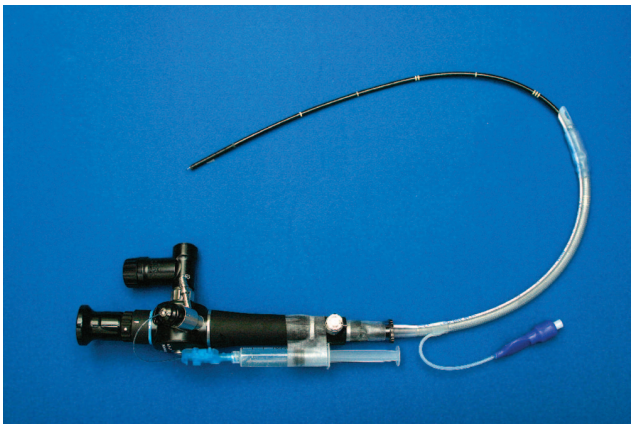

**Fig. 1. Bronchoscope (Olympus PortaView® LF-GP Fiberscope) prepared with endotracheal tube and 20-gauge nylon closed-end multiorifice epidural catheter.**

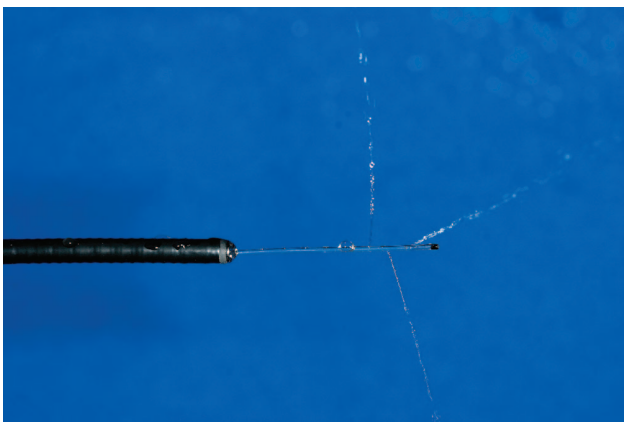

**Fig. 2. Local anesthesia atomization after advancement of the epidural catheter through the distal tip of the bronchoscope (Olympus PortaView® LF-GP Fiberscope).**

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# More Information on Patients with Factor XI Deficiency

*To the Editor:*—It has been called to our attention that our recent Clinical Concepts and Commentary article, "Current Concepts of Hemostasis: Implications for Therapy," contains a statement that implies that postoperative bleeding in patients with factor XI deficiency is usually mild.[1] We wish to clarify this implication. Patients with factor XI deficiency over a lifetime are mild bleeders who do not usually experience the chronic, crippling hemarthrosis or other severe bleeding episodes so typical of severe classic hemophilia or hemophilia B. Nonsurgical bleeding episodes in factor XI–deficient patients are usually mild over a lifetime. We wish to make it clear, however, that it is quite possible for patients with factor XI deficiency undergoing surgery to bleed severely unless they are pretreated. The replacement therapy for factor XI deficiency in the United States usually consists of plasma replacement therapy before an operation. More recently, recombinant factor VIIa has been used for factor XI deficiency, and it has been found to be effective, although it is not yet approved by the US Food and Drug Administration for this indication.[2] One of the readers

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of the journal pointed out to one of us *via* e-mail that patients with factor XI deficiency undergoing cardiopulmonary bypass may bleed excessively. We agree with this statement, and at our institution, such patients would be treated, preoperatively and postoperatively, with recombinant factor VIIa or with plasma replacement therapy, which may require plasma exchange transfusions to increase factor XI to 50% or greater. Factor XI concentrates are available in Europe but not in the United States, and these concentrates have occasionally been associated with thrombotic side effects. In summary, we wish to emphasize that even though patients with factor XI deficiency usually have mild bleeding episodes over a lifetime, this does not mean that they may not experience extensive hemorrhage after severe trauma or surgery. Although some patients with factor XI deficiency do not bleed after operative procedures, a family history of bleeding after surgery is suggestive that relatives of such patients will also bleed during surgery.

It has been recommended that replacement therapy for factor XI deficiency also include the use of antifibrinolytic agents such as tranexamic acid because it seems that one function of factor XI is to boost thrombin generation to the extent that the "thrombin activatable fibrinolytic inhibitor" (TAFI) can be activated.[3] Adding tranexamic acid enhances the antifibrinolytic effect.

We are grateful to the reader who called this potential interpretation of factor XI deficiency to our attention.

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