Anaesthesia

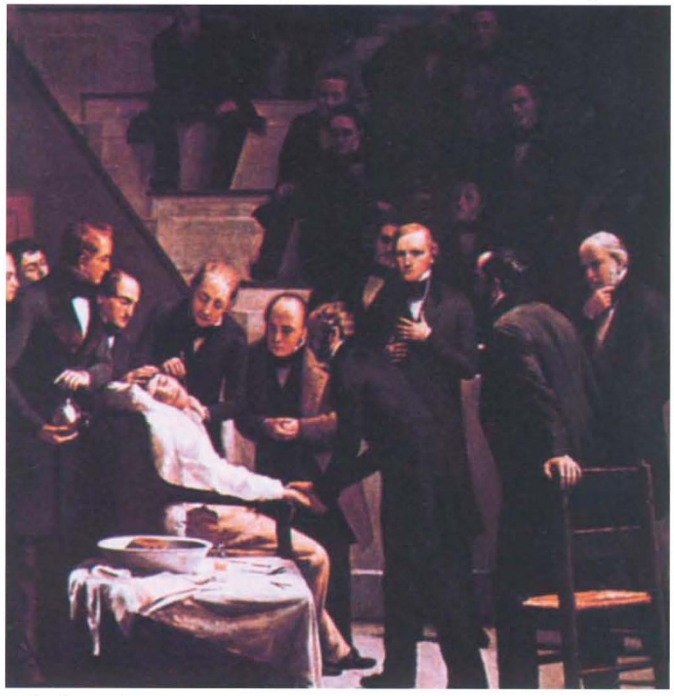
Models of consciousness

from Keith W. Miller

How simple molecules cause general anaesthesia has been a puzzle for 140 years. It is agreed that the potency of the structurally diverse general anaesthetics is proportional to their solubility in lipid bilayers and that pressure can reverse general anaesthesia. To some this suggests that a single molecular mechanism giving rise to bilayer expansion or disordering is involved. To others the same observations implicate protein–anaesthetic interactions, probably involving separate sites for each of the major structural classes of anaesthetic. Ignorance of the physiology of consciousness forces these seekers of the molecular mechanisms of general anaesthesia to study simple but arbitrarily chosen model systems, such as lipid bilayers or pure proteins, in the hope that eventually the behaviour of the whole may be reconstructed from the sum of its parts. Few have been bold enough to attempt such a synthesis, but recently Alec Bangham and Martyn Hill[1], building on previous work on their proton pump/leak hypothesis, have made such an attempt.

Bangham and Hill set out to explain how consciousness can be lost not just by the action of an anaesthetic, but also by other perturbations such as cold or anoxia. Neuronal membranes are involved in maintaining a non-equilibrium balancing act in which the tendency of ion concentration gradients to decay is balanced by energy-requiring pumps. In such a steady-state system any change in the opposing fluxes will alter the point of equilibrium. The pumps are both energy and temperature dependent but little affected by general anaesthetics, whereas passive ion permeability (leak) is known to be increased by general anaesthetics. If it is assumed that anaesthesia results in some way from this increased leak discharging the ion gradients, then cold would have the same net effect by slowing the energy-dependent pumping of ions, hence inducing cold insensibility. Similarly one can explain other changes in the conscious state, such as the fact that pressure reverses the leak and thus anaesthesia; or that anoxia interrupts energy supplies to the pumps and leads to unconsciousness. One specific example of these effects is that the ATP-dependent accumulation of the neurotransmitter dopamine in rat brain synaptic storage vesicles is reversed by general anaesthetics, perhaps because an anaesthetic-induced inward leak of cations facilitates the outward leak of hydrogen ions, increasing the proportion of dopamine in the uncharged, membrane-permeable form.

The hypothesis can be criticized on several grounds. For example, most ion pumps are unlikely to be overwhelmed by leaks of the magnitude induced by anaesthetics, although such a situation could arise locally if the pump density were low. Nonetheless, its emphasis on the need to consider the inter-relationship between separate components of a neurone is valuable. This emphasis is echoed by recent attempts to explain the behaviour of intact neurones in terms of the plethora of ion channels that have been discovered in the past decade. These channels are often coupled to each other by changes in voltage in ways that may profoundly modify overall electrical activity. This modulation in turn may be regulated by the activities of neurotransmitters and other agents acting on allosteric sites (see ref. 2 for a review). That general anaesthetics can modulate such channels is suggested by the drastic modification that low concentrations of halothane induce in the stable rhythmical discharge exhibited by a crayfish stretch receptor under tension[3].



The first public demonstration of surgery under general anaesthesia on 16 October 1846, exactly 140 years ago, in the Bulfinch Building, now known as the Ether Dome at the Massachusetts General Hospital. The painting is by Robert Hinckley.

Specific effects of general anaesthetics are well known — the only controversy concerns whether they cause or accompany anaesthesia (see refs 4–7 and references cited therein). Allosteric actions of barbiturates have been demonstrated at the voltage-sensitive sodium channel as well as at the γ-aminobutyric acid and nicotinic acetylcholine receptors. These actions on the receptors are stereoselective, and saturable binding of radiolabelled barbiturates to the acetylcholine receptor can be demonstrated. However, the pharmacology of barbiturates suggests these actions are less related to general anaesthesia than to anticonvulsant or other actions.

On the other hand, gaseous anaesthetics act on channels by a mechanism independent of these allosteric sites. In the voltage-sensitive sodium channel and in the acetylcholine receptor these anaesthetics reduce the number of channels in the resting state. In both channels this stabilization of the inactivated or desensitized state is pressure-reversible. How common are such actions and what structural features underlie them? More systematic information might provide an indication of the physiological sites involved.

Traditional studies on lipid bilayers have not pointed to such sites because there are membranes of appropriate composition in most cells. This situation could be about to change as a result of intriguing new evidence from *in vivo* studies[7,8] of adaptive changes in membrane lipid composition in animals chronically exposed to ethanol. Although the adaptive change in average physical properties is disturbingly small, there is growing evidence that it is confined to specific lipid species, implying a much larger change in some microregion of the membrane[8]. If this proves to be the case, it would be a useful pointer to the physiological site of action of ethanol and perhaps of other general anaesthetics. Without some such pointers the way may be long. □

1. Bangham, A.D. & Hill, M.W. *Chem. Phys. Lipids* **40**, 189 (1986).
2. Adams, P.R. & Galvan, M. *Adv. Neurol.* **44**, 137 (1986).
3. Roth, S.H. *Fdn Proc.* **39**, 1595 (1980).
4. Franks, N.P. & Leib, W.R. *Nature* **300**, 487 (1982).
5. Miller, K.W. *Int. Rev. Neurobiol.* **27**, 1 (1985).
6. Roth, S.H. & Miller, K.W. (eds) *Molecular and Cellular Mechanisms of Anesthetics* (Plenum, New York, 1986).
7. Alcohol and the Cell *Ann. N.Y. Acad. Sci.* (in the press).
8. Tarachi, T.F., Ellington, J.S., Wu, A., Zimmerman, R. & Rubin, E. *Proc. natn. Acad. Sci. U.S.A.* (in the press).

Keith W. Miller is Edward Mallinckrodt Professor of Pharmacology in the Department of Anaesthesia, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA.