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In Reply:

We thank Dr. Hogan for his interest in our article¹ and for offering his interpretation of our findings. He is correct that 94% of our subjects exposed to general anesthesia received nitrous oxide. However, the duration of nitrous oxide exposure was variable and often brief. During the time that our cohort of subjects underwent their surgical procedures as infants, it was a common and prevailing practice at our study site to use nitrous oxide during induction only and discontinue it during maintenance. All subjects who received nitrous oxide also received one or more other anesthetics during their surgery. Therefore, our study findings cannot be attributed to the effect of nitrous oxide alone. Although we accept Hogan's statement that nitrous oxide may inactivate methionine synthase, the only evidence that he cites that nitrous oxide causes demyelination, cerebral atrophy, and loss of developmental milestones is his own case report of a single child with 5,10-methylenetetrahydrofolate reductase deficiency.²

The relevance of our study to contemporary pediatric anesthesia practice is that anesthetics have been shown to have

neurotoxic effects in neonatal animals and pertinent human evidence is limited. Therefore, we sought to probe the long-term effects of anesthetic agents in a structural neuroimaging study. We emphasized that, although our findings may be related to anesthesia and surgery during infancy, other explanations are possible. Our study sought to examine brain structure years after anesthetic exposure. Although this approach provides important information, one limitation is that anesthetic practices change over the years, so that, for maximal value, this approach needs to be combined with other approaches, including shorter-term follow-up as well as longitudinal studies. Our findings provide no basis to recommend for or against use of nitrous oxide when providing anesthesia for infants undergoing surgery, nor to reassure parents about contemporary anesthesia safety based on changes in anesthetics used in clinical practice. At present, we believe that individual pediatric anesthesiologists should decide whether to use nitrous oxide based on current evidence and their own clinical judgment of risks and benefits. Finally, we think that Hogan's belief that nitrous oxide use is associated with neurotoxicity in young children merits further evaluation.

Competing Interests

The authors declare no competing interests.

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