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Hyperoxia in Pediatric Anesthesia: Time for Reconsideration?

To the Editor:—Kalkman *et al.*[1] link anesthesia to clinically deviant behaviors in children anesthetized for urologic procedures before age 2 yr but make no mention of intraoperative oxygen measurement in their study cohort. Wilder *et al.*[2] link multiple pediatric anesthetic exposures to learning disabilities using a sophisticated database, albeit one built before pulse oximetry was in wide use. Editorially, Patel and Sun[3] provide a review of molecular mechanisms with "relevance" to human development that overlooks the current state of data pertaining to oxygen's neurotoxic effects in cell and animal models. Although all exemplify Engle's proposition that scientists and clinicians must account for how submolecular or molecular actions ramify through a "continuum of natural systems" to produce events at higher systems levels—persons, families, communities, cultures, the biosphere—none acknowledge that early and multiple anesthetic exposure is also a marker for early and multiple oxygen exposure.[4,5]

Anesthesiologists and the anesthesia literature, by and large, tend to discount supplemental oxygen effects in patient care in the absence of ischemia–reperfusion injury.[6] Others have more balanced views. Maltepe and Saugstad[7] note that evolution equips humans with numerous hypoxemia defense responses; hyperoxia, however, always iatrogenic, is not as easily defended against, biologically speaking. Neonatologists know hyperoxia is not always beneficial in neonatal resuscitation.[8] Supplemental oxygen use for 3 min or more at birth shows a vexing connection to an increased cancer incidence for children younger than 8 yr.[9] The now well established association of retinopathy of prematurity with supplemental oxygen use was incorrectly overlooked for decades.[10]

Degos *et al.*[11] list hypoxia-induced oxidative stress reduction among potential targets for neuroprotective efforts. But significant hypoxemia may be less common than intentional hyperoxia in pediatric anesthesia practice. Even with the classic 70% nitrous oxide–30% oxygen plus volatile anesthetic inhalational induction sequence, hyperoxia exists. Recent bench research using cell cultures and animal models shows that hyperoxia alters cell ultrastructure and function across multiple organelle and neuronal action sites: mitochondria, membrane surfaces, cell nuclei, and progenitor cell lines.[12–14] Reactive oxygen species, with other mechanisms, are a source of submolecular injury where hyperoxia is induced experimentally. Such data suggest that neurocidal/neurotoxic potential effects research must account for hyperoxia's submolecular effects, too—effects Engle's model predicts will express at higher levels of biopsychosocial organization.

Endeavors such as Safety of Key Inhaled and Intravenous Drugs in Pediatrics (SAFEKIDS) and General Anesthesia for Effects on Neurodevelopmental Outcome and Apnea in infants (GAS) are much needed.[15] Should protocols in future clinical studies include control anesthetics administered at atmospheric or "capped" oxygen partial pressures? Controlled for, hyperoxic effects—known and unknown—might be reasonably addressed as answers emerge to the question, Do anesthetics damage the developing human brain? How else can we gain certainty that iatrogenic hyperoxia does not also play a role in the human developmental adverse outcomes we are now tempted to attribute predominantly to anesthetic agents? Sound science dictates that any known factors that might contribute to pediatric behavioral problems, such as lead, iron, and mercury levels—not just anesthetic exposure—should be taken into account.[16] Iatrogenic hyperoxia, sadly, might need to be investigated, too.

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In Reply:—We read with considerable interest the critical commentary of Kopp with respect to our editorial in the April issue of ANESTHESIOLOGY.[1] That editorial presented a brief introduction to the research articles that were presented at the ANESTHESIOLOGY/Foundation for Anesthesia Education and Research Symposium on Anesthetics and the Developing Brain; the intent was to summarize current research in anesthetic neurotoxicity with an emphasis on the molecular mechanisms that underlie the adverse impact of anesthetics. The central concern expressed by Kopp is the potential toxicity of oxygen. Given that oxygen administration is a routine practice in the clinical practice