

to their inclusion in a broadly study-defined LD group. For example, 2 children who were subsequently diagnosed with an LD had Sturge-Weber syndrome, and another child had cerebral palsy. It thus seems reasonable to question whether the LDs in these children are really "in excess" of those usually associated with these medical conditions.

Furthermore, the authors report an incidence of LDs in the Olmsted County, Minnesota general population as 20.0% for children not receiving an anesthetic, and 20.4% and 35.1% in children receiving one or multiple anesthetics, respectively. This is significant because the inclusion criteria used for the diagnosis of an LD in the authors' study resulted in an incidence more than double that reported in the 2007 Summary Health Statistics for U.S. Children: National Health Interview Survey, which reported an LD incidence of 8% in children aged 3–17 yr.³ In addition, the LD prevalence reported in the *Diagnostic and Statistical Manual of Mental Disorders* ranges from 2% to 10%, depending on the diagnostic criteria used.² Finally, in examining the authors' previous publications based on the same population cohort, the "low achievement criteria" diagnosed reading disability (11.8% vs. 5.3%) and math disability (13.8% vs. 5.9%) at more than double the rate of the criteria used by the Minnesota Department of Education, and significantly higher than the other diagnostic criteria used in the current study.^{4,5} Indeed, it would be interesting to view the results obtained when each diagnostic criterion used in the current study was displayed individually (similar to the authors' previous studies of this same population).

The study of anesthetic effects on childhood neurodevelopment is both timely and clinically relevant, and the authors are to be commended for attempting the difficult task of translating animal research findings into humans. However, more rigorous clinical evaluations of

the effects of anesthetics on the developing human brain, including controlling for potential confounders (e.g., medical diagnoses, type of surgery, prenatal history) using a multivariate model and propensity scoring are needed before drawing a link between anesthetic use in children and the subsequent development of LDs. As suggested by the title, the lay media is all too quick to jump on such an extremely controversial and sensitive topic, while at the same time preying on parents' worst fears.

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Anesthesia in Infancy Linked to Later Disabilities: Causation, Association, or Coincidence?

To the Editor:—"Anesthesia in Infancy Linked to Later Disabilities" is a provocative, if not sensational headline published by *Time* magazine Tuesday, March 24, 2009,¹ regarding the findings of a retrospective cohort study of anesthetic exposure and learning disabilities between 1967 and 1982 by Dr. Wilder *et al.*² The articles in the April 2009 issue of *ANESTHESIOLOGY* regarding anesthesia and the developing brain are of great interest to practitioners of pediatric anesthesia. The alarms are ever increasing regarding the risk of anesthesia for the developing human brain. But the significance of the animal studies to clinical practice is uncertain, and there is little to support a causal link between anesthesia and learning disabilities. There does seem to be an association between anesthetic exposures and learning disabilities, but a similar correlation undoubtedly exists between hospital admission, intravenous fluid administration, and repeated invasive and/or noninvasive hemodynamic monitoring and these same learning disabilities. A few comments regarding both the animal research and the retrospective studies will, I hope, provide some perspective on the issue of anesthetic neurotoxicity.

Previous animal studies do not evaluate anesthetic effect in the presence of surgical or medical stressors. The tail clamp model of Stratmann *et al.*³ more closely resembles the response to surgery, and they are to be applauded for detailing the effects of hypercapnia and acidosis on outcome.⁴ However, they report a mortality of 25%, including deaths in the animals exposed to "only" 2 h of anesthesia. Although the phrase "clinically relevant doses of anesthetics" is now commonly used, I would remind readers that the life expectancy of a rat is only 9 months. One might ask what a comparable anesthetic exposure in humans is. Simple mathematics would suggest that 4 h in the life of a rat might represent as many as 16 days for humans with a

life expectancy of 75 yr. Interestingly, in an early study, Jevtovic-Todorovic *et al.*⁵ demonstrated a threshold response to cerebrocortical injury and reported that inclusion of isoflurane (1%), halothane, pentobarbital, and diazepam all prevented neurotoxic reactions in adult rats during a 3-h exposure to nitrous oxide and/or ketamine. These specimens demonstrated histologically normal neurons. It is unclear why subsequent studies of anesthetic neurotoxicity in rodent pups subjected the animals to longer exposures when a threshold effect was seen with various anesthetic agents. Perhaps an animal model with mortality statistics that resemble outcomes in anesthetized neonates would be more appropriate for evaluating the long-term effects of anesthesia on the developing brain. One must also be aware that exposure of the developing brain to increased oxygen concentrations produces similar neuropathologic changes.⁶

