partial pressure did not fall within a range of 24 to 56 mmHg were excluded.

Partial pressures of isoflurane for all samples were divided (that is, normalized) by the mean partial pressure of isoflurane in brain after 90 minutes of administration. The partial pressures of isoflurane increased and decreased rapidly in brain, blood, and end-tidal gas (Fig. 1). The normalized value for brain decreased to 3.7% after 270 minutes of elimination. This value is an order of magnitude smaller than that reported at 240 minutes by Wyrwicz *et al.* (Fig. 1). Isoflurane partial pressures in brain increased and decreased at rates consistent with those predictable from known values for perfusion and solubility of isoflurane in brain. Our results imply that the patient given isoflurane (or halothane) will rapidly recover from anesthesia.

A possible criticism of our results is that isoflurane may have escaped from the brain before our transfer of the sample to the closed flask. However, comparison of partial pressures of isoflurane in blood and brain after 30 and 90 minutes of administration does not reveal a significant difference (Fig. 1). Unlike the samples of brain, the samples of blood were transferred anaerobically from vessel to flask; although the brain samples were susceptible to loss of anesthetic, the blood samples were not. The fact that blood and brain results were comparable after 30 and 90 minutes indicates that no appreciable amount of anesthetic was lost from the brain samples. Even if loss had occurred, were the loss proportional to anesthetic partial pressure, our findings would not be affected.

Several factors may account for the findings of Wyrwicz *et al.* If isoflurane is covalently bound to brain tissue, we would not have recovered all of the isoflurane in the brain. Contradicting this interpretation are the findings that isoflurane is not readily broken down to a compound that might form a covalent bond (*10*) and that nearly 100% of the administered isoflurane may be recovered in expired gas (*11*).

An alternative interpretation that would reconcile our results with those of Wyrwicz *et al.* is that isoflurane binds reversibly to sites in the brain. However, we found that solubility of isoflurane in rabbit brain follows Henry's law over a 100-fold range of anesthetic partial pressures (*9*). We would not expect this behavior if a large number of cerebral sites were saturated progressively by isoflurane.

Finally, the presence of isoflurane in a tissue adjacent to brain requires comment. In the rabbit, fat lies just behind the skull and under the mandible. Fat accepts 23 times as much isoflurane as does the brain (*11*, p. 15). Thus, the partial pressure of isoflurane in brain is five times greater than that in fat after 90 minutes of administration, but the concentration in brain is 6.5 times less than that in fat. After 270 minutes of elimination, 96% of the isoflurane has left brain, but only 60% has left fat (Fig. 2). The 60% decrease in the value for fat is comparable to the 55% reported by Wyrwicz *et al.* for brain. Thus it is possible that the focus of the NMR surface coil may have provided images of isoflurane in fat rather than brain.

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REFERENCES AND NOTES

1. A. M. Wrywicz *et al.*, *Science* **222**, 428 (1983).
2. A. M. Wrywicz, M. H. Pszenny, B. J. Nichols, P. C. Tillman, *Anesthesiology* **61**, A156 (abstr.) (1984).
3. P. Divakaran, B. M. Rigor, R. C. Wiggins, *Neurochem. Res.* **6**, 77 (1981).
4. J. Moss, *Intell. Rep. Anesth.* **4**, 5 (1984).
5. E. I. Eger II, *Anesthetic Uptake and Action* (Williams & Wilkins, Baltimore, 1974).
6. E. N. Cohen, K. L. Chow, L. Mathers, *Anesthesiology* **37**, 324 (1972).
7. M. S. Wolff, *J. Toxicol. Environ. Health* **2**, 1079 (1977).
8. J. Lerman, G. A. Gregory, M. M. Willis, E. I. Eger II, *Anesthesiology* **61**, 139 (1984).
9. C. Coburn and E. I. Eger II, *Anesth. Analg.* **65**, 960 (1986).
10. E. I. Eger II, *Isoflurane, a Compendium and Reference* (Anaquest, Madison, WI, 1985), pp. 91–98.
11. D. A. Holaday, V. Fiserova-Bergerova, I. P. Latto, M. A. Zumbiel, *Anesthesiology* **43**, 325 (1975).

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*Response:* Strum *et al.* report a rapid decrease of isoflurane levels in brain after exposure to this anesthetic and compare these results with our data for halothane (*1*), a different anesthetic agent that had a longer retention time. Retention times of these two compounds are not comparable, since isoflurane (as described in standard anesthesiology texts) is known to have a rapid onset and a short duration of anesthetic action compared with those of halothane. The studies of Cohen *et al.* (*2*) and by Wolff (*3*), cited by Strum *et al.* as giving results in conflict with ours, employed $^{14}$C-labeled halothane introduced into a rat by intravenous injection. It was shown by Topham and Longshaw (*4*) that the distribution and retention time of intravenously administered halothane differ from those of halothane administered by inhalation. Therefore, neither the Cohen nor the Wolff studies are relevant to general anesthesia, where volatile anesthetics are introduced via the lungs.

