correct that some anesthetic toxicity is due to biotransformation. I am not convinced of their contrapositive argument that all biotransformation results in toxicity. No clinical pharmacologist believes this either. It is unfortunate that Tinker and Baker are prepared to pontificate with the statement that sevoflurane "is a step backward," a statement obviously made without access to the facts established with the clinical development of sevoflurane.

I again propose that the major hypothesis that nephrotoxicity is agent-specific, occurs primarily because of intrarenal fluoride ion production, and is not primarily dependent on fluoride ion plasma concentration is impressive.[6] It underscores the rule that medicine can never rest on its laurels[1]: minds should remain open, vigilance should be maintained, and new data should be continually sought.

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In Reply:—Tinker and Baker disagree with our analysis that "neither peak systemic fluoride concentrations nor duration of fluoride increase alone can be applied nonselectively to all anesthetics to explain or predict nephrotoxicity." We believe the data support our statement: Enflurane anesthesia in isoniazid-treated humans resulted in peak plasma fluoride concentrations exceeding 50 μM (as great as 130 μM), but there was no evidence of renal dysfunction.[1] Prolonged isoflurane anesthesia resulted in peak plasma fluoride concentrations exceeding 50 μM for 2–3 days but had no deleterious effect on any measure of renal function.[2] Prolonged isoflurane sedation resulted in peak plasma fluoride concentrations exceeding 50 μM (as great as 93 μM) but no adverse effects on renal function.[3] During prolonged isoflurane sedation, in which fluoride concentrations remained increased for as long as 32 days, there were no significant changes in renal function.[4] Sevoflurane anesthesia resulted in peak plasma fluoride concentrations exceeding 50 μM, but no adverse effects on renal function have been observed to date.[5–8] In contrast, enflurane anesthesia can result in significantly diminished urine concentrating ability at plasma fluoride concentrations less than 50 μM.[9] Thus, the methoxyflurane experience does not appear to apply equally to all anesthetics.

Tinker and Baker attribute to us the notion that serum fluoride is no longer important in nephrotoxicity. We have made no such assertion.

Tinker and Baker claim that we "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." There is no such statement in our paper, and furthermore, there are no data on which to argue the point. Renal parenchymal fluoride concentrations *in vivo* resulting from either renal anesthetic metabolism or tubular fluoride reabsorption have never been measured with methoxyflurane or any other volatile agent. Tinker and Baker are correct in that we proposed no mechanisms of nephrotoxicity. We did not propose any mechanisms of nephrotoxicity because we did not study nephrotoxicity—we studied metabolism.

Tinker and Baker reject the potential that a metabolite or metabolic consequence of methoxyflurane biotransformation other than plasma fluoride may contribute to nephrotoxicity because, "after many years of methoxyflurane study, none has been found." However, there has been scant study of methoxyflurane nephrotoxicity in the last two decades. The absence of proof is not the proof of absence. Indeed, in one of only two papers published since 1980 which even remotely address this issue, the use of analytical methodologies not available during the methoxyflurane era led to a reevaluation of methoxyflurane hepatic metabolism.[10]

Methoxyflurane nephrotoxicity is intimately and unquestionably related to biotransformation. Methoxyflurane is biotransformed to a number of metabolites. Identification of fluoride as the nephrotoxic metabolite was based on associations between serum fluoride concentration and toxicity in humans; on correlations between changes in metabolism, serum fluoride concentrations, and nephrotoxicity in rats; and on the ability of fluoride (at unknown serum concentrations) to cause toxicity in animals. However, data in humans establishing a causal link between increased serum fluoride concentrations and nephrotoxicity of methoxyflurane or any other anesthetic has never been published. The clinical observations about enflurane, isoflurane, and sevoflurane cited above are pertinent. They call into question the appropriateness of applying a fluoride hypothesis developed to explain methoxyflurane nephrotoxicity nonselectively to

all anesthetics without supporting data. We seek to understand the basic mechanisms of anesthetic nephrotoxicity in the post-methoxyflurane era.

We presented experimental results that human kidneys can metabolize volatile anesthetics. We presented a hypothesis that intrarenal anesthetic metabolism may contribute to nephrotoxicity. All the associative data for methoxyflurane metabolism and toxicity are congruent with such a hypothesis. Formation of another nephrotoxic metabolite with fluoride, whether hepatically or renally, would be congruent with the associative data for methoxyflurane metabolism and toxicity. This, too, would be a hypothesis.

We carefully presented these new hypotheses as such, not as conclusions. We look forward to the rigorous testing and confirmation or refutation of these, or other hypotheses, toward the goal of elucidating the mechanism(s) of volatile anesthetic nephrotoxicity. We hope the editorial by Brown[11] and the letter from Tinker and Baker will draw attention to this issue and stimulate further investigation.

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