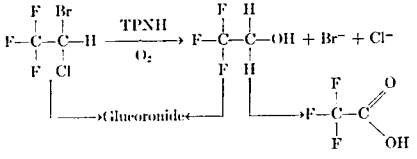
Metabolism of Halothane

THE REPORT by Rehder *et al.* on Biotransformation of Halothane in Man appearing in this issue of ANESTHESIOLOGY represents an important contribution. It not only confirms previous work by Van Dyke *et al.*[1] on the metabolism of halothane in animals, but attempts to place the process on a quantitative basis in man. This study further extends an earlier observation by these same workers of a debromination process involved in metabolism of halothane.[2]

The extent of metabolism of halothane found by Rehder *et al.* (estimated at 18.4 per cent of that taken up in 2 subjects within 75 minutes) is surprisingly high. Although this study does not provide rates or avenues of metabolism, the total urinary bromide and bound fluoride excreted would place halothane among the more highly metabolized of the halogenated anesthetic agents. It is important to note from these studies the considerable species variation (in enzyme systems) that exists between animals and man. Van Dyke *et al.* found in the rat at 14 days, less than 3 per cent of the intraperitoneally injected halothane recoverable as urinary metabolite and proposed the following metabolic pathway:



Reassuring in the study by Rehder *et al.* (although by no means proven) is the suggestion that "trifluoroacetic acid is the prevailing, if not the only aliphatic metabolite in man." This suggestion contrasts with the significant degree of metabolism of trichloroethylene to both trichloroacetic acid (6–16 per cent) and to monochloroacetic acid (4 per cent).[3] This is most fortunate since the LD_{50} of monofluoroacetate in man is estimated at 0.002–0.005 mg./kg.[4] Both the nonreactivity of the trifluoromethyl group and the high energy of the carbon-fluorine bond undoubtedly account for the significant differences in metabolism between halothane and trichloroethylene.

The implications of this study are many. The continuous mode of administration of inhalation anesthesia ensures a constant blood concentration of unchanged anesthetic, despite significant degrees of associated metabolism. Unfortunately, information is lacking with respect to time constants and actual localization of metabolic sites. Most likely, major degrees of metabolism occur in the liver,[1] and of considerable interest would be the measurement of metabolites within the hepatic circulation. Nonetheless, it is evident that metabolic products continually accumulate within the body, exerting their unmeasured effects on vital organ systems. The fact that toxic manifestations resulting from administration of halothane occur infrequently may be a fortuitous circumstance. Individual variations in total enzymatic activity, genetically inborn errors of enzyme systems, and the influence of drug induction systems (barbiturates, steroids, etc.) may all represent significant causative factors in those rare complications that have been recorded.

It is hoped that further work by this group and by other investigators, utilizing sophisticated and safe analytic techniques (nonradioactive), will provide sorely needed information on the metabolism of halothane and other anesthetic agents in man.

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