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.

ALFRED FEINGOLD, M.D.
Adjunct Associate Professor
Biomedical Engineering
University of Miami
School of Medicine
Miami, Florida 33152

DUNCAN A. HOLADAY, M.D.
Professor
Department of Anesthesiology
University of Miami
School of Medicine
Miami, Florida 33152

REFERENCES

1. Stacey HS, Priestly BG, Hall RC: Toxicity of halogenated volatile anesthetics in isolated rat hepatocytes. ANESTHESIOLOGY 48:17–22, 1978
2. Feingold A, Holaday DA: The pharmacokinetics of metabolism of inhalation anaesthetics: A simulation study. Br J Anaesth 49:155–162, 1977

(Accepted for publication September 6, 1978.)

Anesthesiology
50:274–275, 1979

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-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/50/3/274/299994/0000542-197903000-00035.pdf by guest on 20 April 2024

tional data that show that when the dose of enflurane is increased to 30, 40 or 60 μl (*i.e.*, an estimated 14–28 MAC), only the highest dose produces slight alanine aminotransferase release (compare with Eger's fig. 2), and there is no K^+ leakage at an estimated 14 MAC (compare with Feingold and Holaday's fig. 1).

If the mechanism of toxicity operating at high concentrations is different from that at low concentrations, then we would agree that the data must be interpreted cautiously. It is probably more likely that cellular damage in these *in-vitro* experiments was mediated by physical effects on the membranes, rather than by a mechanism involving metabolite-mediated damage. However, the hepatotoxicity associated with clinical use of those agents is idiosyncratic, and the mechanisms are still obscure. We do not know at this stage why dose-dependent relative toxicity in isolated or cultured hepatocytes seems to correlate with clinical hepatotoxic potential, but it seems to be a point worthy of further study.

B. G. PRIESTLY, PH.D.
N. H. STACEY, B.SC. (HONS)
Department of Human Physiology and Pharmacology

TABLE 1. Concentration (mM) of Anesthetics in Isolated Hepatocyte Suspensions*

Dose (μl)	n	Enflurane	Halothane	Chloroform	Methoxyflurane
5	2	3.2	2.9	5.9	3.8
10	3	5.2	6.8	11.7	8.4
15	2	6.7	9.4	15.9	9.9
20	3	10.1	14.1	19.8	13.2

* Figures represent the mean for two or three separate experiments after 20 min incubation. Anesthetic concentration in 2 μl of medium after protein precipitation was determined by gas–liquid chromatography on a 2-foot glass column containing 5 per cent OV-210 on Varaport 30, isothermally at 45 C, using a Becker 409 gas chromatograph equipped with a flame ionization detector. Peak heights were compared with those from completely filled containers of cell suspensions spiked with standard anesthetic volumes.

University of Adelaide
Adelaide, South Australia

REFERENCE

1. Goto Y, Dujovne, CA, Shoeman, DW, et al: Liver cell culture toxicity of general anesthetics. Toxicol Appl Pharmacol 36: 121–130, 1976

(Accepted for publication September 6, 1978.)

Anesthesiology
50:275, 1979

Radio Headset for Use with Regional Anesthesia

To the Editor:—A novel way of allaying a patient's anxiety during operations with regional anesthesia is by the use of a completely self-contained, battery-operated AM-FM radio headset. One such device is made by Archer (catalog number 12-192A). Because many patients express anxiety over what they may hear during regional anesthesia, the special feature of a muff-type ear fit serves to lessen background noise even when the radio volume is low. In addition, there are no wires leaving the headset that can tangle on other equipment. The use of music in the operating room is not new, and music has been delivered by headphones to patients during outpatient dilatation and evacuation procedures.[1] I have used this headset with a variety of regional anesthetics and have found that patients like it.

RONALD L. VAN NEST, LT, NC, USN
Staff Nurse Anesthetist, CRNA
U.S. Naval Hospital
Beaufort, South Carolina 29902

REFERENCE

1. Shapiro AG, Cohen H: Auxiliary pain relief during suction curettage. Contraception 11:25–30, 1975

FIG. 1. Patient listening to radio station of choice during regional anesthesia is nearly oblivious to background noise and conversation.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/50/3/274/299994/0000542-197903000-00035.pdf by guest on 20 April 2024