Anesthesiology 2006; 105:649–51

Nicholas P. Franks, Ph.D.

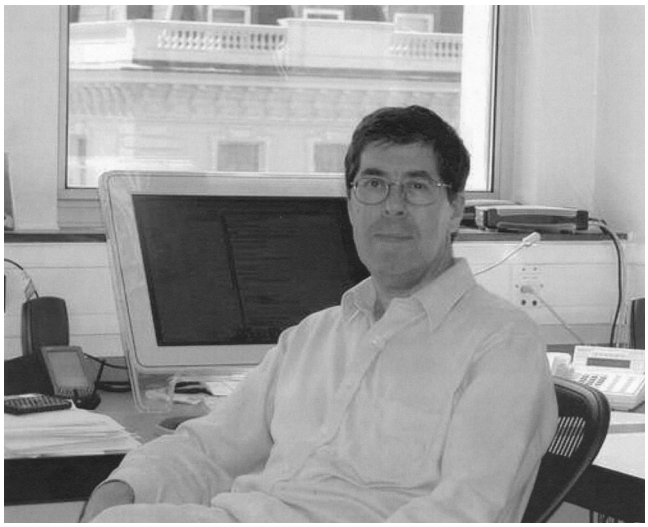
Recipient of the 2006 Excellence in Research Award

*Alex S. Evers, M.D.**

THE stated purpose of the American Society of Anesthesiologists Excellence in Research Award is to recognize an individual who has made "original, mature and sustained contributions to the extension and advancement of knowledge in anesthesiology" and whose work has "altered understanding of the science of anesthesiology." The mechanism of anesthetic action is the long-standing pharmacologic enigma at the core of anesthetic knowledge; no one has done more to unravel this mystery than Nicholas P. Franks, Ph.D., Professor of Biophysics and Anesthetics at Imperial College and Head of Biophysics at the Blackett Laboratory in London, United Kingdom. Nick Franks' discoveries and insights have revolutionized research on mechanisms of anesthetic action and have created an intellectual framework that has facilitated remarkable advances in understanding how anesthetics work.

Nick's pedigree for medical science begins with his father, "Sammy" Franks, a world-renowned pathologist who made noteworthy contributions to the cell biology of prostate cancer. His formal career in science began with an undergraduate education in physics at Brunel University, London, United Kingdom, followed by Ph.D. training in biophysics with the Nobel laureate Maurice Wilkins, Ph.D., at King's College, also in London. At King's, he used neutron diffraction techniques to determine how general anesthetics alter the structure of lipid membranes.[1,2] The surprising results of these studies refuted the universally held "lipid perturbation" theories of anesthetic action and initiated Nick Franks' lifelong quest to understand the mechanisms of anesthetic action. During this period he also met William R. Lieb, Ph.D. (recently deceased), with whom he would forge a lifelong collaboration that would focus on molecular mechanisms of general anesthetic action.

When Nick entered this field in the 1970s, it was widely agreed that general anesthetics acted by disrupting the structural or dynamic properties of biologic membranes, a view that had dominated the field since the work of Meyer and Overton in the 1890s. Franks' and Lieb's initial studies showed that clinical concentrations of general anesthetics had minimal effects on membrane structure and that these effects could not explain anesthetic action.[1,2] They postulated that anesthetics must act at amiphilic sites on proteins and not on the lipid bilayer.[3,4] These results were vigorously attacked by the protagonists of the lipid perturbation theory and would not begin to be accepted for nearly a decade.



Nicholas P. Franks, Ph.D., in his office.

Franks and Lieb next undertook a series of studies examining anesthetic effects on the water-soluble protein firefly luciferase. They showed that a host of general anesthetics inhibited luciferase activity in proportion to their octanol/water partition coefficient; thus the Meyer-Overton correlation could be entirely explained by anesthetic interactions with a protein rather than by effects on the lipid components of the membrane.[4] In a landmark article (recently republished in ANESTHESIOLOGY as a Classic Paper), they went on to show that anesthetic inhibition of luciferase was competitive with respect to the substrate luciferin, indicating that anesthetics bind to specific sites on luciferase.[5] The demonstration of a specific anesthetic binding site that obeyed the Meyer-Overton rule immediately suggested that anesthetics might act by binding to discrete protein binding sites on neuronal proteins. In 1998, Franks *et al.*[6] published a high-resolution x-ray crystallographic structure of firefly luciferase with an anesthetic molecule in the luciferin-binding site, confirming the conclusions they had drawn from functional studies in the early 1980s.

