

EDMOND I. EGER, II, M.D.
Professor
Department of Anesthesia
School of Medicine
University of California
San Francisco, California 94143

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To the Editor:—In response to Dr. Eger, it is well known that lower concentrations of general anesthetics depress synaptic transmission (thereby causing general anesthesia), whereas higher concentrations produce axonal block.¹ Therefore, in our studies of the hypothesis of Frank² and Seeman,³ high concentrations of general anesthetics are necessary to demonstrate that conduction blocks by local and general anesthetics are due to the same mechanism. Although the conduction block induced by general anesthetics may be irrelevant to their *in-vivo* action, due to synaptic failure, it seems likely that general anesthetics exert similar membrane effects on synapses and axons.

Whether the ionized or nonionized species of the local anesthetic is active is irrelevant to the aim of this study. If, indeed, the non-ionized local anesthetic is the active species, we have then been testing the effects of non-ionized procaine; conversely, if the ionized form is the active species, then local anesthetics must interact with negatively charged groups in the nerve membrane⁴; therefore, our conclusion that these sites of action are different from those of neutral anesthetics is necessarily true. Furthermore, the differential influences of D₂O on the actions of anesthetics exist regardless of pH.⁵ As Dr. Eger points

out, our experiments confirm differential effects of general and local anesthetics.

BRUCE I. DIAMOND, Ph.D.
HENRI S. HAVDALA, M.D.
HECTOR C. SABELLI, M.D., Ph.D.
Department of Anesthesiology
Mount Sinai Hospital
Medical Center of Chicago
California at 15th St.
Chicago, Illinois 60608

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To the Editor:—Diamond *et al.*¹ conclude that general and local anesthetics interact with excitable membranes in quite distinct ways. This conclusion is based on the observation that altering the calcium concentration or replacing H₂O with D₂O in the bathing Ringer's solution has differential effects on these two classes of anesthetics with regard to their effects on the excitability of frog sciatic nerves. The effects of such manipulations at the molecular level, in this system, are not completely clear. Hence these observations supply only indirect information as to the actual interaction between the anesthetics and the neural membrane. There are, however, data derived from experiments using phospholipid bilayer membranes indicating that general and local anesthetics possess similar properties. This model system is particularly attractive since there is good evidence that the phospholipids of biological membranes are arranged in bilayer form.² The cationic local anesthetics interact with

membrane negative charges. However, since these agents can bring about a reversal of the sign of the (bilayer) surface charge they must be interacting by forces other than those of purely electrostatic origin.³ These same local anesthetics also perturb the hydrocarbon core of the bilayer, resulting in an increase in the "fluidity" of this region. This effect has been demonstrated in experiments involving permeability measurements,³ electron spin resonance spectroscopy,⁴ and differential scanning calorimetry.⁵ General anesthetics are also capable of increasing the "fluidity" of the interior of a phospholipid membrane.⁶ Hence both groups of anesthetics share the capacity to cause disorder within a phospholipid bilayer. General anesthetics probably "dissolve" in the membrane, whereas local anesthetics, anchored to the interface by their charged group, would have their "tail" penetrate into the hydrocarbon core. How might this ability to produce disorder relate to the mechanism of anesthesia? According to current evidence, the proteins of biologic membranes are embedded to variable depths in a phospholipid bilayer.⁷ The state of fluidity of the bilayer is important for proper functioning of these proteins,⁷ many of which have transport functions. Anesthetics, by altering the "fluidity" of the lipid matrix, might secondarily impair the function of those proteins, which constitute the so-called "sodium channel."

MICHAEL A. SINGER, M.D.
Department of Medicine
Queen's University
Etherington Hall
Stuart Street
Kingston, Ontario
Canada K7L 3N6

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- To the Editor:*—We agree with Dr. Singer that in our nerve experiments modifying the concentration of calcium or replacing H₂O with D₂O in the bathing Ringer's solution can only supply indirect evidence as to the actual interaction between anesthetics and neuronal membranes. Such experiments, however, address themselves more directly to this question than observations on artificial bilayer membranes. Certainly such models must be able to explain all the observations made on living tissue if they are to be considered relevant to this biologic problem. Table 5 of our paper¹ lists a series of differences between local and general anesthetics. Most important, specific receptors for acetylcholine, histamine, catecholamines, 2-phenylethylamine (PEA), serotonin, gamma-aminobutyric acid (GABA), cyclic adenosinemonophosphate (cAMP) and cyclic guanosinemonophosphate (cGMP) and other putative neuromodulators have been found to be present in axonal, synapse-free, membranes^{2,3}; their activation can elicit action potentials on isolated nerves.⁴ The local anesthetic effect of procaine is antagonized by L-epinephrine, cAMP, serotonin and histamine.^{3,6} In contrast, the conduction blocking effects of general anesthetics such as halothane, enflurane, and ether are accentuated by L-epinephrine, cAMP and serotonin.^{3,6} These observations suggest to us that general and local anesthetics interact in selective and opposite manners with specific