

This Week's Citation Classic

Crandell W B, Pappas S G & MacDonald A. Nephrotoxicity associated with methoxyflurane anesthesia. *Anesthesiology* 27:591-607, 1966.
[Veterans Administration Hospital, White River Junction, VT & Dartmouth Medical School, Hanover, NH]

Inappropriate diuresis with consequent metabolic changes occurred in 16 patients of 94 exposed to methoxyflurane anesthesia. Nothing similar was seen in 100 patients who received other anesthetic agents for comparable operations during the same period. Tests showed that the concentrating defect originated in the kidney rather than in the posterior pituitary. [The *SCI*[®] indicates that this paper has been cited over 140 times¹ since 1961.]

Walter B. Crandell
Veterans Administration Center
White River Junction, VT 05001

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"It seems likely that our paper has been cited frequently because it first documented a problem of wide potential concern to surgeons and anesthesiologists and pointed out that postoperative renal failure may sometimes be characterized by diuresis rather than the more usual oliguria. The paper was not the product of a planned research effort, but of a lucky meeting of inquiring minds and technical capabilities. The surgical residents were alert to metabolic changes and fluid shifts; some had spent several months of their training working in the research laboratory. That laboratory, in turn, was geared to do the tests needed to confirm their clinical judgments.

"So when Chief Surgical Resident, Dr. Stephen Pappas, on teaching rounds, asked what had led up to a serum sodium of 162 mEq/L, the tools were at hand to find the answer. The patient had had an abdominal operation three days before. He was having a large diuresis, with consequent metabolic changes. On the next day diuresis and resultant dehydration appeared in another patient; he too had had an abdominal operation three days before. In order to distinguish between a disorder of the renal concentrating mechanism and one of the posterior pituitary, we measured the urine osmolality in response to fluid deprivation, rapid infusion, and Pitressin I-V. The defect, in both patients, was shown to be primary in the kidney.

"We saw and studied four more cases; meanwhile we tried unsuccessfully to find the cause of the disorder. None of the many drugs used was common to all cases. Then we heard that surgical residents at a large city hospital had noticed that some of the patients exposed to methoxyflurane required more intravenous fluids than usual because of high urine output. A check of our problem patients' charts showed that all had received methoxyflurane.

"Dr. Pappas reviewed the charts of all 94 patients exposed to methoxyflurane, as well as those of 100 patients who had had comparable operations during the same period, but with other anesthetic agents. Ten more of the methoxyflurane recipients had evidence of renal dysfunction—not a single one of the other one hundred.

"Nevertheless, our anesthesiology department rejected the implication that methoxyflurane was responsible; although this disturbed us, their skepticism was useful in forcing us to strengthen our evidence. We were concerned because the use of methoxyflurane was expanding rapidly—we were convinced that it could damage the kidney and wanted to share our information. We were encouraged that Dr. Gilbert Mudge and Dr. Heinz Valtin, experts in nephrology at the Dartmouth Medical School, after reviewing our data, acknowledged that our conclusions were sound.

"A meeting was arranged with a representative of the distributor of methoxyflurane and two prominent anesthesiologists. Reluctantly accepting our data, they suggested that it be shelved, since there had been favorable reports on methoxyflurane from authoritative sources—moreover, the anesthesiologists wanted to avoid the kind of predicament that they had been in with halothane.

"Unwilling to suppress our information, we submitted a paper to *Anesthesiology*. The editor and his board were critical, but eventually published the paper, accompanied by a qualifying editorial.

"Numerous reports corroborating our findings have been published since then, and the mechanism of the kidney damage has been elucidated. Use of the drug is now commonly limited to brief exposures. The fair but skeptical editor of *Anesthesiology* was a joint editor, six years later, of a report of fatal renal failure ascribed to methoxyflurane anesthesia."