The increase in ICP with halothane was accompanied by a significant increase in cerebral blood flow (CBF), while the increase in ICP with isoflurane was not. 3) Isoflurane decreased cerebral metabolic rate of oxygen (CMR_{O_2}) to a greater extent than halothane. From these observations the authors conclude that isoflurane ". . . may be a more reasonable choice in neurosurgical settings."

We feel that the exact opposite conclusion may be drawn from these observations. That an increase in ICP is detrimental to the brain, particularily in neurosurgical patients, is universally accepted.[2] Assuming that all other parameters remain the same, an increase in ICP would decrease cerebral perfusion pressure, and this in turn would decrease the CBF and reduce the supply of oxygen and other nutrients to the brain. The authors' observation that halothane and isoflurane in equipotent concentrations caused similar increase in ICP suggests that both anesthetics are detrimental to the brain in a closed skull. However, halothane increased CBF while isoflurane did not, suggesting that no relationship existed between ICP and CBF in this study. The increase in CBF with halothane was not necessarily the cause for the increased ICP in this group. It was, perhaps, a salutary response that improved oxygen and nutrients supply to the compressed brain.

Whether the decrease in CMR_{O_2} caused by isoflurane, and to a lesser extent by halothane, is a sign of brain protection or brain starvation remains moot. It is not clear why the authors chose to interpret the effect of isoflurane on CMR_{O_2} as beneficial; it may be interpreted just as easily as detrimental. Hagerdal *et al.*,[3] using common metabolic criteria, showed that a 25% reduction in CMR_{O_2} was protective in cerebral hypoxia if it was caused by hypothermia and nonprotective if it was caused by pentobarbital. The fall in CMR_{O_2} with isoflurane possibly could be a result of poor distribution of blood in the brain or a toxic cellular effect. In order to determine whether the fall in CMR_{O_2} was beneficial or detrimental the cerebral energy state[4] should have been determined concomitantly,

Admittedly, our interpretation of this study needs just as much verification as that of the authors', however, it is as viable as theirs.

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In reply:—Drs. Azar and Thiagarajah are entirely correct in their basic premise: The jury is indeed still out in the matter of isoflurane *versus* halothane for neurosurgery. While we believe that isoflurane will "come to play a major role in future neuroanesthetic practice"—and, in fact, is already doing so—we share their general concern. This was expressed several times in our article, but perhaps our concentration on the physiologic differences between these drugs overshadowed this message. The simple fact that isoflurane given to normocarbic animals can increase intracranial pressure (ICP) (although the increases were small) indicates that ". . . it should be used with caution in situations where intracranial compliance is compromised." This is reinforced by the findings of Adams *et al.*, who noted that even low concentrations of isoflurane could increase ICP in normocarbic humans.[1] Whether such changes are "better or worse" than seen with equivalent halothane doses is unknown, as is the impact on clinical outcome.

We do have several minor disagreements with the writers' comments. In particular, we do not consider the equivalent ICP effects of isoflurane and halothane to be one of our "main observations" and, in fact, devoted a full paragraph in the "Discussion" presenting our reservations concerning this finding. It is important to understand that the ICP changes were small and occurred in normally compliant animals in the head-up position, and hence ". . . it is probable that substantial differences in CBV (cerebral blood volume) may not

have produced detectably different ICP effects." In fact, two other studies quoted in the text suggest that these agents do have different effects on CBV and ICP.[2,3] We agree that if, in a situation of reduced compliance, both drugs did produce identical and severe ICP increases, then the concerns of the writers would be supported. However, we do not feel it appropriate to conclude that "both anesthetics are detrimental to the brain" until these additional studies are done. We also should emphasize that the attention focused on ICP changes may be diverting attention from other important—but more difficult to measure—effects of anesthetic drugs on the *injured* brain. Very little work has been devoted to examining and comparing drug effects on factors such as local CBF and metabolism, oxygen delivery, blood brain barrier function, cerebrospinal fluid (CSF) dynamics, neurotransmitters, local electrical activity, *etc. in the presence of an experimental injury or tumor.* In the absence of clinical outcome studies, conclusions regarding the advantages or disadvantages of a particular anesthetic technique (including intravenous methods) ideally should be based on such work, not on a single project such as ours.

Several other comments are difficult to accept. This includes the suggestion that the increase in CBF noted with halothane was a "salutory" response that improved O_2 delivery to the compressed brain. An appropriate compensatory response to brain compression (decreased CPP) is to *maintain* CBF and oxygen delivery, not to generate a substantial hyperemia. However, this easily could be resolved by measuring drug-induced CBF changes after performing a wide craniectomy so that brain compression cannot occur (no ICP rise). The suggestion that a fall in CMR_{O_2} reflects brain starvation is also not well founded. Several groups have shown that CMR_{O_2} is well maintained in the face of severe hypoxemia or ischemia, even though glucose consumption and lactate production increase (see Seisjo[4]). Tissue starvation sufficient to reduce CMR_{O_2} also will lead to cerebral venous hypoxia and acidosis, neither of which were seen (although the data were not included in the article). The suggestion that isoflurane may be protective was based indirectly on the CMR_{O_2} changes noted in our work, as well as our familiarity with the work of others. Readers should be aware of two studies directly addressing the issue of isoflurane protection. Newberg and Michenfelder[5] noted increased survival with isoflurane in the hypoxic mouse model and better maintenance of cerebral metabolic parameters during severe hemorrhagic hypotension. More recently, Newberg *et al.*[6] also have noted a well-maintained cerebral energy state (tissue ATP, ADP, phosphocreatine, lactate, *etc.*) during isoflurane-induced hypotension to cerebral perfusion pressures of 22 mmHg, something not seen with any other hypotensive method. We therefore feel that work other than our own supports the protective potential of this agent, although this obviously does not mean that isoflurane is a drug of *proven* protective benefit in clinical situations.

In conclusion, we would like to thank the writers for their thoughtful comments and would like to emphasize our agreement with their basic premise. It would be inappropriate to allow the current enthusiasm for isoflurane to cloud the fact that far more data are needed before we firmly can conclude that it is "better" than halothane. However, it is worth noting that none of the currently popular anesthetic techniques for neurosurgery, including narcotic or barbiturate-based methods, have ever been shown to be "better" in terms of clinical outcome.

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