As he points out, it is reasonable to expect that halothane stimulates the reaction at the type II site by interfering with the type I reaction, thus diverting the flow of electrons to the type II site. This is a good possibility but probably not the entire answer, for two reasons. First, the high specificity on the part of the stimulating agents: one would expect that any chemical that reacts with the type I site would do this. Second—and a stronger point—if the type I site were destroyed, then type II reactions would be stimulated. This does not happen.[6] Therefore, in view of our limited knowledge of the enzyme systems responsible for drug metabolism, the only conclusion that can be reached is that halothane, as well as methoxyflurane and acetone, stimulates certain drug oxidations in a reasonably specific manner.

What is the importance of this to the clinician? Again, unfortunately, little can be said. However, the phenomenon should be kept in mind by the clinician administering drugs to the anesthetized patient, since the patient may not respond to those drugs in the same manner as he would in the unanesthetized state.

Despite the uncertainties of the mechanism and the scope of this stimulation, the work of Brown is an important step, furthering our understanding of the extent of the biochemical reactivity of the volatile anesthetics.

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Fluoride and Methoxyflurane Nephropathy

IN THE PAST FIVE YEARS several reports indicating that methoxyflurane is capable of producing renal damage have appeared. The validity of these reports has been questioned, however, and acceptance of methoxyflurane as a nephrotoxin has not been widespread. Since the early studies were retrospective, they suffered from deficiencies in experimental design. A recent report by Mazze *et al.*[1] has overcome a good many of such deficiencies. In a well-controlled prospective clinical trial, these authors found that six of 12 patients anesthetized with methoxyflurane developed high-output renal insufficiency after operation. None of the control patients, anesthetized with halothane, showed signs of renal damage. The nature of the renal lesion was uncovered when polyuria was not reversed by infusions of vasopressin. Since patients were receiving potassium supplementation, potassium-depletion nephritis was ruled out, leading the authors to conclude that methoxyflurane or one of its metabolites acted directly on the kidney to inactivate the renal concentrating mechanism.

A second report from Mazze's laboratory appears in this issue of ANESTHESIOLOGY. In this study, the authors have demonstrated metabolic biotransformation of methoxyflurane in man to two major metabolic products, fluoride and oxalic acid. Patients with clinical signs of high-output renal failure had significantly higher plasma levels of fluoride and oxalic acid, suggestive of enhanced metabolism of methoxyflurane. These patients also

excreted more oxalic acid than patients without clinical signs of renal failure. The authors have interpreted these data to support the hypothesis that the increased plasma fluoride was a causative factor in the renal damage. They present a convincing argument to support their position. Oxalic acid is ruled out as the causative agent, inasmuch as the type of renal damage and the clinical signs observed in this study differed from those characteristic of oxalic acid intoxication. The authors point out that fluoride is known to inhibit several enzyme systems and that chronic ingestion produces renal damage.

An effect of a drug on the concentrating mechanism could result from a biochemical lesion in either of two areas in the nephron. The most obvious would be the vasopressin-sensitive cells along the collecting duct. A defect here would render the cells unresponsive to vasopressin. The authors suggest that this might be due to inhibition of the enzyme, adenyl cyclase, which appears to mediate the permeability changes produced by vasopressin in the collecting duct.[2] However, there is evidence that fluoride would not affect renal adenyl cyclase.[3] The other region where a biochemical lesion would obliterate the concentrating mechanism is the ascending limb of the loop of Henle. Derangement of metabolic mechanisms here would diminish reabsorption of sodium, resulting in a loss of medullary hypertonicity, thereby reducing the osmotic force for the absorption of water. This is an attractive feature of the authors' hypothesis, because a great deal of sodium reabsorption in the renal medulla is derived from anaerobic metabolism,[4-6] which can be inhibited by the fluoride ion.[7] Assuming these energy systems are necessary for sodium reabsorption, their inhibition would block sodium reabsorption. Inhibitors of anaerobic metabolism in the renal medulla, such as iodoacetamide, have been shown to have a profound effect on excretion of water, with a lesser effect on excretion of sodium[4, 6] similar to that of methoxyflurane.

Although the authors' premise is interesting and highly tenable, its acceptance must await experimental verification. Like previous studies with methoxyflurane, this work suffers from its retrospective design. Urine and plasma samples were analyzed after the experiment and were not part of the original design. The increases in plasma fluoride and oxalic acid may be merely coincident with the effect on the kidney. Quite possibly, one of these compounds is nephrotoxic, but it is also possible that other metabolites, or methoxyflurane itself, may have a direct effect on renal function. Alternatively, the increased plasma fluoride could be the result of the diuresis rather than the cause. Fluoride excretion of patients who had polyuria was the same as that of those who had only laboratory evidence of dysfunction. Diuresis would be expected to contract the plasma volume (also reflected as loss of body weight), thereby increasing fluoride concentration. Assuming the defect to be in the concentrating mechanism, the lesion would be located in the distal area of the nephron. As polyuria ensued and plasma volume contracted, reabsorption in the proximal nephron would increase; this would explain the retention of sodium and fluoride. Oxalic acid reabsorption, probably a passive phenomenon, would be more directly related to urinary volume. Thus, the increased plasma fluoride can be interpreted as an indicator of renal damage rather than the cause.

To verify causation it is necessary to demonstrate: 1) the potential of the suspected material for producing damage; 2) the presence of the material in adequate amounts within the system; 3) an appropriate temporal relationship. As pointed out above, fluoride can depress renal function. In the patients who had polyuria, fluoride appeared to be present in concentrations adequate to alter renal function. Taves *et al.*[8] suggest that concentrations of fluoride greater than 100 μM might produce renal changes similar to those seen here. The primary question in these experiments is related to the temporal arrangement. Unfortunately, no data concerning the very early effects of methoxyflurane on fluoride concentration and renal function are available. It would be expected that the highest plasma levels of fluoride would appear early in anesthesia, and the authors report that in some patients the polyuria developed in the recovery room. Assuming fluoride to be the causative agent, plasma levels of fluoride should have predictive value in terms of renal function,

that is, it should be possible to predict changes in renal function based upon the early changes in plasma fluoride.

Several experiments could be conducted to verify the authors' hypothesis. Random groups of patients could receive infusions of sodium fluoride and renal function could be monitored. Since the effect of fluoride appears reversible, it should be possible to study it in patients without exposing them to undue hazard. I recommend that properly dehydrated patients receive slow infusions of increasing concentrations of fluoride and that plasma fluoride be continuously monitored. The relationship between plasma fluoride and renal concentrating capacity could then be determined. In addition, metabolites of methoxyflurane should be infused to determine their effects on renal function. These experiments could be done in experimental animals and their results confirmed in man. For instance, using the dog, split-function tests in which the agent is infused directly into one renal artery and the differential effect on that kidney is determined could be done. Preliminary experiments could determine whether there were a relationship between infusion of any of these agents and alterations in renal function. Similarly, it should be possible to distinguish between the effects on renal function of methoxyflurane and those of its metabolites by altering the rate of metabolism with drugs such as phenobarbital. Phenobarbital should enhance the metabolism and thereby enhance toxicity, assuming toxicity is indeed secondary to metabolism.

In summary, Mazze and his colleagues have demonstrated unequivocally that methoxyflurane or its metabolites, or both, can produce renal damage in man. They suggest that the specific nephrotoxin is a metabolic product, fluoride ion. They present a very solid argument in favor of their hypothesis. Establishment of the hypothesis as fact awaits experimental verification.

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