Correspondence

The Biotransformation of Halothane

To the Editor: The editorial by Dr. Cohen with regard to the article by Rehder *et al.*, "Halothane Biotransformation in Man: A Quantitative Study," which appeared in the July–August 1967 issue of ANESTHESIOLOGY,[1] elicits some comment stemming from my experimental work done with animals on "rates and avenues of halothane metabolism."[2]

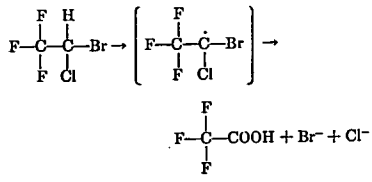
From the proposed mechanisms of halothane biotransformation (*vide infra*) the amount of inorganic bromide formed can be considered a measure of the portion of halothane transformed. This amount, though eliminated protractedly, can be determined fairly accurately in the urine of rabbits.[3] After dechlorination[4] and debromination[5] trifluoroacetic acid is produced as another metabolite.[6] This acid was found to be excreted biphasically in the urine of rabbits, with average halftimes of two days for the main portion and ten days for the residual portion which possibly had been stored in cell nuclei.[7] The time course of elimination of trifluoroacetic acid is the same whether this acid is administered to the animals as the sodium salt or produced by the animals from halothane. The total amount of acid generated by biotransformation of halothane in rabbits was, on a molar basis, equivalent to the amount of bromide formed. Moreover, no other fluorine-containing organic metabolite could be observed in the urine, nor was there any elevation of the normal basic excretion of inorganic fluoride. This proves that trifluoroacetate is the main, possibly the only, aliphatic metabolite of halothane.

The quantity of halothane metabolized was proportional to the product of the concentration of inhaled halothane and the time of exposure ($c \times t$-rule): 15–20 mg. being transformed per kilogram body weight, per hour of exposure and per volume per cent of inhaled mixture. Corresponding values for the two human beings studied by Rehder *et al.*—calculated by applying the $c \times t$-rule—are 14.5 and 15 mg. These individuals metabolized at least 11 per cent of halothane absorbed; rabbits average 13 per cent. Rabbits, rats and guinea pigs biotransformed halothane in a 2:1.5:1 quantitative ratio. Thus, there is no considerable species variation. The results cited here cannot be compared with those of Van Dyke *et al.*[4] because of the different routes of administration used in the two studies (inhalation vs. intraperitoneal). With rabbits the transformation yield was independent of sex. Furthermore, the same yield was obtained when anesthesia was repeated for as many as three times in ten days.

Because a lack of knowledge about metabolism of halogenated hydrocarbons in man, halothane cannot be "placed among the more highly metabolized of the halogenated anesthetic agents." It can be compared only with trichloroethylene,[8] which, as calculated with the aid of the $c \times t$-rule, is biotransformed in man after inhalation about 12 times faster than halothane. Rats metabolize trichloroethylene,[9] chloroform,[4, 10] tetrachloroethylene,[9] carbon tetrachloride[10] and 1,1,1-trichloroethane[11] with a relative yield ratio of about 15:5:2:1:1, respectively, after intratestinal or intraperitoneal administration. The results of Van Dyke[4] place halothane between chloroform and tetrachloroethylene.

Extensively-metabolizable halogenated hydrocarbons like trichloroethylene or chloroform, inhaled in mixtures with halothane, interfere considerably with halothane biotransformation. This is not the case with poorly-metabolizable substances like tetrachloroethylene or 1,1,1-trichloroethane. The biotransformation of trichloroethylene and that of halothane are inhibited by the same chemicals: Diethyldithiocarbamate and 3-amino-1,2,4-triazole. In addition, the same tissues and subcellular particles metabolize under similar conditions *in vitro* halothane[12] and other halogenated hydrocarbons.[13, 14, 15] Infor-

mation from these studies, together with the observation of stimulation or suppression of halothane biotransformation by pretreatment with phenobarbital[2, 16] or hepatotoxic agents,[7] respectively, presents evidence that halothane is biotransformed predominantly in the liver (and perhaps to a minor extent in the kidney) by a microsomal redox system which is responsible for the oxidation of many xenobiotics (see Estabrook *et al.*[17]). A radical mechanism of biotransformation of halogenated hydrocarbons has been proposed.[13, 18] Radicals might preferentially attack a carbon-hydrogen bond of a carbon group bearing a single hydrogen atom in addition to halogen atoms. This explains why chloroform is metabolized more rapidly than carbon tetrachloride, trichloroethylene more rapidly than tetrachloroethylene, and 1,1,1-trichloroethane hardly at all. It also accounts for the above-mentioned relative rates of competition with halothane metabolism of these compounds, and suggests a different mechanism of halothane breakdown working instead of or parallel to that proposed by Van Dyke *et al.*[19]: A primary abstraction of hydrogen would lead to an instable intermediate which, after recombination with an oxygen radical and synchronous hydrolysis of the carbon-chlorine and carbon-bromine bonds, rapidly decomposes to trifluoroacetic acid.



Van Dyke's mechanism involves as an intermediate trifluoroethanol, which is partially oxidized to trifluoroacetic acid. However, in analogy with the biotransformation of fluroxene (2,2,2-trifluoroethylvinylether),[20] this mechanism can be only a minor pathway. In this case considerable amounts of trifluoroethanol were found, in addition to trifluoroacetate, whereas in the case of halothane trifluoroacetate is formed as the prevailing if not only aliphatic metabolite.

