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tention that sevoflurane is not biotransformed to a greater extent than enflurane simply is not tenable.

Also, nothing was mentioned in the editorial about the *other* products of the biotransformation by cytochrome P450 of sevoflurane *in vivo*, namely hexafluoroisopropanol (HFIP) and the single carbon product that eventually results from the broken-off fluoromethoxy group of sevoflurane. Sevoflurane is unique compared to enflurane, isoflurane, and desflurane in that it contains a monofluorinated methoxy group rather than a difluoromethoxy group. The former by necessity undergoes a different mechanism of biotransformation after initial P450 metabolic attack.

The frenetic push toward convincing us that all this fluoride (and stoichiometric amounts of HFIP plus single carbon fragments) is not clinically important, is an attempt to obfuscate the fact that sevoflurane is an old anesthetic that moves us back in the direction of the heavily biotransformed agents of the past. How long did it take to report methoxyflurane nephrotoxicity after its introduction to clinical practice in 1959? Seven years. How many millions of anesthetics had been given with it by then before that particular toxicity became apparent? How long did it take before (most of us) recognized the existence of halothane-related hepatotoxicity? Are these toxicities related to biotransformation? Of course. Can we remotely predict these toxicities? No. Our recent strategy has been to develop volatile agents that undergo the lowest possible biotransformation, a strategy that makes sense.

The notion that somehow serum fluoride is no longer important in nephrotoxicity, to which Brown² and Kharasch *et al.*¹ have attached so much importance, obscures a more basic and important fact about this drug, which soon may be given to millions of Americans. Sevoflurane *is* heavily biotransformed. The editorialist's aversion to "shibboleths and jigsaw puzzles"¹ notwithstanding, the "fluoride issue" is *not* resolved.

Kharasch *et al.*¹ point out that inorganic fluoride is a nephrotoxin and cite the example that deuteration of methoxyflurane, which decreases methoxyflurane P450-dependent metabolism and fluoride release, diminishes renal toxicity. Despite their own citation, these authors attempted to dissociate serum fluoride concentrations from renal toxicity, by concluding that "neither peak systemic fluoride concentrations nor duration of fluoride increase alone can be applied nonselectively to all anesthetics to explain or predict nephrotoxicity." They imply that there may be some other metabolite or unknown metabolic consequence of methoxyflurane biotransformation that

causes renal toxicity. After many years of methoxyflurane study, none has been found. Further, they 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.

We moved steadily, after the first fluorocarbon anesthetics were introduced, toward agents with less biotransformation, for sound toxicologic reasons. Sevoflurane, which was rejected by Baxter-Travenol and Anaquest (Ohmeda) for clinical development, is a step backward, despite the likelihood that it will have desirable clinical characteristics.

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(Accepted for publication April 29, 1995.)

Anesthesiology
83:233-234, 1995
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Lippincott-Raven Publishers

In Reply:—My editorial¹ was focused only on my thoughts concerning the article by Kharasch *et al.*² in the same issue. The toxicity of compound A, hexafluoroisopropanol toxicity, and other aspects of sevoflurane, both political and scientific, were not discussed. The editorial was strictly confined to commentaries of the novel concept that local renal production and hence high local renal concentrations of fluoride ion may be of greater importance in renal toxicity from fluorinated inhalation anesthetics than is hepatic fluoride production as measured by the plasma fluoride concentration. Contrary to Tinker and Baker's contention, neither my editorial (nor Kharasch *et al.*'s

original paper²) discounted the nephrotoxic potential of fluoride ions. The issue was whether renal or hepatic production of fluoride was the more important vector of nephrotoxicity with inhalation anesthetics. The fact remains that several publications have documented plasma fluoride concentrations well in excess of $50 \mu\text{M}$, whether from sevoflurane, enflurane, isoflurane, or fluoride ion intoxication,³ without evidence of renal toxicity.

Tinker and Baker refer repeatedly to "heavy biotransformation." Let me supply the facts. Eight percent of the enflurane dose and 3-5% of the sevoflurane dose^{4,5} are metabolized. Tinker and Baker are

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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 laurels¹; minds should remain open, vigilance should be maintained, and new data should be continually sought.

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Anesthesiology
83:234-235, 1995
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Lippincott-Raven Publishers

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

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(Accepted for publication April 29, 1995.)

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

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all anesthetics without supporting basic mechanisms of anesthetic nephrotoxicity.

We presented experimental results that metabolize volatile anesthetics. We presented experimental results that anesthetic metabolism may contribute to nephrotoxicity. For such a hypothesis, we need data for methoxyflurane metabolism with fluoride, whether metabolite with fluoride, whether congruent with the associative data and toxicity. This, too, would be a contribution.

We carefully presented these new data. We look forward to the refutation of these, or other hypotheses, or the mechanism(s) of fluoride metabolism. We hope the editorial by Brown¹ and others will draw attention to this issue.

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