Figure 1 shows typical elimination curves for halothane and isoflurane (*5*) measured noninvasively by us with fluorine-19 nuclear magnetic resonance (NMR) spectroscopy. These data show that isoflurane is eliminated from the brain more rapidly than is halothane. These results parallel those of Divakaran *et al.* (*6*), who have shown that halothane, when administered by inhalation, decreases to 50% of its initial concentration within 3 hours of the last exposure, which is consistent with longer retention. There is no conflict between our observations and those

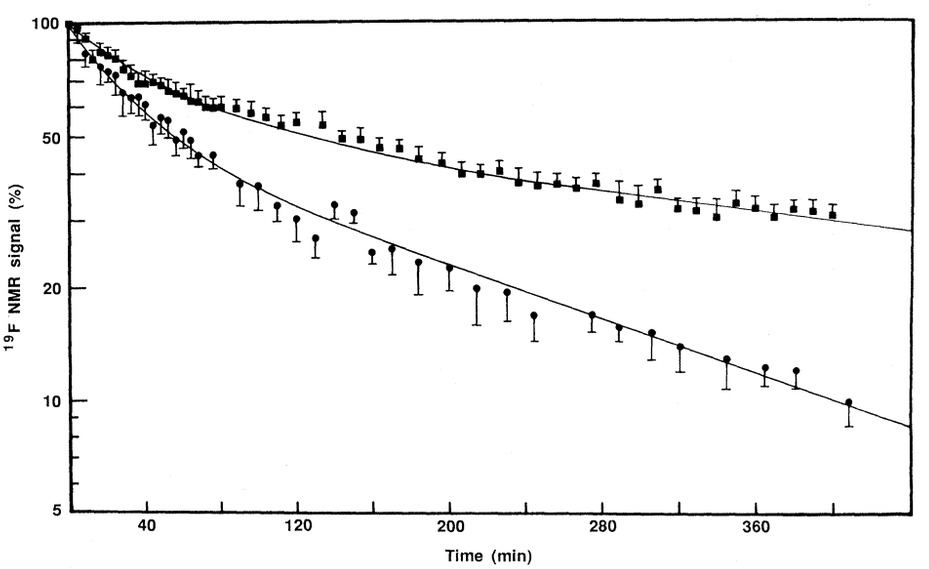


Fig. 1. Comparison of isoflurane (●) and halothane (■) elimination from rabbit brain measured in vivo with fluorine-19 NMR spectroscopy. Fluorine-19 signal areas expressed as percent signal remaining in the brain (after anesthesia) are plotted against time (points are means for $n = 6$ rabbits; the bars indicate standard error of the mean). Isoflurane decay curve was measured after 90 minutes of exposure to 1.5% isoflurane, and the halothane decay curve was measured after 90 minutes of exposure to 1% halothane. Only elimination for the first 7 hours is shown. Experimental details will be provided in (*5*).

of other researchers when the correct comparisons are made, that is, those which take into account differences between the volatile anesthetic agents and the means by which they are administered. The conflict arises when a random comparison of results is made.

Another point brought up by Strum *et al.* concerns the spatial origin of the fluorine-19 signal observed in our NMR experiments. Strum *et al.* suggest that "the focus of the NMR surface coil may have provided images of isoflurane in fat rather than brain." It is important to note that the data we have reported are based upon fluorine-19 spectra obtained with a surface coil, and are not from NMR images. These and other studies (*7*) in our laboratory using fluorine-19 rotating-frame zeugmatography, imaging, and spatially localized relaxation time methods indicate that the region sampled is indeed within the brain. These results were corroborated by in vitro experiments on isoflurane and halothane distribution in brain and other tissues. The data of Strum *et al.* show longer retention times in fat than in brain or muscle, which agrees with our own results. Thus, they report for isoflurane in fat a decrease of 60% at 270 minutes, whereas we observe in that time an 85% decrease in brain concentration (*8*). The loss of isoflurane we reported is greater than the loss reported for fat by Strum *et al.* Therefore, it would be difficult to conclude that our detected NMR signal originated from fatty tissues.

