shown to be directly affected by volatile anesthetics and have been shown to affect anesthetic sensitivity in multiple organisms.[5–7] By dismissing mitochondrial complex I as a possible anesthetic target, it seems that Dr. Forman does not appreciate the full power of a genetic approach to solve difficult problems.

Because to date no single target has been identified as both necessary and sufficient to produce the anesthetic state for most drugs and because more than one pathway contributes to the anesthesia state even for the same drug, other relevant targets clearly exist. The search for the mechanism of action of volatile anesthetics started many decades ago, and yet new targets are occasionally discovered and validated—why should we believe that we have discovered them all? Unbiased approaches such as forward genetics seem well suited to help discover these elusive remaining targets.

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In Reply:

I thank Drs. Sedensky and Morgan for highlighting an area of genetic research on general anesthetics that, because of space limitations, was not included in my editorial.[1] Their research dating back to 1987[2] has used unbiased forward genetic screens in a nematode, *Caenorhabditis elegans*, identifying genes that influence sensitivity to volatile anesthetics in tests of motor function. Others have similarly exploited the fruit fly, *Drosophila melongaster*. This research has contributed to our understanding of anesthetic mechanisms and bolsters my view that volatile drugs probably act *via* a wide variety of targets, which may include ion channels, neurotransmitter release mechanisms, mitochondria, and others not yet discovered.

One area where my thinking diverges from that of Sedensky and Morgan relates to the role of mitochondrial complex I as a putative anesthetic target. Logically, unless confounding effects perturb the pertinent phenotype, knockout of an important primary anesthetic target gene should *reduce anesthetic sensitivity* in the transgenic organism. However, knockout of Ndufs4 in mitochondrial complex I in mice results in a dramatic *gain of sensitivity* to volatile anesthetics,[3] undermining the idea that volatile anesthesia depends on the presence of this protein in normal animals. Clearly, other targets are mediating general anesthesia in the knockout animals. As noted by the authors,[3] there are myriad mechanistic explanations for this phenotype, including that inhibition of complex I contributes to anesthesia. Thus, inferences regarding a role of mitochondrial complex I in general anesthesia are quite weak and require more rigorous experimental assessment. Nonetheless, the Ndufs4 knockout animal is a useful model for patients with mitochondrial diseases, who are also remarkably sensitive to volatile anesthetics.[4]

Volatile anesthetics are a mainstay of clinical practice, and understanding the mechanisms of their therapeutic actions and toxicities is a worthy scientific goal with potential implications for future drug development. As noted by Sedensky and Morgan, volatile anesthesia is a "difficult problem." Its solution will require sophisticated research models and approaches, as well as thoughtful data analysis.

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