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In Reply:—We are grateful for Dr. Prall's interest in our case report[1] and appreciate the opportunity to respond to his comments.

In his letter, Dr. Prall states "the flexible catheter tip extends only 0.5 mm beyond the rigid cranial bolt, when applied according to the manufacturer's guidelines." However, there is a 10- to 20-fold discrepancy between the manufacturer's (Camino Laboratories) and Dr. Prall's claims. Specifically, placement of the fiberoptic intracranial pressure (ICP) monitor—according to the insertion method suggested by the manufacturer—should result in the catheter tip being 0.5 to 1.0 cm (not 0.5 mm, as cited by Dr. Prall) beyond the end of the rigid bolt. Nonetheless, as alluded to by Dr. Prall, the risk of catheter movement in a magnetic field should diminish as the length of catheter protruding into the brain decreases.

Of greater concern, the package insert clearly indicates that the ICP monitor may be inserted deeper into the brain at the discretion of the surgeon. Specifically, the package insert states, "The surgeon may easily vary the insertion depth by locating his fingers at the proper cm mark . . . For example, placing the fingers at 5.5 cm will locate the tip of the catheter 1 cm beyond the end of the bolt, into the parenchyma" (OLM Intracranial Pressure Monitoring Kit, Camino, Model 110-4B). In this manner, it is possible to insert the catheter tip up to 4 cm (beyond the bolt) into the parenchyma of the brain. At this depth, it may be possible for the ferromagnetic catheter tip to move and cause parenchymal injury when exposed to strong magnetic fields (*e.g.*, 1.5 Tesla, as cited in our case report). In fact, we are installing a magnetic resonance (MR) imager with a field strength of 3.0 Tesla. Therefore, in the setting of the new scanner, we anticipate that the results of our laboratory investigation would substantially *underestimate* the likelihood of patient injury during MR imaging.

Regarding the potential for thermal injury, our point is as follows: the antenna-like effect of ferromagnetic and nonferromagnetic metals (*e.g.*, aluminum or copper) is most likely to occur when loops with a circumference of approximately one quarter the radiofrequency wavelength are formed. This set of circumstances creates an environment in which radiofrequency energy may be absorbed by the metallic biomedical device, which, in turn, may result in heating of the device and injury to adjacent tissues. The length of the ICP catheter was 64 cm, which met the one-quarter wavelength criteria. However, it deserves mention that this measurement was the total length (*i.e.*, intracranial plus extracranial segments). The fact of the matter is neither the intracranial nor the extracranial segment of this fiberoptic monitoring catheter is long enough to result in loops fulfilling this criteria. Therefore, we are not surprised by Dr. Prall's observations in his unpublished data.

Lastly, the manufacturer is under no obligation to prove the safety of their ICP monitor when exposed to MR imaging. Dr. Prall cites clinical experience and unpublished data, demonstrating the lack of morbidity associated with the use of this catheter during MR imaging at his institution. However, the scientific literature is devoid of this information.

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Studies' Divergent Results

To the Editor:—The article by Ebert *et al.*[1] describing an absence of renal injury in volunteers anesthetized with 1.25 minimum alveolar concentration sevoflurane for 8 h raises several issues. First, in a recent letter[2] a colleague of Dr. Ebert's questions the clinical relevance of a study by Eger *et al.*[3] nearly identical to this study and further comments that "it is alarming that Eger *et al.*[3] would design and conduct a research protocol that maximized the likelihood that sevoflurane administration would result in human renal injury and that this protocol received approval from the human research review committee." Are we to infer that the concern expressed in the cited letter no longer exists, and, if not, what in fact were the volunteers and the human research committee evaluating the merits of this study[1] told about the real possibility of renal damage?

Second, the results of this apparently well-done study are substantially different than those of the previous and apparently equally well-done study.[3] More specifically, Eger *et al.*[3] found evidence of worrisome, albeit transient, renal function changes in volunteers breathing 1.25 minimum alveolar concentration sevoflurane for 8 h, whereas Ebert *et al.*[1] found little or no renal impairment in volunteers after the same exposure to sevoflurane. It may be that this difference

is caused by the greater concentration of compound A reached in subjects in the study by Eger *et al.*[3] than in those of Ebert *et al.*[1] Unfortunately, as Ebert *et al.*1 state, "an explanation for the divergence of compound A concentrations . . . is not apparent."