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REFERENCES AND NOTES

1. A. M. Wyrwicz *et al.*, *Science* **222**, 428 (1983).
2. E. N. Cohen, K. L. Chow, L. Mathers, *Anesthesiology* **37**, 324 (1972).
3. M. S. Wolff, *J. Toxicol. Environ. Health* **2**, 1079 (1977).
4. J. C. Topham and S. Longshaw, *Anesthesiology* **37**, 311 (1972).
5. A. M. Wyrwicz *et al.*, *Biochim. Biophys. Acta*, in press; *ibid.*, in press.
6. P. Divakaran, F. Joiner, B. M. Rigor, R. C. Wiggins, *J. Neurochem.* **34**, 1543 (1980); P. Divakaran, B. M. Rigor, R. C. Wiggins, *Neurochem. Res.* **6**, 77 (1981).
7. C. B. Conboy and A. M. Wyrwicz, *Soc. Magn. Resonance Med. 4th Ann. Meet. London* (abstr.) 775 (1985); *Soc. Magn. Resonance Med. 5th Ann. Meet. Montreal* (abstr.) 249 (1986).
8. In their figures 1 and 2, Strum *et al.* cite one anomalous value for isoflurane elimination taken from an abstract submitted prior to an Anesthesiology Society meeting where more complete data were presented.

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# Mediation of Interactions Among Insect Herbivores

Raupp *et al.* (*1*) describe experiments that purport to demonstrate that methylcyclopentanoid monoterpenes released from exocrine glands mediate interactions between larvae of the leaf beetle, *Plagiodera versicolora*, and larvae of another insect herbivore. While the conclusion that the secretion mediates these behaviors is valid, the assumption that the methylcyclopentanoid terpenes are responsible is not directly demonstrated.

The authors do not appear to sufficiently acknowledge that the larval exocrine secretions of *Plagiodera* are complex biphasic mixtures. Sugawara (*2*), in one of the few quantitative studies in this area, showed that less than 10% of the larval secretion of *Plagiodera versicolora distincta* is nonaqueous (4.6 mg extracted in pentane from 50.2 mg of crude larval secretion). Similar data were given for two other species (*2*). By using only the natural secretion in their bioassays, Raupp *et al.* do not appear to justify their title "Methylcyclopentanoid monoterpenes mediate interactions among insect herbivores." They may have verified that methylcyclopentanoid monoterpenes were present in the secretion, but they did not employ standard compounds in their behavioral tests to prove that the monoterpenes themselves elicited the behaviors observed. Authentic compounds do not appear to have been used as controls in the bioassays or as standards for analysis of the extract. In fact, the mass spectroscopic data differed from that previously reported for *P. versicolora* (*3*).

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REFERENCES

1. M. J. Raupp, F. R. Milan, P. Barbosa, B. A. Leonhardt, *Science* **232**, 1408 (1986).
2. F. Sugawara, K. Matsuda, A. Kobayashi, K. Yamashita, *J. Chem. Ecol.* **5**, 929 (1979); *ibid.*, p. 635.
3. J. Meinwald, T. H. Jones, T. Eisner, K. Hicks, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 2189 (1977).

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*Response:* Duffield and Wheeler (*1*) make an interesting comment concerning the methodology used to assay the biological activity of leaf beetle defensive secretions. The defensive secretions of many Chrysomelinae larvae, including the one we studied, are biphasic blends of compounds. Attention to the biological activities of these secretions has focused primarily on the naturally occurring blends or the nonpolar components found in the mixture (*2–5*). Little work has been done on the biological activity of the aqueous fraction of these secretions. However, we have good reason to believe that the nonaqueous components such as the methylcyclopentanoid monoterpenes are biologically active for the following reasons. At least three recent studies have examined the biological activity of natural secretions or derivatives of secretions of Chrysomelinae beetles. The larvae of *Chrysomela vigintipunctata costella, C. populi*, and *Gastrolina depressa* produce salicylaldehyde and benzaldehyde, salicylaldehyde alone, and juglone alone, respectively, in the nonaqueous portion of their defensive secretions. Bioassays of larval secretions of the predatory ant *Lasius niger* indicated that the biological activity of the natural parent secretion was identical to that of each isolated nonpolar component (*4*). In another study salicylaldehyde was found to be biologically active against the predatory ant *Myrmica rubra* (*5*). Salicylaldehyde is a nonaqueous component in the defensive secretion of at least eight species of Chrysomelinae found worldwide (*6*). Also, Duffield and his colleagues (*3*) demonstrated in a recent study that the natural larval secretion of the Chrysomelinae leaf beetle *Gastrophysa cyanea* was strongly repellent to a predator, the fire ant *Solenopsis invicta*. They went on to demonstrate that one of the cyclopentenic monoterpenes found in the secretion elicited the same avoidance response by fire ants as did the natural blend. We concede that the title of our report may have been too specific because we did not test individual components in the secretion. However, the weight of the evidence clearly indicates that the isolated nonaqueous compounds found in these secretions have the same biological activity as the natural parent secretion. Duffield and Wheeler are correct in pointing out that we know very little about the composition or biological activities of the aqueous fractions of these secretions. This criticism holds for all the studies described above.

Finally, Duffield and Wheeler note that our mass spectroscopic data did not indicate the presence of chrysomelidial as did one other previous account for a North American population (*7*). However, they do not mention that other groups of scientists studying secretions of *P. versicolora* did not find chrysomelidial for populations in North America, Europe, and Japan (*6, 8*). Recent-