As the parent of a 17 year old with moderately severe learning disabilities and a history of multiple anesthetic exposures before the age of 4 yr, I found the article by Dr. Wilder *et al.* linking early exposure to anesthesia and learning disabilities both intriguing and troubling. They do provide some interesting data, most of which they do not address in the discussion. To their credit, they admit that one cannot determine whether the results reflect exposure to anesthesia or the need for anesthesia. However, in the discussion, despite controlling for birth weight, sex, and gestational age, they do not address the confounders cited, including prolonged labor and hemorrhagic complications of pregnancy. They do not speak to the comorbidities of children presenting to the operating room for multiple procedures. One would expect this information to be available in their hospital database. Certainly, one should analyze the data for the effects of factors such as perioperative hemorrhage, sepsis, seizure disorders,

severe lung disease and its associated episodes of hypoxemia and prolonged ventilation, neurologic malformations, and cerebral palsy. I would suggest that the complex medical history of my own son is representative of the learning disabled who have had multiple anesthetic exposures. His American Society of Anesthesiologists physical status never exceeded II during his four anesthetics as a young child, despite the fact that during that critical period of development, he experienced neonatal sepsis, disseminated osteomyelitis, hepatic insufficiency with attendant coagulopathy, postfebrile partial complex seizure disorder, perioperative hemorrhage, and postoperative anemia. I have searched for explanations for his learning disabilities, but not once in 17 yr have I thought to attribute them to his anesthetic exposures.

A rational understanding of the potential neurotoxicity of anesthetic and sedative agents in the developing brain requires an animal model that closely mimics the clinical reality of serious illness and surgical stress requiring intervention. Clinical reviews, both retrospective and prospective, that address the association of anesthetic exposure and compromised neurodevelopment in young children are critical to our understanding. A threshold toxic dose should be sought and the possibility of a biphasic response of the developing brain should be considered, much like oxygen exposure where both hypoxia and hyperoxia result in permanent deficits. Paracelsus stated that "Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy." His observation is as relevant today as it was nearly 500 yr ago.

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Surgical Diagnosis Is an Important Variable to Consider in Postanesthesia Exposure-associated Learning Disabilities

To the Editor:—We commend Dr. Wilder *et al.*¹ for their work titled "Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort." In their article, they report that patients younger than 4 yr, with two or more exposures to general anesthesia, had a greater proportion of learning disabilities (LDs) compared with children who had one or no exposure to general anesthesia. This represents a clinically important epidemiologic correlate to compliment the worrying animal observations demonstrating the detrimental effects of general anesthesia on the developing brain.

A primary assumption in cohort analyses is that the groups observed are the same before exposure. However, children requiring anesthesia for surgical treatment may be inherently different from those who do not; these differences may present unique factors that predispose to LDs independent of anesthesia *per se*. In particular, we are concerned that a subpopulation at risk for learning disabilities—children undergoing ears, nose, and throat surgery—is overrepresented. Typical ears, nose, and throat surgeries in this age group include adenotonsillectomy and bilateral myringotomy with tympanostomy tube placement. The former is associated with obstructive sleep apnea, which can result in neurocognitive defects²; the latter may be associated with otitis media with effusions, which can yield poor performance in expressive speech and math testing in younger children.³

These coexisting conditions may have skewed the diagnosis of LD in this population. This is relevant because children tested within a short period of time from their ears, nose, and throat surgery may not have had sufficient time to "catch up" with their peers in terms of testing, should the surgery have improved their condition. Furthermore, given the frequency of achievement tests administered to the cohort population, is it possible to find children who no longer met LD definitions at some time point during follow-up testing? This

would be of particular interest for those children undergoing ears, nose, and throat surgeries.

In addition, we are concerned that the third definition of LD included patients in the low-average IQ range *versus* average intelligence. Moreover, using a cutoff of 1.75 SDs below their predicted standard score, as opposed to the conventional 2 SDs, might be an oversensitive method of identifying patients with LDs.

We are interested to know whether the authors could remove patients who underwent adenotonsillectomy and bilateral myringotomy with tympanostomy tube surgeries from the analysis and apply conventional definitions of LD to determine whether a relation between general anesthesia and LD persists.

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