certainly establish ANESTHESIOLOGY as a major eleemosynary institution, and that is not one of the editorial objectives of ANESTHESIOLOGY.

No, the increase in page size of ANESTHESIOLOGY must realistically be ascribed purely and simply to economic factors. The larger page size will afford modest savings in the cost of printing the same amount of information. More important, the increase in page size will enable ANESTHESIOLOGY to retain its competitive edge for advertisers' dollars. Advertisers enjoy larger pages, the better to offer their messages. Advertisers not only like larger pages, however: in this day and age they have to have them to include all the fine print that federal regulations demand be printed for so many products of interest to anesthetists. The FDA requirement that pharmaceutical manufacturers essentially reproduce package inserts makes it almost impossible for the reader to grasp an advertiser's message if it is restricted to a 6¼ by 10 inch page.

Changing times require changing formats. But the reader can rest assured that though the form changes the substance will remain the same. ANESTHESIOLOGY will continue to present all that is new, all that is significant, and all that is valid in the art and science of anesthesia. Perhaps we, like the editors of Lancet, can say in future years: "We now have ample reason to be satisfied at the resolution we adopted, and for congratulating ourselves on the soundness of the views [on page size] which we have entertained."

NICHOLAS M. GREENE, M.D.

Towards the Molecular Bases of Anesthetic Action

IN THE EARLY SIXTIES, Professor D. K. de Jongh could write of pharmacologists' concepts of the receptor:

To most modern pharmacologists the receptor is like a beautiful but remote lady. He has written her many a letter and quite often she has answered the letters. From these answers the pharmacologist has built himself an image of this fair lady. He cannot, however, truly claim ever to have seen her, although one day he may do so.

Today, acetylcholine receptors can be obtained, and purified in high yield, in the test tube. The existence of high concentrations of receptor in the specialized organs of certain electric fish, together with the use of certain components from snake venom that bind specifically with high affinity to the receptor, paved the way for this achievement. The pharmacologist can now test his old image against reality.

In our attempts to understand the bases for anesthetic action we are, however, still in the romantic age. The problem is in many ways more difficult: there is no receptor, and there is very little structural specificity to guide us. There are, however, a number of advantages: the agents themselves are extremely simple molecules and we therefore know a good deal about how they behave in different environments; we recognize that only the simplest physical forces are involved in anesthetic action; inhaled agents reach equilibrium readily with the brain so that we have a very good idea of the levels involved during anesthesia, and the dose-response curves are so steep that accurate values of anesthetic potency can be readily obtained.

The complicated nature of the central nervous system poses us an additional experimental problem; we may sidestep this problem biochemically with brain homogenates (a comparatively under-utilized approach), or we may apply an electrophysiologic approach to simpler peripheral nervous systems, as was done in the classic work defining the synapse as the site most sensitive to anesthetic action. Happily, however, the advantages cited in the last paragraph make feasible an approach based on testing physical models against data obtained in the intact animal. In many ways the situation is analogous to that facing the early pharmacologists of whom Professor de Jongh wrote. They obtained defined conditions of drug concentration by perfusion of, for example, isolated neuromuscular junctions and, using this approach, built up a model of drug–receptor interactions that later proved to be quite accurate in certain particulars. Their model did not prove there were receptors, but it was consistent with that assumption. After a while a number of models, all requiring receptors but differing in detailed assumptions, appeared, and it often proved difficult to distinguish between them. Finally, isolation of the acetylcholine receptor resolved some of these questions.

The observations of Meyer and Overton led to the first, and most successful, model of anesthetic action, which bears their names. Many other models have been postulated, but when careful tests, using the widest possible set of experimental data, are made, the lipid-solubility hypothesis is vindicated. Dr. Robert Kaufman reviews this approach in this issue of ANESTHESIOLOGY. It is interesting to note how fast this so-called physicochemical approach can be taken when an accurate data base is available for comparing the predictions of rival models. Nonetheless, a number of models pass the test unless a very critical choice of anesthetics is made;
FIG. 1. The critical-volume hypothesis is based on simple model solvents (e.g., olive oil, benzene, or carbon disulfide). It accounts accurately both for the relative potencies of gaseous anesthetics and for pressure reversal of anesthesia (see R. D. Kaufman's review in this issue). Three interpretations of this hypothesis attempt to provide a more detailed model of the membrane action. The fluidized-lipid hypothesis suggests that the increased freedom of motion of the lipid bilayer may affect the excludability of some protein yet to be identified. The lateral-phase separation hypothesis, which postulates that anesthetics "melt" a coexisting region of liquid-like and solid-like lipid about such a protein, is proposed and more fully described by J. R. Trudell in this issue. The phase-transition model of Lee postulates that the "melting" of solid-like lipid around an excitable ion channel stabilizes the channel in the closed state. The possibility of direct interaction between membrane proteins and anesthetics cannot be ruled out.

In particular, the use of fully fluorinated anesthetics has been decisive. Even then, one cannot distinguish the Meyer-Overton and Mullins versions of the lipid theories.

