error. The solution of this equation for seven anesthetic agents is also given in table 1 (column 5). The actual ml. of anesthetic dissolved per 100 ml. of olive oil is always more than the amount predicted from Raoult's Law. This deviation from Raoult's Law presumably results from a variable attraction between anesthetic and oil molecules.

Two more minor points may be made. First, the correlation of vapor pressure of the particular agent at 37° C. with MAC is not a new observation (see Ferguson, J.: Proc. Roy. Soc. (Biol.) 127: 387, 1939, or Brink, F., and Pasternak, J. M.: J. Cell. Comp. Physiol. 32: 211, 1948). Similarly, in our opinion, it was not surprising that MAC was closely correlated to lipid solubility: such a relationship had been previously observed by others (see Meyer, K. H., and Cottlieb-Billroth, H.: Hoppe-Seyler's Zeit. F. Physiol. Chem. 112: 55, 1920, and Meyer, K. H., and Hopff, H.: Hoppe-Seyler's Zeit. F. Physiol. Chem. 126: 281, 1923).

EDMOND I. EGER, II, M.D.
Professor
University of California
San Francisco Medical Center
San Francisco, California

On the Metabolism of Trichloroethylene

To the Editor:—Some statements concerning the metabolism of trichloroethylene made by Greene in his review on "The Metabolism of Drugs Employed in Anesthesia"[1] demand comment. First, Greene states that the initial step in the formation of trichloroethanol and trichloroacetic acid from trichloroethylene is the conversion of the ethylene linkage to an epoxide. This is indeed an attractive hypothesis; however, it is merely that, for it has never been demonstrated. Work in my laboratory[2,3] has demonstrated that the first stable product which can be detected during the oxidation of trichloroethylene in liver microsomes is chloral hydrate. This finding confirmed a long-standing suggestion that had been made by Butler.[4] I have postulated[3] that either an epoxide or glycol (or both) might be an intermediate in the oxidation of trichloroethylene to chloral hydrate. Epoxides have been proposed as intermediates in the oxidation of aromatic[5,6] and nonaromatic[7-9] double bonds. Nevertheless, in none of these cases has an epoxide intermediate been isolated. Only in the cases of the halogenated insecticides such as aldrin have epoxide products been demonstrated[10,11] in mammalian metabolism of xenobiotic chemicals.

Second, a very surprising undocumented statement appears in Greene's review: "It should be noted that trichloroethanol derived from metabolism of trichloroethylene is different structurally from trichloroethanol resulting from metabolism of chloral hydrate. In the former, all three Cl atoms are attached to a common carbon atom, whereas in the latter the Cl atoms are attached ot both." Early chemical workers, in attempting to prepare α-haloalcohols, showed that the configuration in which a halogen atom and a hydroxyl group occupy the same carbon atom is a most unstable one.[12-14] It is highly doubtful that an alcohol of the second type described by Greene, *i.e.*, 1,1,2- or 1,2,2-trichloroethanol, could exist for any finite time. The metabolite formed from trichloroethylene in liver microsomes was reduced, in the presence of liver soluble enzymes or of alcohol dehydrogenase and NADH, to 2,2,2-trichloroethanol, identical in gas chromatographic behavior to an authentic reference standard.[3] These are the conditions under which Friedman and Cooper[15] found the reduction of chloral hydrate to occur; they identified their product as 2,2,2-trichloroethanol by means of a specific colorimetric reaction. I see no basis for the assertion that these two trichloroethanols are different.

In the review under discussion, reference is made to the self-induction of methoxyflurane metabolism.[16] It is pointed out that such a phenomenon becomes evident only after many exposures to methoxyflurane of relatively long duration. It is interesting to note that a similar requirement exists for the self-induction of trichloroethylene metabolism.[17] It is not at all surprising that this should be so; whereas an inducing agent such as phenobarbital is relatively slowly cleared from the body after a single administration, inhalation anesthetics are quite rapidly cleared by the pulmonary route. Long duration of respiratory exposure to vola-

tile anesthetics thus is required to provide a degree of exposure of the liver analogous to that accomplished after a single injection of phenobarbital.

