not really surprising. Those of us who have labored to solve the mysteries of CPB-related brain injury know that nothing is so straightforward. This report represents just one step in a sequence that will ultimately make CPB a safer experience for our cardiac surgical patients. Dr. Hindman and his research group have contributed greatly to this endeavor by developing a valid small-animal model of brain injury with an appropriately tested outcome measure and hopefully will continue with this work.

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Anesthesiology
1998; 88:566-8

Optical Isomers Open a New Window on Anesthetic Mechanism

THE traditional dogma on mechanisms of general anesthesia highlights the ease with which many anesthetic agents dissolve in olive oil and other "membrane-like" substances. The suggestion was made that general anesthetics occupy a critical volume of the bulk phospholipid compartment of the neuronal membrane and in doing so alter membrane fluidity and excitability. Several problems have arisen with these ideas, chief of which might be the observation that bulk membrane fluidity changes, such as may be produced by other manipulations (*e.g.*, small changes in temperature) do not elicit anesthesia.[1] Secondly, the so-called Meyer-Overton "rule," which states that the product of an anesthetic's potency and lipid solubility should be a constant, fails to predict the lack of anesthetic activity of several fluoroalkanes that are extremely hydrophobic, but nonanesthetic.[2] Last, but not least, lipid theories predict that pairs of optical isomers (which have identical chemical and structural formulae, but differ in the arrangement of chemical groups about a single chiral carbon atom) should possess equal potency as anesthetics.[1] The optical isomers of isoflurane have been reported to have unequal potencies as anesthetics.[3] However, the differences in potency between (+) and (−) isoflurane *in vivo* are small enough to leave this issue in doubt.[4] A new study by Tomlin *et al.*,[5] published in

This Editorial View accompanies the following article: Tomlin SL, Jenkins A, Lieb WR, Franks NP: Stereoselective effects of etomidate optical isomers on gamma-aminobutyric acid$_A$ receptors and animals. ANESTHESIOLOGY 1998; 88:708-17.

Accepted for publication November 26, 1997.

Key words: Enantiomers; intravenous anesthetics; lipid bilayers.

this issue of ANESTHESIOLOGY, demonstrates a large (~15-fold) difference in anesthetic potency in tadpoles between the optical isomers of the potent intravenous anesthetic, etomidate. Such stereospecificity obviously cannot be accounted for by "classical" lipid theories, a conclusion bolstered by the observation that the etomidate isomers have identical effects on the physical properties of lipid bilayers.[5] This degree of stereospecificity is characteristic of a target site on a protein, and so the data reported by Tomlin *et al.* represent another significant nail in the coffin for the traditional "nonspecific" dogma of anesthetic mechanism.

Tomlin *et al.*'s study is significant in a second way, as the study of these optical isomers may help illuminate the nature of the protein targets for etomidate anesthesia. The most likely candidates as targets for many anesthetics are the ligand-gated ion channels, which function as receptors for neurotransmitters such as acetylcholine, L-glutamate, and γ-aminobutyric acid (GABA).[1] One such receptor has been associated with anesthesia since Sir John Eccles noted a prolongation of spinal presynaptic inhibition during Nembutal anesthesia in 1946. Of course, Eccles was unaware of the existence of GABA at the time! The explosive growth of neuroscience in the second half of the twentieth century has enabled an enormous increase in our level of understanding of general anesthetic effects in the brain and spinal cord. Much evidence now links anesthesia and GABA, most crucially the observation that clinically relevant concentrations of many general anesthetics, including isoflurane, halothane, propofol, pentobarbital, and the steroid alphaxalone, enhance the inhibitory actions of GABA on central neurons[1] *via* an action on postsynaptic $GABA_A$ receptors (although presynaptic effects also may occur). Etomidate also regulates $GABA_A$ receptors at clinical concentrations, and Tomlin *et al.*[5] show that (+)etomidate is more potent and more efficacious than the (−)isomer in regulating recombinant $GABA_A$ receptors expressed in *Xenopus* oocytes. This observation argues strongly *against* indirect effects of the anesthetic on the function of the receptor protein *via* perturbation of bulk phospholipid and *in favor of* the existence of specific anesthetic-binding "pockets" or cavities within proteins such as the $GABA_A$ receptor.