To identify the specific neuronal protein targets that he had postulated, Franks then taught himself patch clamp electrophysiology. He soon made another seminal

* Henry E. Mallinckrodt Professor and Chair, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri. eversa@wustl.edu

Submitted for publication July 4, 2006. Accepted for publication July 7, 2006.

discovery, identifying a novel potassium channel (I_{Kanest}) in identified neurons in the pond snail (*Lymnaea stagnalis*) that was selectively activated by inhalational general anesthetics.[7] The mammalian homologs of I_{Kanest} were subsequently cloned and identified as two-pore domain potassium channels. Some members of the two-pore domain potassium channel family (*e.g.*, TREK and TASK) were found to be activated by inhalational anesthetics with properties similar to I_{Kanest}.[8,9] Recent studies have shown that knockout of TREK-1 in mice results in a substantial reduction in sensitivity to inhalational anesthetics,[10] indicating that Franks' initial finding identified an important protein target of inhalational anesthetic action.

Another important discovery was the finding that inhalational anesthetics such as isoflurane[11] and intravenous agents such as etomidate[12] and thiopental[13] act enantioselectively on ion channels. This work led to the use of enantioselectivity as a powerful criterion for identifying relevant molecular targets of anesthesia. The demonstration that anesthetics act in an enantioselective manner also dealt a final blow to nonspecific lipid perturbation theories, because anesthetic enantiomers are equally soluble in lipid membranes but have markedly different anesthetic potency in animals.

In 1994, Franks and Lieb[14] wrote the most important and best-cited review in the field of molecular mechanisms of anesthetics. This review identified the principal targets for general anesthetics and set a road map for subsequent work on anesthetic mechanisms. Franks' own contributions in the ensuing years have led the way in characterizing anesthetic binding sites on proteins and investigating the "anesthetic-sensitive superfamily" of receptors including the nicotinic acetylcholine receptor,[15,16] glycine receptor,[17] and γ-aminobutyric acid type A receptor.[18] Franks has also recently shown that xenon, long known to be an anesthetic, acts on the *N*-methyl-D-aspartate–type glutamate receptor rather than on the anesthetic-sensitive superfamily of ion channels.[19]

By the late 1990s, Franks' protein hypothesis for anesthetic action had become dogma. While many investigators have continued to map specific protein targets to specific actions of specific anesthetics, Franks has directed his work to the next steps in understanding anesthetic action. First, he has focused on the molecular details of anesthetic binding to protein sites. Using x-ray crystallography, he has defined the specific orientation of anesthetic molecules in their binding sites on soluble proteins.[6,20] Franks has also begun to look at the systems level actions of anesthetics. In collaboration with Mervyn Maze, M.B., Ch.B., Imperial College, London, he has made the seminal discovery that a specific hypothalamic nucleus, the tuberomammillary nucleus (which is known to play an important role in natural sleep), may be critical in anesthetic-induced loss of consciousness.[21] The idea that general anesthetics may produce their primary effects *via* actions at specific anatomical sites in the brain will doubtless be an important focus of Franks' subsequent work.

In concert with his fervent pursuit of research, Nick engages in an eclectic range of extravocational activities. Before his knees took their toll from constant pounding on the rugby pitch, he was a vigorous lock forward. Now he continues to enjoy rugby and other team sports vicariously through his beloved English national teams. For the past three decades, he has tempered his hitherto unbridled enthusiasm for England by respecting the aspirations of his wife, Ange's, Spanish teams; sadly, his two sons, Peter and Pablo, have sided with their mother! Nick is also a keen practitioner of fly-fishing and can be seen musing and casting in equal measure on the rivers of south Wales. His appetite for entertainment spans the gamut of both conventional and experimental theater and music. In short, Nick is a well-rounded man with a keenly developed sense of perspective, humility, and humor.

Throughout his career, Nick Franks has passionately engaged himself in a quest to understand how general anesthetics work and to communicate this understanding to the anesthetic community. He has married skepticism with creativity, marshalling his exceptional knowledge and skills in an array of physical and biologic sciences to repeatedly make groundbreaking discoveries. When his ideas were scorned, he persevered, using logic and a compelling "quiet charisma" to convince the skeptics. Nick's presentations at international meetings on Cellular and Molecular Mechanisms of Anesthetic Action were always a tour de force, never failing to hush and galvanize the audience with yet another clever but unexpected insight. He has actively engaged the community of anesthesiologist–scientists and has been a frequent speaker and participant at the American Society of Anesthesiologists, an Associate Editor of ANESTHESIOLOGY, and an active faculty member in the Department of Anesthesiology at Imperial College School of Medicine. In pursuing his quest, Nick Franks has made staggering contributions to our understanding of anesthetic mechanisms and has been *the* dominant figure in this field for 30 yr. I greatly admire Professor Nick Franks for his intellect, his insights, his vision, and his many contributions to our field. I can imagine no one more deserving of the American Society of Anesthesiologists Excellence in Research Award for 2006 than Nick Franks.

