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,† elicits some comment stemming from my experimental work done with animals on "rates and avenues of halothane metabolism."‡

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 slowly, can be determined fairly accurately in the urine of rabbits.§ After dehalogenation and debromination, trifluoroacetic acid is produced as another metabolite.¶ This acid was found to be excreted in the bile of rabbits, with average half-lives of two days for the main portion and ten days for the residual portion which possibly had been stored in cell nuclei.¶ 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 trifluoroacetic acid 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 × 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 × 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.¶ because of the different routes of administration used in the two studies (intravenous 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,§ which, as calculated with the aid of the c × t-rule, is biotransformed in man after inhalation about 12 times faster than halothane. Rats metabolize trichloroethylene,§ chloroform,¶,10 tetrachloroethylene,§ carbon tetrachloride10 and 1,1,1-trichloroethane11 with a relative yield ratio of about 15:5:2:1:1, respectively, after intraperitoneal administration. The results of Van Dyke¶ 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: Diethylidithiocarbamate and 3-amino-1,2,4-triazole. In addition, the same tissues and subcellular particles metabolize under similar conditions in vitro halothane12 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\textsuperscript{13,16} or hepatotoxic agents,\textsuperscript{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.\textsuperscript{17}). A radical mechanism of biotransformation of halogenated hydrocarbons has been proposed.\textsuperscript{13,15} 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.\textsuperscript{19}: A primary abstraction of hydrogen would lead to an unstable intermediate which, after recombination with an oxygen radical and synchronous hydrolysis of the carbon-chlorine and carbon-bromine bonds, rapidly decomposes to trifluoroacetic acid.

\[
\begin{align*}
F\quad H &\quad \rightarrow \quad F \quad Cl \\
F \quad O \quad Br &\quad \rightarrow \quad F \quad Cl \\
F \quad C \quad COOH + Br^- + Cl^- &\quad \rightarrow \\
\end{align*}
\]

Van Dyke's mechanism involves as an intermediate trifluoroethanol, which is partially oxidized to trifluoroacetic acid. However, in analogy with the biotransformation of fluoroxyene (2,2,2-trifluoroethylvinyl ether),\textsuperscript{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 Soucek et al.\textsuperscript{21} for identification of monochloroacetic acid in human urine are unreliable. In fact, no monochloroacetic acid was detected when $^{35}$Cl-trichloroethylene was used in animal experiments.\textsuperscript{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.\textsuperscript{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,\textsuperscript{23} and to make a safe anesthetic still safer.

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REFERENCES

9. Daniel, J. W.: The metabolism of $^{35}$Cl-labelled trichloroethylene and tetrachloro-


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