The basis for an analogy between trichloroethylene and halothane metabolism, concerning the formation of monochloroacetic acid and monofluoroacetic acid, respectively, is highly questionable, since the methods applied by Souček *et al.*[21] for identification of monchloroacetic acid in human urine are unreliable. In fact, no monochloroacetic acid was detected when ^{36}Cl-trichloroethylene was used in animal experiments.[9]

The acute toxicity of trifluoroacetate in mice is within the same range as that of acetate or chloride. Chronic administration causes enlargement of the rat liver and distinct alterations in its enzyme pattern.[22] This, indeed, may open up a route to be pursued in future research, to determine the factors which, together with halothane application, might have caused liver damage in those rare cases that have been recorded,[23] and to make a safe anesthetic still safer.

A. Stier, M.D., Ph.D.
Max-Planck-Institute for Spectroscopy
Goettingen, Germany

References

1. Rehder, K., Forbes, J., Alter, H., Hessler, O., and Stier, A.: Halothane biotransformation in man: A quantitative study, Anesthesiology 28: 711, 1967.
2. Stier, A.: Der Stoffwechsel des Halothane und seine pharmakologisch-toxikologische Bedeutung, Habilitationsschrift, University of Wuerzburg, 1965.
3. Bodansky, O., and Modell, W.: J. Pharmacol. Exp. Ther. 73: 51, 1941.
4. Van Dyke, R. A., Chenoweth, M. B. and Van Poznak, A.: Metabolism of volatile anesthetics—I. Conversion in vivo of several anesthetics to $^{14}CO_2$ and chloride, Biochem. Pharmacol. 13: 1239, 1964.
5. Stier, A.: Zur Frage der Stabilität von Halothan (2-Brom-2-Chlor-1,1,1-Trifluoräthan) im Stoffwechsel, Naturwissenschaften 51: 65, 1964.
6. Stier, A.: Trifluoroacetic acid as metabolite of halothane, Biochem. Pharmacol. 13: 1544, 1964.
7. Stier, A.: Unpublished results.
8. Bartonicek, V.: Metabolism and excretion of trichloroethylene after inhalation by human subjects, Brit. J. Industr. Med. 19: 134, 1962.
9. Daniel, J. W.: The metabolism of ^{36}Cl-labelled trichloroethylene and tetrachloro-

ethylene in the rat, Biochem. Pharmacol. 12: 795, 1963.
10. Paul, B. B., and Rubinstein, D.: Metabolism of carbon tetrachloride and chloroform by the rat, J. Pharmacol. Exp. Ther. 141: 141, 1963.
11. Hake, C. L., Waggoner, T. B., Robertson, D. N., and Rowe, V. K.: The metabolism of 1,1,1-trichloroethane by the rat, Arch. Environ. Health 1: 101, 1960.
12. Van Dyke, R. A., and Chenoweth, M. B.: The metabolism of volatile anesthetics—II. In vitro metabolism of methoxyflurane and halothane in rat liver slices and cell fractions, Biochem. Pharmacol. 14: 603, 1965.
13. Butler, T. C.: Reduction of carbon tetrachloride in vivo and reduction of carbon tetrachloride and chloroform in vitro by tissues and tissue constituents, J. Pharmacol. Exp. Ther. 134: 311, 1961.
14. Rubinstein, D., and Kanics, L.: The conversion of carbon tetrachloride and chloroform to carbon dioxide by rat liver homogenates, Canad. J. Biochem. 42: 1577, 1964.
15. Leibman, K. C.: Metabolism of trichloroethylene in liver microsomes—I. Characteristics of the reaction, Mol. Pharmacol. 1: 239, 1965.
16. Van Dyke, R. A.: Metabolism of volatile anesthetics—III. Induction of microsomal dechlorinating and ether cleaving enzymes, J. Pharmacol. Exp. Ther. 154: 364, 1966.
17. Estabrook, R. W., Schenkman, J. B., Cammer, W., Remmer, H., Cooper, D. Y., Narasimhulu, S., and Rosenthal, O.: Cytochrome P-450 and mixed function oxidations. In Bloch, K., and Hayaishi, O.: Biological and Chemical Aspects of Oxygenases. Tokyo, Maruzen Comp., 1966, 153.
18. Wirtschafter, Z. T., and Cronyn, M. W.: Free radical mechanism for solvent toxicity, Arch. Environ. Health 9: 186, 1964.
19. Van Dyke, R. A., and Chenoweth, M. B.: Metabolism of volatile anesthetics, ANESTHESIOLOGY 26: 348, 1965.
20. Blake, D. A., Rozman, S. R., Cascorbi, H. F., and Krantz, J. C.: Anesthesia LXXIV: Biotransformation of fluroxene—I. Metabolism in mice and dogs in vivo, Biochem. Pharmacol. 16: 1237, 1967.
21. Souček, B., and Vlachová, D.: Excretion of trichloroethylene metabolites in human urine, Brit. J. Industr. Med. 17: 60, 1960.
22. Schimassek, H., Helms, J., Kunz, W., and Stier, A.: LebervergröBerung unter Trifluoressigsäure, Spaltprodukt des Halothan, Naunyn Schmiedebergs Arch. Pharm. Exp. Path. 255: 67, 1966.
23. Summary of the National Halothane Study, J.A.M.A., 197: 775, 1966.

The Editor-in-Chief and the Editors of ANESTHESIOLOGY wish to thank the following consultants and referees for their help during the past year:

JAMES K. ALEXANDER
ROBERT GALAMBOS
RICHARD A. GREENBERG
ROBERT HUNTER
RONALD KATZ
BERTRAM KATZUNG
HERBERT J. KAYDEN
SEYMOUR LIPSKY
KENNETH MELMON
ALFRED P. MORGAN
JOHN R. MURPHY
SHIH-HSUN NGAI
MALCOLM POWELL
H. L. PRICE
PHIROZE B. SABAWALA
R. M. SMITH
JOHN WADE
WALTER L. WAY
ROE WELLS
ROBERT L. WILLENKIN