The advent of molecular biological techniques now promises to contribute further to dismantling the edifice of the nonselective lipid hypothesis of anesthesia. Two recent studies using site-directed mutagenesis show that mutation of single critical amino acid residues within the $GABA_A$ receptor can completely abolish the allosteric effects of two distinct anesthetic agents. In the case of etomidate, Belelli *et al.*,[6] showed that mutation of asparagine 289 to methionine in the $\beta 3$ subunit abolished the allosteric regulation of the $GABA_A$ receptor, whereas in the case of enflurane, the critical residues were serine 270 and alanine 291 in the α subunit.[7] These experiments usher in a series of new and exciting experiments with genetically engineered animals; in fact, this era has already arrived.[8]

In conclusion, the nonspecific hypothesis of anesthetic mechanism has consistently failed to illuminate the events that follow equilibration of anesthetic with the neuronal membrane or to make useful predictions that can be tested experimentally. However, proponents of this idea were so vociferous (and so numerous) as to create a "dark age" in the science of anesthetic mechanism, from which the field has only recently begun to emerge. Although the nonspecific hypothesis of anesthetic action is not yet completely dead, recent findings with isomeric pairs and mutagenesis now threaten to drive the final stake into its heart. Experiments with optical isomers[5] will not only help us to reject an increasingly enfeebled dogma, but they should also throw new light on the spectrum of genuine anesthetic targets.

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1998; 88:568–71

Rural Realities

RURAL America has long struggled to achieve and maintain access to quality health care. Thwarting this goal are the interrelated challenges posed by economic stagnation; declining population; disproportionate numbers of elderly, poor, and uninsured; high rates of chronic illness; low volumes of care in small facilities with high fixed costs; and shortages of health care providers.[1] Thus, it is timely that Dunbar *et al.*[2] describe in this issue of ANESTHESIOLOGY the workforce available for surgical and obstetric anesthesia in rural Washington and Montana. Their paper is notable less for its message — generally known or at least not surprising to anesthesiologists in community practice — than for highlighting issues underlying national workforce policy discussion, well beyond rural America.

Dunbar *et al.*[2] found few anesthesiologists in rural Washington and Montana in mid-1994, especially in the smaller facilities and in the most remote rural communities, where nurse anesthetists often were the sole anesthesia care providers. Moreover, the rural hospital administrators whom they surveyed perceived no related threat to their facilities' capabilities to provide high-quality surgical and obstetric care. The authors concluded that there appeared no overall shortage of anesthesia providers in those two states. Their study design did not include evaluation of patient outcomes.

Decades before an emerging glut of specialists limited the mobility of physicians, the determinants of the uneven geographic distributions of physicians, in general,[3] and anesthesiologists, in particular,[4] were studied. In short, as middle-class progeny, like other specialists, anesthesiologists have tended to locate in metropolitan areas, generally favoring both coasts.[3,4] These locations provide access to cultural and recreational activities and to practice opportunities in large tertiary care centers providing the most sophisticated care to the sickest patients. Geographic areas with a lower prevalence of anesthesiologists tend to have a higher prevalence of nurse anesthetists, as a reciprocal relationship.[4,5*] The anesthesiologists' geographic distribution, like those of other specialists and other aspects of care, is depicted in the recently published *Dartmouth Atlas of Health Care* (fig. 1).[6]

As one might expect, the variation in geographic distribution of anesthesiologists is even more apparent at the level of the individual hospital. This variation was quantitated for the first time in the early 1980s, when the American Society of Anesthesiologists' (ASA) Committee on Manpower was able to bootstrap a workforce question onto an existing annual survey of hospital administrators, conducted by the American Hospital Association (AHA). With a high response rate, similar to that enjoyed by Dunbar *et al.*, we obtained data documenting the heterogeneous distribution of hospitals and surgical caseloads across communities of different population size (fig. 2).* Most poignant, however, was the large variation in the mix of anesthesia care provider types available to provide anesthesia services in each hospital. Whereas anesthesiologists, either providing direct care or working with nurse anesthetists, were available where 91% of surgical operations were performed, no

This Editorial View accompanies the following article: Dunbar PJ, Mayer JD, Fordyce MA, Lishner DM, Hagopian A, Spanton K, Hart LJ: Availability of anesthesia personnel in rural Washington and Montana. ANESTHESIOLOGY 1998; 88:800–8.

Accepted for publication November 19, 1997.

Key words: Anesthesia; hospitals; workforce.

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