Margaret M. Sedensky, M.D., and Philip G. Morgan, M.D., Recipients of the 2023 Award for Excellence in Research

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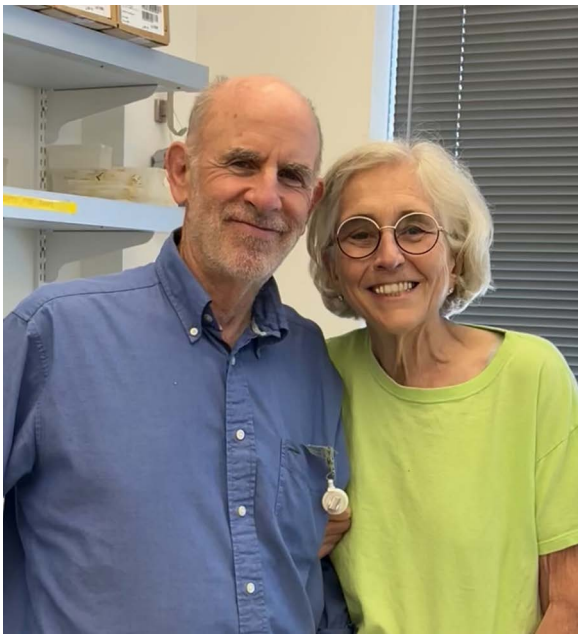

It is our sincere pleasure to congratulate Dr. Margaret M. Sedensky and Dr. Philip G. Morgan, recipients of the 2023 American Society of Anesthesiologists (Schaumburg, Illinois) Award for Excellence in Research. Although a "joint awardee" is unusual—perhaps even unprecedented for this award—we feel that it is appropriate here, because for more than 40 yr of remarkable research, their paths have been inseparable. Moreover, they themselves have always considered their scientific advances to be joint achievements.

Drs. Sedensky (Marge) and Morgan (Phil) were early pioneers in systematically applying genetic approaches to the "mystery" of anesthesia. The goal was to apply available molecular genetic tools to search for anesthetic targets in an unbiased fashion. They started with work on the roundworm (*Caenorhabditis elegans*) and achieved fundamental insights regarding the nature of molecular targets of volatile anesthetics. Their discoveries in this humble invertebrate and powerful model organism founded a new dimension of research in anesthetic mechanisms. Transitioning more recently to more complicated animals, they applied the fundamental insights gained in the invertebrate model organism to targeted mechanistic questions in mammals with important translational extension to human disease.

Central to their research was a discovery that resulted from a mutagenesis screen for anesthetic sensitivity in worms. Its fundamental insight was that mutations in specific genes differentially affected anesthetic sensitivity. The implications of that discovery were not easily reconcilable with the dominant thinking at that time, which postulated that all volatile anesthetics acted on a single (undisclosed) molecular target. One gene (*HSN1*) was later identified as *unc-79*. Marge and Phil noticed that *unc-79* (and also later that *unc-80*) conferred interesting but ambiguous anesthetic phenotypes to the whole animal: increased sensitivity to some volatile agents (*e.g.*, halothane), resistance to others (*e.g.*, enflurane), and no effect to still another (isoflurane). Notably, at that time, all three agents were considered to act in similar fashion on the same targets. These findings prompted a screen of more than 10,000 worm strains with enflurane and isoflurane, resulting in a series of seminal publications in the late '80s and early '90s in *Science* (1987), *Proceedings of the National Academy of Sciences of the United States of America* (1990, 1994), Anesthesiology (1988, 1994), and other high-profile journals, characterizing the modulation by genetic background of anesthetic sensitivity to the commonly used volatile agents enflurane, isoflurane, and halothane. One of the mutations (*fc21*), located on the X-chromosome in the gene *gas-1* (from general anesthetic sensitive), caused behavioral hypersensitivity—that is, the worms were immobilized at lower concentrations of all tested volatile anesthetics compared to the wild-type strain. Importantly, the hypersensitivity to all volatile anesthetics prevailed over the effects of mutations in other genes (*e.g.*, the resistance to enflurane). This epistatic effect pointed to a target of fundamental importance for the responsiveness to all volatile agents. Subsequent cloning identified *gas-1* to be identical to *Ndufs2*, a gene coding for a subunit of Complex I of the

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mitochondrial electron transport chain. Extensive work in Marge's and Phil's laboratories (characterizing the effects of mutations in multiple subunits of Complexes II to V), performed around the turn of the millennium, narrowed the anesthetic-sensitive elements to Complex I, and provided a compelling link to the observation of anesthetic hypersensitivity in children suffering from Complex I dysfunction also described by Drs. Morgan and Sedensky (Anesthesiology 2002, *Anesthesia and Analgesia* 2021)—a flagship example for the role of physician–scientists in bridging laboratory bench and clinic.

Taking advantage of the insights that they had gained from their studies of *C. elegans* to test for translational relevance, Drs. Sedensky and Morgan turned to rodent models. They found striking parallels in anesthetic–Complex I interactions for components of the anesthetic phenotype in mice. Using multimodal techniques that combined genetic manipulations with advanced electrophysiologic methods, they mechanistically dissected the contributions of specific cell types (neurons and astrocytes) to changes in glutamatergic synaptic transmission and thalamocortical signaling induced by Complex I mutations. Most recently, they developed evidence that modulation of Complex I by some inhaled agents contributes substantially to their capacity to interfere with excitatory synaptic transmission—a major insight in an area that has been the subject of intense investigation for decades. Altogether, their work provides a fundamental advance in our understanding of the mechanism of inhaled anesthetic action.

It is notable that the work carried out by Dr. Sedensky and Dr. Morgan has been continuously supported by the National Institutes of Health (Bethesda, Maryland) since 1989 and that it continues to this day.

Throughout the years, Drs. Sedensky and Morgan have mentored highly successful residents, graduate students, and postdoctoral fellows. In addition, both candidates combine their remarkably productive research, mentoring, and clinical activities with extensive humanitarian work outside the United States. As practicing anesthesiologists, they have consistently recognized the crucial interactions with their clinical colleagues for directing their interests.

Based on their outstanding achievements, the quality of their work, the significance of their findings, and their lifelong commitment to research in anesthesiology, we feel that Drs. Sedensky and Morgan are ideal joint recipients of the 2023 American Society of Anesthesiologists Award for Excellence in Research. We congratulate them on this honor.

Competing Interests

The authors declare no competing interests.

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