

model to an age group, which is outside of the age range of our study population (e.g., to very young patients, where, in fact, the predicted risk can be exaggerated using our model). However, the scope of our current investigation did not include pediatric cases. The increase in the incidence of PONV among pediatric patients and the decrease in the incidence of PONV with increasing adult age means that the association is not linear if we combine pediatric and adult patients. It does not mean that a bimodal distribution exists between PONV and age, in which there should be two peaks in the distribution. There is one peak (i.e., one mode) in late childhood, with a lower incidence of PONV in early childhood and adulthood.

We have developed and validated a mathematical model to calculate the risk of PONV among ambulatory surgical patients. We believe that

this model will predict patients' risk of PONV and promote efforts to reduce the incidence of PONV.

David Sinclair, M.D.
University of Pittsburgh
Pittsburgh, Pennsylvania 15213
drsinclair@yahoo.com
Frances Chung, M.D.
Gabor Mezei M.D., Ph.D.
Toronto Western Hospital
University of Toronto
Toronto, Ontario

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Perturbation of Lipid and Protein Structure by General Anesthetics: How Little Is Too Little?

To the Editor:—Lipid-based theories of general anesthetic action have long endured because numerous studies have shown that the *in vivo* pharmacology of an anesthetic correlates remarkably well with its ability to perturb the structural properties of simple lipid bilayers. The Meyer-Overton correlation between anesthetic potency and hydrophobicity, the inactivity of nonanesthetic long chain alcohols and highly halogenated volatile compounds (nonimmobilizers), and pressure reversal have all been demonstrated in studies using protein-free lipid bilayers.¹⁻⁶ Nevertheless, a most persuasive and often mentioned argument against lipid-based theories is that at clinically relevant concentrations, anesthetics induce only small perturbations in lipid bilayer structure.^{7,8} For example, halothane reduces the order parameter (increase the "fluidity") of lipid bilayers by only 1% at clinically relevant concentrations.⁹ An equivalent reduction in order parameter may be obtained by raising the temperature of the bilayer by less than 1°C. Similarly, halothane reduces the transition temperature between a lipid bilayer's liquid and gel phases by only 0.5°C at anesthetic concentrations and by only 5°C even at 10 times the minimum alveolar concentration (MAC).¹⁰ I was, therefore, very interested to read the study by Johansson *et al.* quantifying the effects of isoflurane and halothane on structural properties of bovine serum albumin, a lipid-free protein model used in mechanistic studies of anesthetic action.¹¹ What did their studies show? At approximately 1 MAC, isoflurane and halothane increased the fluorescence anisotropy of bovine serum albumin by 1%. An equivalent reduction was obtained by raising the temperature of bovine serum albumin by approximately 1°C. Similarly, isoflurane and halothane raised the transition temperature between the folded and unfolded states of bovine serum albumin by less than 1°C at anesthetic concentrations and by only 3-4°C even at 10 times MAC. Studies of anesthetic binding to other protein models have been similarly unable to demonstrate significant anesthetic-induced changes in protein structure.^{12,13} Thus, anesthetics induce similarly small changes in the structural properties of lipids and proteins. For consistency, shouldn't we now conclude that such insensitivity argues strongly against a protein site of anesthetic action?

The inability to detect significant anesthetic-induced structural changes in either lipid or protein model systems highlights the practical (and obvious) limitations of such studies: we can only measure what we can measure. Fluorescence anisotropy, denaturation temperature, phase transition temperature, and order parameter have been used by biophysicists for many years as indicators of lipid bilayer and protein structure in large part because they are easily quantitated. There is no compelling theoretical reason to believe that changes in these properties *directly* accounts for the functional effects of anesthetics on relevant targets in the central nervous system. In fact, it seems quite likely that the anesthetic state results from changes in other lipid and/or protein physical properties that are not so easily measured.

Douglas E. Raines, M.D.
Assistant Professor of Anesthesia
Harvard Medical School
Assistant Anesthetist
Massachusetts General Hospital
Department of Anesthesia
Boston, Massachusetts 02114
Raines@etherdome.MGH.harvard.edu

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In Reply:—Dr. Raines correctly points out that the effects of either 1 MAC isoflurane or 1 MAC halothane on tryptophan side-chain mobility in bovine serum albumin is comparable to what follows from a 1°C reduction in temperature. Changes in lipid fluidity in the presence of anesthetic molecules can be mimicked by small variations in temperature, and this has been argued to indicate that lipids are an implausible site of anesthetic action.¹ By analogy then, as noted by Dr. Raines, the same line of argument would suggest that a protein target would be an equally unlikely *in vivo* site of anesthetic action.

