

CORRESPONDENCE

Anesthesiology

1999; 90:632

© 1999 American Society of Anesthesiologists, Inc.
Lippincott Williams & Wilkins, Inc.

Plus Ça Change

To the Editor:—I read with great interest and enjoyment the recent contribution of Forman and Raines¹ whose data add to a body of information demonstrating that lipid solubility is a necessary, but not sufficient, physical correlate of anesthetic potency. It is always useful to go back in history and demonstrate that *plus ça change* . . . because nearly a quarter of a century ago, Nahrwold, Clark, and I² demonstrated that biological function, *i.e.*, depression of mitochondrial respiration, could more precisely predict ability to perturb the central nervous system than the physical characteristic of lipid solubility. Analogous to the current study,¹ we found that highly lipophilic compounds that had no effect on the central nervous system were also devoid of inhibitory effect on mitochondrial respiration. These findings were not completely specific: hexafluorodiethyl ether depressed mitochondrial respiration but produced convulsions rather than "anesthesia," whereas its isomer, hexafluoroisopropyl methyl ether, was associated with both mitochondrial depression and anesthesia.²

I wonder whether Forman and Raines have any data regarding the ability of their elegant preparations to distinguish between the two central nervous system activities of anesthesia and convulsions? Such

findings would be useful in the further formulation of a predictive *in vitro* model for the anesthetic state.

Peter J. Cohen, M.D., J.D.

Special Expert

National Institute on Drug Abuse

Bethesda, Maryland 20892

ccohenp@aol.com

References

1. Forman ST, Raines DE: Nonanesthetic volatile drugs obey the Meyer-Overton correlation in two molecular protein site models. *ANESTHESIOLOGY* 1998; 88:1535-48
2. Nahrwold ML, Clark CR, Cohen PJ: Is depression of mitochondrial respiration a predictor of in-vivo anesthetic activity? *ANESTHESIOLOGY* 1974; 40:566-70

(Accepted for publication October 12, 1998.)

Anesthesiology

1999; 90:632

© 1999 American Society of Anesthesiologists, Inc.
Lippincott Williams & Wilkins, Inc.

In Reply:—We appreciate the comments of Dr. Cohen and his experimental contributions to understanding the molecular and cellular mechanisms of anesthetic compounds and their relatives. Indeed, we are reminded that exceptions to the Meyer-Overton solubility rule have been identified for more than half a century, including helium and neon, compounds beyond the "cut-off" length in several molecular families, some perfluoroalkanes and sulfur hexafluoride, and the relatively recently described "nonanesthetic" volatile compounds.^{1,2} These compounds, some of which are convulsants, are critically important to testing models of anesthetic mechanisms, because robust hypotheses should account for both anesthetic potency and the inactivity of compounds that do not cause anesthesia.

Despite advances in neurobiology and the incorporation of molecular biology in studies of anesthesia, a testable hypothesis that convincingly links the molecular interactions of anesthetics with behavioral effects in animals is still lacking. Putative targets that affect the activity of neurons include ligand-gated ion channels, such as the gamma-aminobutyric acid type A (GABA_A) receptor, glycine receptors, and N-methyl-D-aspartate receptors, but how the functions of these dynamic macromolecules are modulated by anesthetics remains unknown. One popular idea, based on the now classic Franks and Lieb³ studies of lipid-free firefly luciferase, is that anesthetics act by interacting directly with protein sites. Can such sites distinguish between an anesthetic molecule and a nonanesthetic one? Our study⁴ explored this question using experimental protein models in which direct interactions between anesthetic molecules and proteins have been established.

Our results indicate that known hydrophobic protein sites, such as the ion channel of the nicotinic acetylcholine receptor and human serum albumin, do a poor job of discriminating nonanesthetic from anesthetic

compounds. However, our results also suggest that these compounds may differ in their ability to reach binding sites that alter protein function. We look forward to using molecular biophysical methods in future experiments on putative anesthetic target proteins. Such approaches may establish the existence of functional anesthetic binding sites on these targets, leading us another step closer to a robust hypothesis.

Stuart A. Forman, M.D., Ph.D.

Douglas E. Raines, M.D.

Department of Anesthesia and Critical Care
CLN-3

Massachusetts General Hospital

Boston, Massachusetts 02114

forman@helix.mgh.harvard.edu

References

1. Miller KW: The nature of the site of general anesthesia [review]. *Int Rev Neurobiol* 1985; 27:1-61
2. Koblin DD, Chortkoff BS, Laster MJ, Eger EI II, Halsey MJ, Ionescu P: Polyhalogenated and perfluorinated compounds that disobey the Meyer-Overton hypothesis. *Anesth Analg* 1994; 79:1043-8
3. Franks NP, Lieb WR: Do general anaesthetics act by competitive binding to specific receptors? *Nature* 1984; 310:599-601
4. Forman SA, Raines DE: Nonanesthetic volatile drugs obey the Meyer-Overton correlation in two molecular protein site models. *ANESTHESIOLOGY* 1998; 88:1535-48

(Accepted for publication October 12, 1998.)