However, in my opinion, what is more important is that these studies and their divergent results may represent an example of the potential problems related to close, prolonged, and repeated relationships between investigators and pharmaceutical companies. Dr. Eger's studies are and have long been supported by Ohmeda (the manufacturer of desflurane, the anesthetic for which the clinical pharmacology has been principally defined by Eger and his colleagues), whereas the studies of Ebert *et al.*[1] are and have long been supported by Abbott (the manufacturer of sevoflurane). This in turn recalls my concern expressed several years ago[4] in response to additional apparently well-done studies from Dr. Eger's lab[5,6] that demonstrate the potential for renal damage in laboratory animals after exposure to sevoflurane. At that time, I suggested that it might "have been more appropriate . . . for the sponsor (Ohmeda) to have engaged alternative investigators to conduct these studies." I reiterate my concern that investigators (in this case, both Eger *et al.*[3] and Ebert *et al.*[1]) may be too strongly linked (emotionally, economically, and scientifically) to one drug, device, technique, or company and that the independence necessary for truly valid, important, and clinically relevant studies might be compromised, if ever so slightly, in subtle and, in many cases, unknown ways. The current situation *vis a vis* Ebert and Abbott and Eger and Ohmeda reminds me of knights on a field of battle jousting in the names of their respective patrons. Perhaps it is time for Sir Edmond and Sir Thomas to collaborate on a joint study using an agreed-on protocol and a respected, but independent, analytical laboratory that cared little about the data other than as accurate results.

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In Reply:—The first issue raised by Dr. Saidman concerns the ethics of performing a study in which human volunteers were administered a high concentration of sevoflurane over a long period,[1,2] when a previous publication had already demonstrated transient renal "injury" in volunteers in an identical protocol.[3] The history and rationale for this research follows.

First, the majority of our research has been in human volunteers, and the protocols dictate that these volunteers be anesthetized with potent volatile anesthetics for extended periods of time to carefully determine their neurocirculatory effects. Several years ago, Dr. Eger sent a draft of his volunteer study to me for comment before its submission for publication. Therefore, we were aware early on that his data demonstrated a marked, albeit transient, increase in urinary albumin and glucose in volunteers exposed to sevoflurane. This raised concerns that our ongoing protocols, which included randomizing some volunteers to sevoflurane, might in fact be causing these subjects unsuspected harm because none of our studies included evaluations of renal function. However, there were some inconsistent findings in the Eger *et al.*[3] study that prompted us to pursue our own studies. First, Dr. Eger shared with us that some of the urinary albumin findings from his research were unexplainable. Several of the research subjects in his study had significant increases in urinary albumin on the first day after administration of sevoflurane anesthesia that returned to normal on the second day but were abnormal again on the third day after the sevoflurane exposure. Consultation with several nephrologists suggested that this picture of near-random albuminuria was not consistent with any known pathologic lesion to the kidney. Second, the average inspired compound A concentrations recorded from Dr. Eger's volunteers while receiving 3% sevoflurane in a FGF of 2 l/min, exceeded the average compound A concentrations that have been reported in the literature when providing sevoflurane in an FGF of less than 2 l/min to patients.[4–7] Third, Dr. Eger's report of "nephrotoxicity" from sevoflurane seemed inconsistent with the absence of any case report of nephrotoxicity from sevoflurane in the 10 million patient exposures that had occurred up to that time.

Therefore, scientific enquiry and troubling inconsistencies prompted our research. Because daily laboratory analyses were immediately available from each volunteer, a vigilant surveillance system was in place. Had we observed the pattern of transient albuminuria that was suggested by Eger and colleagues,[3] we most likely would have halted the research or modified it to seek answers for the renal findings. Instead, we found substantially different renal outcomes. Dr. Eger reported 24-h urine albumin concentrations in the range typical of the nephrotic syndrome, *i.e.,* 1–4 g/day that persisted for several days in most of his eight volunteers. In contrast, we noted "abnormal" levels of urinary albumin in only 3 of 13 volunteers, and their levels were only 100–140 mg on a single day after sevoflurane. Our measured compound A concentrations in the inspired gases were lower than those in