If anesthetics interact directly with protein targets and alter their function, then binding must influence either the structure of the protein or its dynamics. Alternatively, anesthetics may compete with native ligands for their binding sites.² The latter mode of action does not appear to apply in the case of ligand-gated ion channels, since anesthetics increase the affinity of the native neurotransmitter.³ The limited information on protein structural changes induced by bound anesthetic molecules indicates that secondary structure is not altered.⁴⁻⁷ It is therefore likely that a bound anesthetic molecule instead perturbs the tertiary structure of the protein, or perhaps the quaternary structure. Examples of the latter structural change are the effects of halothane and diethyl ether on the aggregation state of the membrane-bound Ca-ATPase.^{8,9} The 2.2 Å X-ray crystal structure of firefly luciferase with two bound bromoform molecules revealed that anesthetic binding caused minimal overall protein structural changes.⁷ Another possibility is that anesthetics may not alter protein structure but instead modify amino acid side-chain dynamics,¹⁰ which are intimately related to protein function. In line with changes in dynamics is the finding that bromoform binding caused a neighboring histidine residue (H310) in the firefly luciferase crystal structure to become less mobile.⁷ High resolution X-ray crystallography will be required to detect the small structural changes that are likely in the case of weakly interacting ligands such as the volatile general anesthetics. A promising alternative approach for examining the effect of a bound anesthetic

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molecule on protein structure and side-chain mobility is to perform molecular dynamics simulations.¹¹

The effect of anesthetic agents on bovine serum albumin dynamics suggested a potential mechanism for how protein function is altered. It was proposed that anesthetic binding traps the protein in a substate with a lower free energy minimum than the native substate, and therefore effectively prevents the conformational changes required for normal protein activity at a physiologic temperature.¹⁰ Studies with additional proteins will reveal whether this model has wide applicability. It certainly remains plausible that physical properties of lipid and proteins not amenable to experimental analysis at present are responsible for the clinical effects of inhaled anesthetics. One example of this is the lipid-based mechanism of general anesthetic action proposed by Cantor.¹² However, until such theories can be experimentally tested, we remain optimistic that currently available biophysical tools will provide useful information, and generate testable hypotheses, regarding how these important clinical agents may exert their effects on the central nervous system.

Jonas S. Johansson, M.D., Ph.D.

Assistant Professor of Anesthesia

Department of Anesthesia

The Johnson Research Foundation

johansso@mail.med.upenn.edu

Jonathan W. Tanner, M.D., Ph.D.

Assistant Professor of Anesthesia

Department of Anesthesia

University of Pennsylvania

Philadelphia, Pennsylvania 19104

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Is the System at Fault, or Its Players?

To the Editor:—We read with great interest the article and accompanying editorial describing the mismatch between potential and actual claims and remedies in anesthesia malpractice litigation. The authors conclude that the discrepancy resides either in the peer review process of the study or in the legal system. Despite use of residents in training as peer reviewers, the authors argue for the latter. Both pairs of writers decry the existing tort system and put forward proposals for its overhaul. As a third interpretation, we suggest that the problem lies not so much in the system of litigation society has adopted, as in the training and credentialing of its practitioners. To scrap a system that has accomplished much good (handicap access, gender equity, the tobacco settlement to name a few) would be unwise. To do so at a moment in time when the personal injury tort system and its incentives represent the physician's best weapon in the battle for autonomy against managed care intrusions, would be foolhardy in the extreme. While the pathophysiology of contemporary malpractice litigation runs deep, we believe less radical solutions will be sufficient to meet the challenge of assuring heightened patient safety.

As a first step anesthesiologists must put our own house in order. Together with Liang and Cullen we share the call for a stronger focus on evidence-based medicine and safety outcomes, but this alone will fall far short. It is crucial that the principles of scientific medicine be introduced to first year medical students in depth, to include biostatistics, experimental design, hypothesis testing, epidemiology, and public health. Skilled use of these tools must be reinforced and sharpened during the years spent in residency and fellowship training. Wherever possible reliance on anecdote, peer pressure, appeal to authority, economic expectation, personal bias, and imposition from the boardroom must be abandoned before application of civil law instruments (*e.g.*, expert witnesses, peer review) can be expected with

maximal efficacy. Accusations of "junk science" in the courtroom ring hollow to the extent we are tolerant of junk science in the operating room, pain clinic, or intensive care unit.

Second, we advocate the founding of a Specialty Board of Legal Medicine. While comprehension of the framework of legal medicine must be part of every medical student's education as a requisite to graduation, the magnitude and subtlety of relevant law, and explosion in biomedical knowledge, warrant full specialty status for legal medicine practitioners. Proliferation of board accreditation is not to be lightly countenanced for fear of fractionating medical specialties along the faultlines of conflicting agendas. But legal medicine, which penetrates every aspect of anesthetic practice as well as that of our colleagues, carries the unique potential to promote coherence and unity in the face of mounting external threats. Only practitioners with mastery of both medicine and law will be equipped to negotiate the tidal changes we now face; those versed in one but not the other operate with an arm tied behind their backs.

Third, efficient execution of the existing system obliges the legal profession to create a corresponding Medical Malpractice Bar, with documentation of an undergraduate degree in the life sciences, specialty training during law school, passage of a rigorous exam, and continuing legal education to retain the credential. Precedent for such a scheme may be found in the successful operation of the Intellectual Property Bar. Factual arguments before a jury selected from the community must be preserved, but with courts controlled by a specifically skilled and experienced judiciary.

In the survey, 13 individuals were harmed by deviations from standard care determined by peer review, yet none resulted in legal action. Were the circumstances of disclosure to these patients at the time of the injury investigated? Did the injured patients seek legal counsel but