KENNETH C. LEIBMAN, PH.D.
Department of Pharmacology and Therapeutics
University of Florida College of Medicine
Gainesville, Florida

REFERENCES

1. Greene, N. M.: The metabolism of drugs employed in anesthesia, part II, ANESTHESIOLOGY 29: 327, 1968.
2. Leibman, K. C.: Metabolism of trichloroethylene in liver microsomes. I. Characteristics of the reaction, Molec. Pharmacol. 1: 239, 1965.
3. Byington, K. H., and Leibman, K. C.: Metabolism of trichloroethylene in liver microsomes. II. Identification of the reaction product as chloral hydrate, Molec. Pharmacol. 1: 247, 1965.
4. Butler, T. C.: Metabolic transformations of trichloroethylene, J. Pharmacol. Exp. Ther. 97: 84, 1949.
5. Boyland, E.: Biological significance of metabolism of polycyclic compounds, Biochem. Soc. Symp. 5: 40, 1950.
6. Holtzman, J. L., Gillette, J. R., and Milne, G. W. A.: The incorporation of ^{18}O into naphthalene in the enzymatic formation of 1,2-dihydronaphthalene-1,2-diol, J. Biol. Chem. 242: 4386, 1967.
7. Booth, J., Boyland, E., Sato, T., and Sims, P.: Metabolism of polycyclic compounds. 17. The reaction of 1:2-dihydronaphthalene and 1:2-epoxy-1:2:3:4-tetrahydronaphthalene with glutathione catalyzed by tissue preparations, Biochem. J. 77: 182, 1960.
8. Leibman, K. C., and Ortiz, E.: Oxidation of indene in liver microsomes, Molec. Pharmacol. In press, 1968.
9. Leibman, K. C., and Ortiz, E.: Microsomal hydration of epoxides, Fed. Proc. 27: 302, 1968.
10. Wong, D. T., and Terriere, L. C.: Epoxidation of aldrin, isodrin, and heptachlor by rat liver microsomes, Biochem. Pharmacol. 14: 375, 1965.
11. Nagatsugawa, T., Ishida, M., and Dahm, P. A.: Microsomal epoxidation of cyclodiene insecticides, Biochem. Pharmacol. 14: 1853, 1965.
12. Hanriot, M.: Sur l'éther bichloré symétrique, Ann. chim. phys. [5] 25: 219, 1882.
13. Litterscheid, F. M.: Untersuchungen über Chlor- und Bromethylalkohol, Liebig's Ann. 316: 157, 1901.
14. Stepanow, A., Preobraschensky, N., and Schtschukina, M.: Über die Bromierungsprodukte des Paraldehyds, Ber. deut. chem. Ges. 59: 2533, 1926.
15. Friedman, P. J., and Cooper, J. R.: The role of alcohol dehydrogenase in the metabolism of chloral hydrate, J. Pharmacol. Exp. Ther. 129: 373, 1960.
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. Leibman, K. C., and McAllister, W. J., Jr.: Metabolism of trichloroethylene in liver microsomes. III. Induction of the enzymic activity and its effect on excretion of metabolites, J. Pharmacol. Exp. Ther. 157: 574, 1967.

To the Editor:—Some statements by Liebman concerning the review article demand comment. In the first place, it is indeed lamentable that Liebman's work was not included in the review. He has, however, plenty of company, rather eminent company at that, and so should not be perturbed. Some things had to be left out; otherwise the review would have resembled a telephone directory.

Second, Liebman criticizes the hypothesis of Daniel (Biochem. Pharmacol. 12: 795, 1963) that an ethylene linkage may be formed transiently as an intermediate during trichloroethylene metabolism. Liebman criticizes this hypothesis because the ethylene compound has not been isolated. In its place he proposes the hypothesis that either an epoxide or glycol (or both) might be intermediate products prior to formation of the first stable product he could isolate. Since neither the epoxide nor glycol has been isolated either, Liebman's theory is an attractive hypothesis, as attractive as Daniel's; however, it is merely that, for it has never been demonstrated.

The next point Liebman makes is absolutely correct. The review should have emphasized that intramolecular translocation of chlorine atoms occurs during trichloroethylene but not during chloral hydrate metabolism.

Liebman's final comment is obscure in its relevancy to the subject under discussion: the ability of methoxyflurane to produce enzyme induction. Of course duration of exposure may be of importance. So? It is not at all surprising that Liebman's work on trichloroethylene induction was not quoted. It appeared eight months after the review had been finished.

NICHOLAS M. GREENE, M.D.