While awaiting arrival of the emergency team, the nurse administered 100% O_2 by a self-inflating device. On arrival, the emergency team noted no spontaneous respirations, pinpoint pupils, pulse 78 beats/min, and blood pressure 118/60 mmHg. She was unresponsive to verbal commands and vigorous shaking. Fetal heart rate (FHR) was 60 beats/min from a baseline of 130. Naloxone (0.4 mg) was given as an intravenous bolus to which the patient responded immediately with prompt awakening. Seven minutes after naloxone, FHR increased to 150–160 beats/min. The rest of her labor course was unremarkable.

At 4:20 PM, the patient underwent a normal spontaneous vaginal delivery of an 8-lb, 1-oz male infant with Apgar scores of 9 and 10 at 1 and 5 min, respectively.

Sufentanil is a highly lipophilic opioid with a strong affinity for the opioid receptors. Its lipophilicity is advantageous in limiting its mean residence time in CSF, thereby minimizing potential side effects, such as delayed respiratory depression.[1,2] However, early respiratory depression is of concern. Recently, a case report appeared that described respiratory depression after a single dose of intrathecal sufentanil in a laboring parturient.[3]

The exact mechanism by which the respiratory arrest occurred in our patient is not clear. According to the study by Hansdottir *et al.*, intrathecal sufentanil has a mean residence time of 0.9 h in CSF but almost 7 h in plasma.[1] They pointed out that, after repeated doses of intrathecal sufentanil, there was a theoretical risk of accumulation of this drug in plasma but not in CSF. This may explain the respiratory arrest seen in our patient. The second dose of sufentanil was given approximately 3 h, 40 min after the first dose, at a time when the plasma concentration of the first dose, insufficient by itself, may have been augmented by the second dose to that above the threshold for respiratory arrest. However, cephalad migration of sufentanil in the CSF, leading to central respiratory depression, cannot be ruled out. D'Angelo *et al.*, from their observation of the cephalad extent of sensory changes resulting from intrathecal sufentanil administered at the lumbar spinal level, cautioned about the potential for respiratory depression.[4]

There are few data regarding the optimal dose of intrathecal sufentanil for labor analgesia, for either the initial bolus or repeat doses. An abstract addressing this issue suggests that there may be no advantage to using doses in excess of 7.5 μg intrathecal sufentanil.* Whether such a dose would reduce the likelihood of early respiratory depression remains to be investigated.

We wish to emphasize that patients receiving intrathecal sufentanil be monitored closely after each dose. As suggested by Hays and Palmer, this should include checking the respiratory rate every 15 min for the first hour after injection and every 30 min for the next 2 h.[3] It may be prudent to note the cephalad spread of sensory changes after each dose. Appropriate resuscitation equipment and personnel must be immediately available. Furthermore, dose-response studies are necessary to establish the optimal dosage schedule for single injection and continuous intrathecal sufentanil for labor analgesia.

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Sevoflurane, Fluoride Ion, and Renal Toxicity

To the Editor:—In a recent editorial regarding a study by Kharasch *et al.*,[1] Brown[2] claims that sevoflurane is "biotransformed in a quantitative fashion similar to enflurane." How "similar" are they? In patients with renal impairment, sevoflurane administration resulted in average serum fluoride concentrations 85% greater than those given enflurane.[3] It has been reported that 8.1% of adult patients given sevoflurane had a serum fluoride concentration greater than 50 μM.[4] What is the corresponding percentage for enflurane? Brown's con-

tention that sevoflurane is not biotransformed to a greater extent than enflurane simply is not tenable.

Also, nothing was mentioned in the editorial about the *other* products of the biotransformation by cytochrome P450 of sevoflurane *in vivo,* namely hexafluoroisopropanol (HFIP) and the single carbon product that eventually results from the broken-off fluoromethoxy group of sevoflurane. Sevoflurane is unique compared to enflurane, isoflurane, and desflurane in that it contains a monofluorinated methoxy group rather than a difluoromethoxy group. The former by necessity undergoes a different mechanism of biotransformation after initial P450 metabolic attack.

The frenetic push toward convincing us that all this fluoride (and stoichiometric amounts of HFIP plus single carbon fragments) is not clinically important, is an attempt to obfuscate the fact that sevoflurane is an old anesthetic that moves us back in the direction of the heavily biotransformed agents of the past. How long did it take to report methoxyflurane nephrotoxicity after its introduction to clinical practice in 1959? Seven years. How many millions of anesthetics had been given with it by then before that particular toxicity became apparent? How long did it take before (most of us) recognized the existence of halothane-related hepatotoxicity? Are these toxicities related to biotransformation? Of course. Can we remotely predict these toxicities? No. Our recent strategy has been to develop volatile agents that undergo the lowest possible biotransformation, a strategy that makes sense.

The notion that somehow serum fluoride is no longer important in nephrotoxicity, to which Brown[2] and Kharasch *et al.*[1] have attached so much importance, obscures a more basic and important fact about this drug, which soon may be given to millions of Americans. Sevoflurane *is* heavily biotransformed. The editorialist's aversion to "shibboleths and jigsaw puzzles" [1] notwithstanding, the "fluoride issue" is *not* resolved.

Kharasch *et al.*[1] point out that inorganic fluoride is a nephrotoxin and cite the example that deuteration of methoxyflurane, which decreases methoxyflurane P450-dependent metabolism and fluoride release, diminishes renal toxicity. Despite their own citation, these authors attempted to dissociate serum fluoride concentrations from renal toxicity, by concluding that "neither peak systemic fluoride concentrations nor duration of fluoride increase alone can be applied nonselectively to all anesthetics to explain or predict nephrotoxicity." They imply that there may be some other metabolite or unknown metabolic consequence of methoxyflurane biotransformation that causes renal toxicity. After many years of methoxyflurane study, none has been found. Further, they suggest, without proposing any mechanism, that the small amount of fluoride produced *in* the kidney is relevant to nephrotoxicity, whereas the large amount of serum fluoride that passes *through* the kidney for excretion is irrelevant.

We moved steadily, after the first fluorocarbon anesthetics were introduced, toward agents with less biotransformation, for sound toxicologic reasons. Sevoflurane, which was rejected by Baxter-Travenol and Anaquest (Ohmeda) for clinical development, is a step backward, despite the likelihood that it will have desirable clinical characteristics.

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In Reply:—My editorial[1] was focused only on my thoughts concerning the article by Kharasch *et al.*[2] in the same issue. The toxicity of compound A, hexafluoroisopropanol toxicity, and other aspects of sevoflurane, both political and scientific, were not discussed. The editorial was strictly confined to commentaries of the novel concept that local renal production and hence high local renal concentrations of fluoride ion may be of greater importance in renal toxicity from fluorinated inhalation anesthetics than is hepatic fluoride production as measured by the plasma fluoride concentration. Contrary to Tinker and Baker's contention, neither my editorial (nor Kharasch *et al.*'s original paper[2]) discounted the nephrotoxic potential of fluoride ions. The issue was whether renal or hepatic production of fluoride was the more important vector of nephrotoxicity with inhalation anesthetics. The fact remains that several publications have documented plasma fluoride concentrations well in excess of 50 μM, whether from sevoflurane, enflurane, isoflurane, or fluoride ion intoxication,[3] without evidence of renal toxicity.

Tinker and Baker refer repeatedly to "heavy biotransformation." Let me supply the facts. Eight percent of the enflurane dose and 3–5% of the sevoflurane dose[4,5] are metabolized. Tinker and Baker are