gesia. In fact, in another study, again from a retrospective analysis of the ENIGMA trial data,[2] the same authors reported that intraoperative administration of nitrous oxide reduced the risk of chronic postsurgical pain by more than half. The authors also found that chronic postsurgical pain was common after major noncardiac surgery. The authors state, "The presence of chronic postsurgical pain cannot be considered as a trivial event. Our data indicate that it affects all dimensions of general health status, including social function, physical activities, emotion, and mental health. Chronic postsurgical pain also has a major impact on patients' daily living, including loss of productivity, an increase in medical expenses, and costs of repeated hospital admissions."

It is highly likely that a cost-benefit analysis that includes the benefits of nitrous oxide (*i.e.*, reduced chronic postsurgical pain) may tilt the balance toward nitrous oxide. I think the authors may have rushed to conclude that nitrous oxide has no role in modern anesthetic practice. Unfortunately, such selective reporting may inappropriately dissuade anesthesia practitioners from using nitrous oxide and deprive our patients from some potential long-term benefits from its use.

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In Reply:

We appreciate the interest Joshi has taken in our *post hoc* studies of the ENIGMA trial.[1] As we stated in our article, we measured costs from the perspective of an implementing hospital. We did not consider postdischarge costs. The results of the persistent pain study, conducted at one of the institutions involved in the multicenter ENIGMA trial, was not anticipated and had not yet undergone peer review at the time of publication of the cost-benefit study. It should thus be considered as hypothesis-generating rather than as compelling evidence of a protective effect of nitrous oxide. When considered alongside the results of the ENIGMA trial it is possible that nitrous oxide may have adverse effects in the short-term (infection, cardiac events), but if the patient survives these, then nitrous oxide may be beneficial (for pain).

We must emphasize that at no point have we stated that nitrous oxide has no role in modern anesthetic practice. We have previously concluded that the routine use of nitrous oxide in patients undergoing major surgery should be questioned, and that there is no cogent argument to continue using nitrous oxide on the basis that it is an inexpensive drug. We have emphasized that further studies are needed, and are now measuring long-term pain data in such a trial of 7,000 patients that is currently underway.[2]

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Intranasal Application of Xenon: A Shortcut to the Brain or Just a Longer Way to It through the Lungs?

To the Editor:

Intranasal application of low-dose xenon has recently been reported to have beneficial effects on perioperative analgesia in patients undergoing abdominal hysterectomy.[1] This is a novel route of xenon application that could help to circumvent the problem of its high cost and allow wider use of this gaseous anesthetic. However, we have several concerns regarding the pharmacokinetics and route of action of intranasally applied xenon suggested by the authors.

As shown by blood gas analysis undertaken by the authors in two healthy volunteers, a steady-state concentration of approximately 500 nl/ml xenon was reached in the blood of the internal jugular vein (IJV) within 10 min after commencement of intranasal delivery of xenon at 1 l/h. Simultaneously, as stated by the authors, samples of peripheral venous blood were ≤20 nl/ml xenon. The authors consider the concentration of xenon in the IJV to be a reflection of xenon content in cranial blood and target brain tissue.

Here, as well as in their previous work,[2] the authors advocate a direct delivery route of xenon from the nose to brain that is supposedly accountable for the beneficial effects of xenon on pain. Although it is not clearly explained in their article, the authors previously suggested that xenon could reach brain tissue by diffusion from the venous sinuses of the cranial cavity.[2]

A portion of nasal venous blood is indeed diverted to intracranial veins *via* direct communication between the ophthalmic veins, pterygoid plexus, and cavernous sinus, but the other portion of blood is drained extracranially by facial

veins directly into the IJV. Stated differently, the cavernous sinus receives only a portion of xenon-enriched blood from the nasal space, but the IJV collects almost all the blood from it. Therefore, a steady concentration of xenon in the IJV 10 min after intranasal application in volunteers is more a reflection of saturation of the nasal mucosa and nasal (not cranial) venous vascular beds with xenon. The actual concentration of xenon in the cavernous sinus is probably less than 500 nl/ml because the latter collects only a portion of nasal venous blood. Furthermore, although the cavernous sinus does communicate with basilar and superficial cortical veins, it is a "blood collector" that is ultimately drained into the IJV, and retrograde flow of xenon-containing blood toward cortical matter is very unlikely. Diffusion from the sinus itself to surrounding brain tissue and then to the rest of the brain is also unlikely.

Therefore, a likely explanation of how xenon was delivered to the brain, and possibly the spinal cord, to mediate its analgesic effects would be transport with arterial blood from the left heart.

Blood collected from the IJV in the right heart passes through the lungs, so the larger part of xenon will be rapidly exchanged with alveolar air and eventually lost with exhaled gas in spontaneously breathing volunteers or in study subjects mechanically ventilated with relatively high minute volumes. Indeed, as evidenced by a pharmacokinetic study undertaken by the same research team in anesthetized pigs (minute volume, about 5 l/min), arterial blood levels of xenon were $\leq$20 nl/ml in this setting.[3] Clearly, and considering that clinically relevant anesthetic concentrations of xenon are in the micromolar range, the likelihood of such concentrations of xenon exerting clinically significant effects is very unlikely. Hence, the next question would be how intranasally delivered xenon could have reached target tissues at concentrations capable of improving (though only minimally) intraoperative analgesia and reduced postoperative pain reported in their article? Here, in our view, is one feasible explanation.

Given the usage of endotracheal tubes with inflatable cuffs impermeable to xenon, the authors allege that direct pulmonary contamination with xenon was avoided. However, did they consider that xenon-containing central venous blood would be diverted to the lungs? Here, xenon would readily escape into the alveolar space by diffusion because of its very low blood-gas partition coefficient[4] and would accumulate in the anesthetic circuit operated in the minimal-flow ventilation (oxygen flow, 300 ml/min) mode that the authors used. In our view, what the authors intended to present as solely intranasal delivery of anesthetic gas turned into inhalational anesthesia with rebreathed low-dose xenon. We think that the authors should not have limited the pharmacokinetic study to volunteers only; xenon concentrations in the anesthetic gas mixture and in the arterial blood of study subjects should also have been determined.

Finally, if the beneficial effects of low-dose xenon described in their article are indeed clinically significant and if our assumption is correct, then there is probably no need to complicate the anesthetic procedure and administer xenon intranasally. A conventional inhalational route of low-dose xenon (*e.g.*, 15–20 ml/min) implemented as a part of low- or minimal-flow, closed-circuit anesthesia should be more than sufficient to benefit from xenon as an addition to the anesthetic protocol.

Xenon is a valuable anesthetic and we appreciate the authors' efforts to overcome the limitation of its high cost by administering it at low-dose to use it more widely in clinical practice. However, would low-dose xenon result in better analgesia compared with inhalational anesthetics applied at conventional doses (not at 0.5 minimal alveolar concentration desflurane, as tested in their article) or in combination with nitrous oxide; or would the difference be insignificant if xenon is applied at a low dose? These are the questions that have to be answered in the future.

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In Reply:

In our recently published article, "Intranasal application of xenon reduces opioid requirement and postoperative pain in patients undergoing major abdominal surgery: A randomized controlled trial,"[1] we have reported data showing beneficial effects of intranasally applied xenon on intraoperative opioid requirement and postoperative analgesia in patients undergoing abdominal hysterectomy. Beside these main results we have also described the pharmacokinetic of intranasally applied xenon using blood gas analyses. We would like to thank Petrenko and Baba for their interest in our work. We are very pleased to provide additional information regarding our study results and are thankful for the opportu-