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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References

1. Ebert TJ, Frink EJ, Kharasch ED: Absence of biochemical evidence for renal and hepatic dysfunction after 8 hours of 1.25 minimum alveolar concentration sevoflurane anesthesia in volunteers. ANESTHESIOLOGY 1998; 88:601–10

2. Staacke T: Ethics of toxicity study questioned. Anesth Analg 1998; 86:445

3. Eger EI II, Koblin DD, Bowland T, Ionescu P, Laster MJ, Fang Z, Gang D, Sonner J, Weiskopf RB: Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 1997; 84:160–8

4. Saidman LJ: Unresolved issues relating to peer review, industry support of research, and conflict of interest. ANESTHESIOLOGY 1994; 80:491–2

5. Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschmann RL: Toxicity of compound A in rats: Effect of a three hour administration. ANESTHESIOLOGY 1994; 80:556–65

6. Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschmann RL: Toxicity of compound A in rats: Effect of increasing duration of administration. ANESTHESIOLOGY 1994; 80:566–73

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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

the study by Eger *et al.*[3], and the degree of hypotension was not as great as that in Eger's volunteers. These were offered as potential explanations for the markedly different renal outcomes. Since the time these volunteer studies were conducted, we have learned that proteinuria can occur after isoflurane anesthesia,[8] and albuminuria can occur after epidural anesthesia.[9] These findings suggest that renal hypoperfusion, rather than any one volatile anesthetic, may explain the proteinuria. The merits of having repeated this research protocol are clear—we have furthered our understanding and knowledge of renal function after general anesthesia and have generated new questions. The ethics of performing this study also should be clear.

The second issue raised by Dr. Saidman is the potential for conflict of interest resulting from close, prolonged and repeated relationships with pharmaceutical companies. Dr. Saidman incorrectly suggests that our research has long been supported by Abbott and fails to point out our long-standing NIH and VA support to evaluate volatile anesthetics in humans. I am not a consultant to Abbott and do not advise them on their new product development. I have received only a limited amount of funding from Abbott for five studies with sevoflurane over a period of four years. Three studies were preclinical trials used for registration of sevoflurane with the FDA.[10–12] These three studies were tightly regulated and all data were carefully scrutinized by us and by independent study monitors to meet Food and Drug Administration requirements of good clinical practice. The remaining two studies with sevoflurane were Abbott-sponsored, postmarket studies[1,13] that were designed by our research group based on independent research results. We do not believe this constitutes a close, prolonged involvement with a pharmaceutical company. In fact, we also have had several investigator-initiated studies funded by Zeneca and Ohmeda. Similar to several of our studies with Abbott, we defined the hypothesis, designed the protocol, and conducted the study without pharmaceutical oversight or intervention to answer a scientifically valid question. Although these small protocols are not good candidates for government funding, they can and do address important, clinically relevant questions.

Perhaps it is a combination of our previous National Institutes of Health-supported work that demonstrated an undesirable effect of desflurane on sympathetic outflow combined with our current demonstration of preserved renal function with sevoflurane that gives the appearance of a long-standing alliance with Abbott, or the appearance of "a knight jousting on a battlefield." However, battles for country have evolved to more civilized public debates. This is most common in politics, but has become increasingly prominent in science. In contrast to politics, scientific debates mandate scientific evidence to support opposing viewpoints. The present "debate" becomes more difficult to sort out (and perhaps explains Dr. Saidman's concerns) because both Dr. Eger's and our research studies were similar in design but glaringly different in outcomes. However, the fact that some of these studies were supported by a pharmaceutical company rather than by a government agency should not reflect on the integrity of the investigators or on the quality of the science. Despite the reservations of many, a working relationship between academicians and pharmaceutical companies often is essential to understand drugs common to the practice of anesthesia. The key to such support in our lab has been to develop our own protocols based on scientific curiosity, rather than on the marketing strategy of the pharmaceutical company, and to maintain an intellectual independence from the sponsor.

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References

1. Ebert TJ, Messana LD, Uhrich TD, Staacke TS: Absence of renal and hepatic toxicity after four hours of 1.25 MAC sevoflurane anesthesia in volunteers. Anesth Analg 1998; 86:662–7

2. Ebert TJ, Frink EJ, Kharasch ED: Absence of biochemical evidence for renal and hepatic dysfunction after 8 hours of 1.25 minimum alveolar concentration sevoflurane anesthesia in volunteers. ANESTHESIOLOGY 1998; 88:601–10

3. Eger EI II, Koblin DD, Bowland T, Ionescu P, Laster MJ, Fang Z, Gong D, Sonner J, Weiskoph RB: Nephrotoxicity of sevoflurane versus desflurane anesthesia in volunteers. Anesth Analg 1997; 84:160–8

4. Bito H, Ikeda K: Closed-circuit anesthesia with sevoflurane in humans. Effects on renal and hepatic function and concentrations of breakdown products with soda lime in the circuit. ANESTHESIOLOGY 1994; 80:71–6

5. Frink FJ, Malan TP, Morgan SE, Brown EA, Malcomson M, Brown BR: Quantification of the degradation products of sevoflurane in two CO_2 absorbants during low-flow anesthesia in surgical patients. ANESTHESIOLOGY 1992; 77:1064–9

6. Bito H, Ikeda K: Long-duration, low-flow sevoflurane anesthesia using two carbon dioxide absorbents. Quantification of degradation products in the circuit. ANESTHESIOLOGY 1994; 81:340–5

7. Bito H, Ikeda K: Renal and hepatic function in surgical patients after low-flow sevoflurane or isoflurane anesthesia. Anesth Analg 1996; 82:173–6

8. Kharasch ED, Frink EJ Jr, Zager R, Bowdle TA, Artru A, Nogami WM: Assessment of low-flow sevoflurane and isoflurane effects on renal function using sensitive markers of tubular toxicity. ANESTHESIOLOGY 1997; 86:1238–53

9. Ali A, Panagopoulos G, Salimi B, Tempesta R: Micro-albuminuria following epidural anesthesia. Paper presented at: New York Post Graduate Assembly; 1997; New York.

10. Ebert TJ, Kharasch ED, Rooke A, Shroff A, Muzi M: Myocardial ischemia and adverse cardiac outcomes in cardiac patients undergoing noncardiac surgery with sevoflurane and isoflurane. Anesth Analg 1997; 85:993–9

11. Searle NR, Martineau RJ, Conzen P, Al-Hasani A, Mark L, Ebert T, Muzi M, Hodgins LR, Sevoflurane Venture Group: Comparison of sevoflurane/fentanyl and isoflurane/fentanyl during elective coronary artery bypass surgery. Can J Anaesth 1996; 43:890–9

12. Ebert TJ, Muzi M, Lopatka CW: Neurocirculatory responses to sevoflurane in humans. A comparison to desflurane. ANESTHESIOLOGY 1995; 83:88–95

13. Muzi M, Colinco MD, Robinson BJ, Ebert TJ: The effects of premedication on inhaled induction of anesthesia with sevoflurane. Anesth Analg 1997; 85:1143–8

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