CORRESPONDENCE

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Plus Ça Change

To the Editor:—I read with great interest and enjoyment the recent contribution of Forman and Raines[1] 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 I[2] 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.

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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 perfluroalkanes 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-ethyl-D-apartate 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 Lieb[3] 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 study[4] 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.

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