Antagonists played a critical role in the development of receptor theories. In anesthesia studies there are no competitive antagonists or even receptors, but the dramatic fact that hydrostatic pressure reverses general anesthesia does provide a quantitative, if rather inconvenient, tool for testing and extending theories of anesthetic action. Thus, pressure reversal has provided the additional criterion for development of the lipid theories conceptually to the point at which modern ideas of biomembrane structure and function could be integrated into models of anesthetic action.

Kaufman describes how studies of pressure reversal led to the conclusion that it is not the concentration of anesthetic in membrane that causes anesthesia, but the expansion in volume that this intrusion of anesthetic into the membrane causes. The volume expansion required may be estimated to be about $\frac{1}{2}$ to 1 per cent. When it was proposed, this idea fitted very nicely with two other lines of research. Philip Seeman and his co-workers were developing the idea, from studies using erythrocytes as a model, that membrane expansion is responsible for anesthesia. Their observed expansions were similar in magnitude to those predicted by the critical-volume hypothesis, although there is some disagreement as to whether membrane lipid or protein is responsible. Others (see Trudell's paper, ref. 12) were studying spectroscopically the ability of anesthetics to fluidize the ordered bilayer of phospholipid in membranes. Johnson and I suggested this fluidization would cause expansion and so might also consistently be the basis of anesthetic action and pressure reversal. We confirmed this with permeability measurements, as did Trudell et al. (his refs. 13, 14) with spectroscopic studies. In fact, it even turns out that model lipid membranes with lipid compositions similar to those found in nerve best mimic the anesthetic site of action!

At this point it is helpful to make some clear distinctions. The critical-volume hypothesis is based on intact-animal data and provides a simple verified model. The nature of the hydrophobic region it postulates as the site of action of anesthesia is well modelled by fluid hydrocarbons such as olive oil or benzene. The concept of fluidized membranes is derived from this model and must be consistent with it to be accepted, but one must carefully note that it is only one interpretation of the critical-volume hypothesis. We lack, for example, a suitable model, which we could test, of the hydrophobic interior of membrane proteins,
although we know cytoplasmic proteins to have dense rigid interiors incapable of simply dissolving anesthetics.

The fluidized-lipid hypothesis does not directly address the problem of how the fluidized membrane might influence excitable protein. An explanation consistent with the physiologic evidence would be that decreased membrane viscosity allows a stimulated ionophore to turn off more rapidly, thus reducing the net depolarization. Two lipid models that explicitly include the mechanism of lipid-induced perturbation of protein function have been proposed recently. Trudell describes a model that postulates anesthetics "melt" a region of co-existing liquid-like (liquid crystalline) and solid-like (gel) lipid surrounding a membrane protein, thus reducing the membrane’s lateral compressibility and compromising the protein’s ability to undergo conformational changes. This model is formally consistent with the critical-volume hypothesis because the ability to "melt" the lipid (that is, to lower its phase-transition temperature) depends on the number of molecules dissolved in the membrane, just as the depression of freezing point in aqueous solutions does. In Trudell’s model, pressure reversal occurs because of the volume change (expansion) on melting, and he has shown that this volume change is sufficient to be reversed by physiologic pressures. His model has the advantage over the fluidized-lipid hypothesis that it provides a direct mechanism by which the excitable protein is affected via the lipid. Lee has proposed an alternative model involving a phase transition in which a sodium channel is postulated to require an annulus of lipid in the gel state to allow activity. The anesthetic "melts" this lipid (i.e., triggers a transition from gel to liquid crystalline state), stabilizing the channel in its closed state. In figure 1 I have endeavored to present an oversimplified view of these three interpretations of the critical-volume hypothesis. Note that, although we can be quite precise about the lipid perturbations, we know comparatively little about the protein’s involvement.

None of these theories offers a complete explanation of anesthetic specificity, however—why is one excitable process blocked at a concentration at which another still functions—they can go some way towards this, as explored in Trudell’s paper and in the recent work of Pang and Miller. Nor do they simply accommodate the fact that in potkilothersms on lowering the temperature an anesthetic’s potency increases. Resolution of such questions awaits the isolation and study of physiologic structures involved in anesthetic action. It may be that examples of each type of lipid model will be found. It is also probable that membrane proteins manifest a wide range of sensitivities to these lipid bilayer perturbations. The current need, then, is to identify, characterize and isolate such sites, and this is not a trivial problem. We may also continue to use our models predictively, to test them and to refine them. Even these simple models are not fully explored, yet they contain many concepts to guide us, and their deficiencies may form the basis of further insights.

KEITH W. MILLER, M.A., D.PHIL.,
Associate Professor of Pharmacology
Department of Anesthesia
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

The development of the concepts outlined above owes much to the recent tremendous advances in the knowledge of membrane structure and function. Those not familiar with these would do well to read "Cell Membranes," edited by G. W. Weissman and B. Claiborne, Hospital Practice Publishing Co., New York, 1975.

References