by replotting the other data from Stacey, Priestly and Hall's study.

The toxicity of very high anesthetic doses may be unrelated to biodegradation. The partial pressures of halothane or enflurane used far exceed those necessary to saturate the enzymes responsible for halothane or enflurane metabolism[5,6] and, hence, the amount of biodegradation probably does not vary over the ranges applied. On the other hand, the higher partial pressures used approach or equal (methoxyflurane) the saturated vapor pressures for these agents (table 1): for chloroform the highest (20 μl) dose is 42 per cent of the saturated vapor pressure; for halothane it is 30 per cent; for enflurane it is 37 per cent. Such high concentrations may injure by physical rather than metabolic effects. That the saturated vapor pressure for methoxyflurane is exceeded at the 15- and 20-μl doses may explain why these higher doses did not produce significantly more injury than the 10-μl dose.

I share the view of Stacey, Priestly and Hall that we need to understand better the conditions that affect the toxicity of halogenated volatile anesthetics. As they suggest, it would be desirable to be able to investigate those conditions through studies of *in-vitro* preparations, which can be well controlled and are far less expensive than *in-vivo* models. The above discussion emphasizes the importance of relating the doses of anesthetic used in such studies to some index of anesthetic potency.

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To the Editor:—Stacey *et al.*[1] have compared the *in-vitro* cytotoxicity of chloroform with those of halothane, enflurane, and methoxyflurane in freshly isolated rat liver cell suspensions. They conclude that the "relative order of cytotoxic potencies was found to be chloroform = methoxyflurane > halothane > enflurane" and that "extrapolation of our results to the clinical situation infers that enflurane has a lower potential for hepatoxicity than halothane." We differ with these interpretations and their rejection of the possibility that their results could be explained by the differing physicochemical properties of the volatile anesthetics.

We have replotted their data for changes of intracellular potassium ion content (their figure 1) using estimated tissue concentrations expressed as MAC

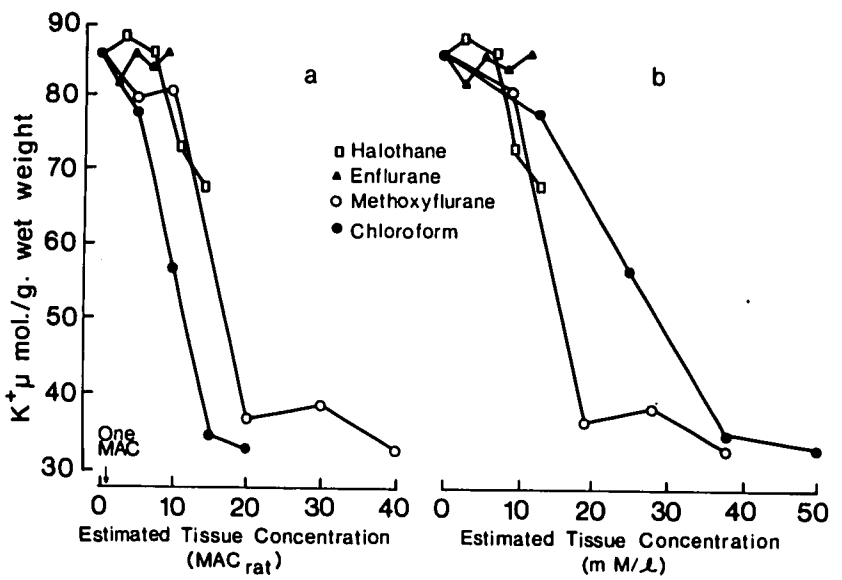

FIG. 1. Replotted data for changes of intracellular potassium ion content.

multiples (fig. 1*a*) and as millimoles per liter (fig. 1*b*). To obtain these estimates we used published values for the specific gravities of the liquid anesthetics, tissue/gas partition coefficients at 37 C, and MAC (for the rat when available). The estimates shown in figure 1 were calculated using blood/gas partition coefficients, the tissue solubility which the authors infer best approximates their liver cell suspension.

From our study of these revised data we offer the following conclusions:

1) The concentrations of all anesthetics used by Stacey *et al.* were far greater than the concentrations used for clinical anesthesia (fig. 1*a*) and therefore have no clinical significance.

2) Enflurane may have appeared the least toxic of the four anesthetics because it was administered in the least concentrations (fig. 1, *a* and *b*).

3) Methoxyflurane may have appeared more toxic than halothane and enflurane because of the relatively higher tissue concentrations (fig. 1, *a* and *b*).

4) The cytotoxicities of the four anesthetics appear to be directly (sigmoid) related to the molar concentrations of the anesthetics (fig. 1*b*).

5) Chloroform may or may not appear more toxic than the remaining three anesthetics depending on how the data are described (fig. 1, *a* and *b*).

These conclusions, which we derived from their figure 1, also apply to their remaining data. Furthermore, we repeated these calculations using solubilities that we believe describe their hepatocyte suspension better than the blood/gas partition coefficient and arrived at the same conclusion.

We believe our revision of their data by changing the units of their experimental variable from microliters of anesthetic liquid to MAC and molar tissue concentration has significantly altered the interpretation of their results. Additionally, we believe that these revised data support our hypothesis[2] that the toxicities of most volatile anesthetics are directly related to their physicochemical properties.

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In reply:—The three letters above have all raised a valid point with regard to the expression of dose relativity in our study. It can be argued that a dose index (*e.g.*, the MAC multiple) that takes into consideration differences in phase partitioning is a more useful basis for comparison of drug effects. We did not ignore the influence of phase partitioning, and neither did Goto *et al.*,[1] who conducted a similar study. Direct estimates by gas–liquid chromatography of anesthetic concentrations in the incubation media confirm that differences do occur, although the values differ from those predicted on the basis of tables of partition coefficients derived from other systems. Our measured values (table 1) for enflurane and halothane in whole-cell suspension concentrations agree quite well with Feingold and Holaday's estimated tissue concentrations, but values for methoxyflurane and chloroform were found to be approximately twofold lower. When one applies similar calculations to the data of Goto *et al.*, the concentrations they measured are also approximately half the theoretical values. It is appreciated that the measured values do not take into consideration the effect of liquid/cell partitioning, but, nevertheless, they do indicate the difficulties involved in extrapolating from dose added to dose estimates derived on theoretical grounds.

The major criticism of our study is that the anesthetic doses at which toxicity was demonstrated were far in excess of those used clinically. This is not disputed, but neither is it unprecedented in toxicologic research. References were made in our paper to comparative toxicity studies in cell suspensions with phenothiazines, tricyclic antidepressants, erythromycins and laxatives, all of which used doses that exceed the likely *in-vivo* therapeutic concentrations. Even when our data are represented by MAC multiples, it is apparent that above an estimated 10 MAC there were differences between halothane and the more lipid soluble anesthetics. Furthermore, we have some addi-