References

1. Franks NP: Is membrane expansion relevant to anaesthesia? Nature 1981; 292:248–51

2. Franks N, Lieb W: The structure of lipid bilayers and the effects of general anaesthetics: An x-ray and neutron diffraction study. J Mol Biol 1979; 133:469–500

3. Franks NP, Lieb WR: Where do general anaesthetics act? Nature 1978; 274:339–42

4. Franks NP, Lieb WR: Molecular mechanisms of general anaesthesia. Nature 1982; 300:487–93

5. Franks NP, Lieb WR: Do general anaesthetics act by competitive binding to specific receptors? Nature 1984; 310:599–601

6. Franks NP, Jenkins A, Conti E, Lieb WR, Brick P: Structural basis for the inhibition of firefly luciferase by a general anesthetic. Biophys J 1998; 75:2205–11

7. Franks NP, Lieb WR: Volatile general anaesthetics activate a novel neuronal K^+ current. Nature 1988; 333:662–4

8. Patel AJ, Honore E, Lesage F, Fink M, Romey G, Lazdunski M: Inhalational anesthetics activate two-pore-domain background K^+ channels. Nat Neurosci 1999; 2:422–6

9. Gruss M, Bushell TJ, Bright DP, Lieb WR, Mathie A, Franks NP: Two-pore-domain K^+ channels are a novel target for the anesthetic gases xenon, nitrous oxide, and cyclopropane. Mol Pharmacol 2004; 65:443–52

10. Heurteaux C, Guy N, Laigle C, Blondeau N, Duprat F, Mazzuca M, Lang-Lazdunski L, Widmann C, Zanzouri M, Romey G, Lazdunski M: TREK-1, a K^+ channel involved in neuroprotection and general anesthesia. EMBO J 2004; 23:2684–95

11. Franks NP, Lieb WR: Stereospecific effects of inhalational general anesthetic optical isomers on nerve ion channels. Science 1991; 254:427–30

12. Tomlin SL, Jenkins A, Lieb WR, Franks NP: Stereoselective effects of etomidate optical isomers on γ-aminobutyric acid type A receptors and animals. ANESTHESIOLOGY 1998; 88:708–17

13. Tomlin SL, Jenkins A, Lieb WR, Franks NP: Preparation of barbiturate optical isomers and their effects on $GABA_A$ receptors. ANESTHESIOLOGY 1999; 90:1714–22

14. Franks NP, Lieb WR: Molecular and cellular mechanisms of general anesthesia. Nature 1994; 367:607–14

15. McKenzie D, Franks NP, Lieb WR: Actions of general anaesthetics on a neuronal nicotinic acetylcholine receptor in isolated identified neurones of Lymnaea stagnalis. Br J Pharmacol 1995; 115:275–82

16. Violet JM, Downie DL, Nakisa RC, Lieb WR, Franks NP: Differential sensitivities of mammalian neuronal and muscle nicotinic acetylcholine receptors to general anesthetics. ANESTHESIOLOGY 1997; 86:866–74

17. Downie DL, Hall AC, Lieb WR, Franks NP: Effects of inhalational general anaesthetics on native glycine receptors in rat medullary neurons and recombinant glycine receptors in *Xenopus oocytes*. Br J Pharmacol 1996; 118:493–502

18. Hall AC, Lieb WR, Franks NP: Stereoselective and non-stereoselective actions of isoflurane on the $GABA_A$ receptor. Br J Pharmacol 1994; 112:906–10

19. Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR: How does xenon produce anaesthesia? Nature 1998; 396:324

20. Bhattacharya AA, Curry S, Franks NP: Binding of the general anesthetics propofol and halothane to human serum albumin: High resolution crystal structures. J Biol Chem 2000; 275:38731–8

21. Nelson LE, Guo TZ, Lu J, Saper CB, Franks NP, Maze M: The sedative component of anesthesia is mediated by $GABA_A$ receptors in an endogenous sleep pathway. Nat Neurosci 2002; 5:979–84