major desaturation events (oxygen saturation measured by pulse oximetry ≤ 85% for 30 s or longer) in 67 children with a higher incidence by a factor of 2 in those whose anesthesiologist did not have the oximeter data available. These studies suggested that the oximeter allowed early recognition and intervention, thus preventing a minor desaturation event from progressing to a major desaturation event.[3,4] We also found a higher incidence of these major desaturation events in children younger than 2 yr. I do not know whether it is possible for Wilder *et al.* to go back and examine the anesthesia records from the 144 children in their cohort who had two or more anesthetic exposures to determine whether hypoxic events were recorded, but it might be a useful endeavor. I suggest that we need to look at other issues beyond simple exposure to anesthetic agents as possible contributory factors and look forward to more wonderful work from the Mayo group.

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The Elephant in the Room

To the Editor:—The conclusion reached by Wilder *et al.*[1] that exposure to multiple anesthetics is a significant risk factor in the development of learning difficulties is a headline-grabbing statement with far-reaching consequences for all providers of children's services. However, we believe there has been an insufficient attempt to draw attention to the elephant in the room: that children who require multiple operations usually have significant medical diagnoses, and/or syndromes with associated morbidities, that in turn are associated with a higher incidence of learning disorders than the general population has. Though this information on diagnoses is essential to interpret the data, it is only accessible on-line, and there is no information at all on the actual surgical procedures involved. Further analysis of the on-line data reveals that 22 of the 45 patients with multiple exposure to anesthesia have severe comorbidity or congenital anomalies that are frequently associated with learning difficulties. It should come as no surprise that children with cerebral palsy, Sturge–Weber syndrome, a history of meningitis, or cleft lip and palate have a higher incidence of learning difficulties than the general population.[2] Of the remaining 23 patients, 13 have serous otitis media. Even such isolated "minor" conditions are known to be associated with an increased incidence of educational delay.[3]

An attempt has been made to adjust statistically for neonatal factors but not for the effect of comorbidity. Though the inability to adjust for comorbidity is referred to in the text, we believe this omission is so significant that it invalidates any conclusion from this study. We are therefore afraid that this study does not contribute sensibly to the important discussion about potential anesthetic neurotoxicity in the immature human brain.

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"If the Odds Are a Million to One Against Something Occurring, Chances Are 50–50 It Will"*

To the Editor:—Given the potential ramifications of findings linking early anesthesia exposure to the later development of learning disabilities (LDs), we expectantly read the article by Wilder *et al.*[1] titled "Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort." This topic was not only of interest to the medical community, but also garnered significant attention from the lay media. However, despite the authors' interesting and thought-provoking conclusion that multiple anesthetic exposure in children before age 4 yr increased the risk of developing a subsequent LD, we caution against the overinterpretation of associations without investigation of potentially important medical, psychological, and psychosocial confounders.

For example, Wilder *et al.* used a less stringent, study-defined definition of LD, as opposed to that of the *Diagnostic and Statistical Manual of Mental Disorders* published by the American Psychiatric Association.[1,2] Included in the *Diagnostic and Statistical Manual of Mental Disorders* criteria is the following caveat: "If a sensory deficit is present, the learning difficulties must be in excess of those usually associated with the deficit."[2] This *Diagnostic and Statistical Manual of Mental Disorders* provision to the diagnosis of an LD is particularly relevant to the authors' study, which included multiple children with known medical diagnoses associated with sensory deficits. Similarly, many of the patients in the study cohort who received multiple anesthetics and were subsequently diagnosed with a LD also had medical diagnoses that may have contributed to their low achievement and led

* —Anonymous.

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,