

## Metabolism of Halothane

THE METABOLISM of the volatile anesthetics has been the subject of considerable research effort in recent years. These studies began with the relatively simple approach of using anesthetics synthesized with radioisotopes and following the isotope to a nonvolatile urinary product or to  $\text{CO}_2$ . The early studies were designed to be quantitative—that is, to determine how much metabolism took place—and not qualitative to the degree that all the metabolites were identified. This was the situation for a number of years, until it was recognized that whatever toxicity resulted from a volatile anesthetic agent was a result of the biotransformation of that agent. The first definitive evidence of this was the case of methoxyflurane. In 1966, Crandell and associates<sup>1</sup> reported a high incidence of polyuria following the use of methoxyflurane. Several years later, Mazze and Cousins<sup>2</sup> and Taves and co-workers<sup>3</sup> reported that the polyuria was a result of the inorganic fluoride released during the metabolism of methoxyflurane.

The situation regarding halothane has never been as clear. It has been known for several years that trifluoroacetic acid and bromide are excreted in high concentrations after halothane anesthesia, but it has not been known whether there are other metabolites, simply because the isolation and identification of metabolites is extremely difficult and time-consuming and requires very sophisticated equipment.

The paper by Cohen and associates in this issue reports a very timely and elegant investigation into the human urinary metabolites of halothane—timely because it has become obvious that halothane is enzymatically activated to a highly reactive material that is capable of reacting with cellular constituents, and elegant because the data are so difficult to obtain and because this is the first attempt to determine the total metabolites of halothane in man. What can be learned from these studies? In terms of chemistry and the route of metabolism of halothane, they are particularly interesting. First, they confirm that trifluoroacetic acid is the main urinary metabolite, and this, of course, confirms that halothane undergoes oxidative metab-

olism. Furthermore, it represents the main means of breakdown. Second, the discovery of the trifluoroacetyethanolamine supports the concept that halothane is activated, probably enzymatically, to a material that reacts with cellular constituents. The halothane intermediate in this case may be trifluoroacetaldehyde or the acyl chloride

$\text{Cl}$   
( $\text{CF}_3-\text{C}=\text{O}$ ). Third, and perhaps most exciting, is the discovery of the chlorobromodifluorethyl mercapturic acid. The formation of mercapturic acids is a frequent means of excretion of drugs and their metabolites. However, the fact that chlorobromodifluoroethylene is formed represents a pathway for metabolism of halothane heretofore not considered. This metabolite would arise from a reductive dehalogenation or dehydrodefluorination. Such a reaction has never been considered to occur in the case of halothane, but is known to occur with other halogenated compounds. Thus, we now can consider both an oxidative and a reductive pathway for the breakdown of halothane, with physiologic factors controlling the amount of halothane passing through each.

What is the biologic significance of these studies? Unfortunately, this question cannot be dealt with satisfactorily at this time, although some speculation can be entertained. The question, of course, is which metabolite would be responsible for an adverse side effect if it were present in high enough concentration. The chlorobromodifluoroethylene conjugates with glutathione. Therefore, the levels of glutathione would have to decrease before this compound could react with cellular constituents, that is, of course, assuming that the binding of the metabolite to cellular constituents is an important step in the development of hepatotoxicity. For example, in the case of acetaminophen a metabolite that reacts with and eventually depletes the glutathione stores is produced, and when this happens, hepatic necrosis occurs.<sup>4</sup> However, halothane does not reduce the levels of glutathione, and therefore, the chlorobromodifluoroethylene is either produced in very small amounts or formed so

slowly that the glutathione levels can be maintained. The trifluoroacetyethanolamine clearly represents the fact that a metabolite is bound to cellular constituents and thus may be interfering with normal metabolic activity, but whether this interference is sufficient to result in cellular necrosis is not known at present. The trifluoroacetic acid, of course, has been shown repeatedly to be nontoxic at the levels achieved after halothane administration.

Some word of caution should be mentioned about using urinary metabolites as clues to discovering toxic metabolites. In the first place, the urinary metabolites do not necessarily reflect all the metabolites, but perhaps only those that appear readily or are bound to cellular constituents that turn over rapidly. Evidence to suggest that a halothane metabolite is bound to cellular protein has been presented,<sup>5</sup> and since the turnover time of protein may be 24 hours or more, such a metabolite would not appear until such a time, and then only at a very slow rate.

Second, the six individuals studied by Cohen and associates might never have experienced an untoward reaction to halothane, and so the metabolites that were found may have no bearing on a toxic reaction. In other words, persons in whom a toxic response might occur may metabolize halothane in a different manner. If this is the case, the data on metabolites reported here can be used only as a basis for comparison with the metabo-

lites released in individuals who do experience adverse reactions to halothane.

The authors are to be complimented on this excellent and important contribution to our knowledge of halothane metabolism. This work presents an understanding of this metabolism that has been needed, and it will allow more rapid solution of some of the remaining mysteries surrounding the biochemistry of halothane.

RUSSELL A. VAN DYKE, PH.D.  
*Department of Anesthesiology  
Mayo Clinic  
Rochester, Minnesota 55901*

### References

1. Crandell WB, Pappas SC, Macdonald A: Nephrotoxicity associated with methoxyflurane anesthesia. *ANESTHESIOLOGY* 27: 591-607, 1966
2. Mazze RI, Cousins MJ: Renal toxicity of anaesthetics: With specific reference to the nephrotoxicity of methoxyflurane. *Can Anaesth Soc J* 20:64-80, 1973
3. Taves DR, Fry BW, Freeman RB, et al: Toxicity following methoxyflurane anesthesia. II. Fluoride concentrations in nephrotoxicity. *JAMA* 214:91-95, 1970
4. Jollow DJ, Thorgeirsson SS, Potter WZ, et al: Acetaminophen-induced hepatic necrosis. VI. Metabolic disposition of toxic and nontoxic doses of acetaminophen. *Pharmacology* 12:251-271, 1974
5. Van Dyke RA, Wood CL: *In vitro* studies on irreversible binding of halothane metabolite to microsomes. *Drug Metabolism and Disposition* 3:51-57, 1974

### Infection

#### ANESTHESIA AND CROSS-INFECTION

The text is taken from the 1974 Baxter-Travenol Lecture. The author examines the many possibilities of cross-infection that may occur in the perioperative situation. His thesis is that the anesthesiologist is a vital link in the spread of infection and must be conscious of his role in this important area. Possibilities for cross-infection involve

equipment, preparation and storage of medication, instrumentation of the airway, and obvious or occult infection of anesthesia personnel. The author suggests that this is an area of considerable importance that frequently is underemphasized. (Walter CW: *Cross-infection and the anesthesiologist. Anesth Analg (Cleve)* 53:631-644, 1974.)