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Learning Disabilities May Be Related to Undetected Hypoxia

To the Editor:—The recent article by Wilder *et al.*[1] presents a concerning correlation between multiple episodes of anesthesia in childhood and later learning disabilities. In the discussion of possible causes for this correlation, they focus on the known neurotoxicity of various anesthetic agents *in vitro* and in animal studies. They identify some possible sources of bias in their study but neglect to mention one of the most significant changes in anesthetic practice, which occurred after the children in the study received their anesthesia.

Pulse oximetry was developed in the 1970s[2] but only became commonly used in anesthesia at the end of the 1980s and was made a part of the American Society of Anesthesiologists standards for basic anesthetic monitoring. The introduction of a standard for monitoring and the availability of pulse oximetry coincided with a great reduction in the incidence of undetected hypoxia and resultant injury as demonstrated at Harvard at the time.[3] Because the children in this study received their anesthesia in the period 1976 through 1986, the possibility that their increased incidence of learning difficulties might have resulted partly from undetected hypoxia brief or mild enough not to have caused injury that was immediately obvious should not be discounted. A comparison with children who received a more current standard of monitoring after 1990 would be helpful in determining the likely magnitude of this effect.

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Learning Disability and Repeated Anesthetics: Drugs or Airway Management Issues?

To the Editor:—Regarding the article by Wilder *et al.*,[1] this research is an important step in the right direction to either prove or disprove the association of learning disabilities with multiple exposures to anesthesia in the early years of life possibly caused by anesthetic agent–induced neuroapoptosis. The authors are to be congratulated for making a stab at this complex issue, and not connecting the dots directly but rightfully pointing out that many factors might contribute to their findings that are unrelated to anesthesia. However, one important factor that seems to have been overlooked is that the majority of these children were likely anesthetized before the routine use of pulse oximetry and capnography (1976–1982) became our standard of care. We do not know what happens to a child who is excessively ventilated for prolonged periods of time, resulting in severe hypocapnia and possibly reduced areas of cerebral perfusion. Nor do we know how many of these children experienced prolonged or repeated short episodes of hypoxemia that were either unrecognized or only recognized late in the event, when the child developed bradycardia that could have resulted in subtle neurologic insults. In the early years when capnography was first being advocated but not yet a standard of care, in a prospective study of 331 children, we found an 11% incidence of hypocapnia (expired carbon dioxide value ≤ 30 mmHg) in intubated children, with a very high incidence in children younger than 1 yr.[2] Likewise, in two randomized blinded studies involving 554 children, we found 94

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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.

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