of anesthesia, it is highly probable that a state of hyperoxemia is induced in subjects undergoing anesthesia and surgery. Kopp suggests that it is this hyperoxemia that can injure the brain, and in particular the developing brain.

There is growing evidence that the administration of oxygen in concentrations that produce hyperoxemia is associated cellular injury. The adverse impact of high concentrations of oxygen on retinopathy of prematurity[2] and on bronchopulmonary dysplasia[3] has long been recognized. In susceptible neonates, the incidence of cerebral palsy is increased in association with hyperoxemia.[4] More recent evidence also indicates that resuscitation of premature neonates with a high fraction of inspired oxygen (FIO_2) is associated with greater mortality and worse outcomes.[5] Indeed, the authors of a recent metaanalysis concluded that the available data support the use of room air for resuscitation of asphyxiated neonates in place of 100% oxygen.[5] Importantly, the use of room air for this purpose does not seem to be associated with worse cognitive outcomes.[6] Preclinical studies in adult animals also suggest that resuscitation from global ischemia with high FIO_2 leads to greater neurologic injury.[7]

In the investigations of Kalkman *et al.*[8] and Wilder *et al.*,[9] the concentration of oxygen that was administered is not clear. It is reasonable to assume, based on the current standard of practice, that supplemental oxygen was administered and some degree of hyperoxemia did occur. Could the association between anesthetic exposure and adverse outcomes be explained by oxygen toxicity rather than anesthetics? Although Kopp's contention is feasible, it is difficult to separate the effects of oxygen from those of the patients' primary disease, anesthetics, surgery, postsurgical inflammation, and use of analgesics. The question of whether oxygen can injure the otherwise normal developing brain is best answered in the laboratory.

Of significant interest are the observations of Felderhoff-Mueser *et al.*,[10] who demonstrated oxygen toxicity in the developing brain. An inspired concentration of oxygen of 80% resulted in widespread neurodegeneration; toxicity was apparent with as little as 2 h of exposure. The pattern of injury was similar to that produced by anesthetics. Moreover, the period of vulnerability, as with anesthetics, was approximately postnatal day 7, with little injury seen at postnatal day 14. By contrast, injury was not observed with the administration of 40% oxygen for as long as 12 h. This begs the question of whether anesthetic toxicity observed in previously published studies might be due to oxygen.

In published studies to date, the reported inspired concentrations of oxygen were 30%,[11] 50%,[12,13] and 21%.[14,15] The duration of exposure ranged from 4 to 6 h. In these studies, injury produced with anesthesia was significantly greater than that in control nonanesthetized animals. With the exception of the studies of Stratmann *et al.*,[12,13] the concentration of oxygen used was well below the level that has been shown to produce injury to the developing brain. Furthermore, the duration of exposure is well below the 12-h exposure to 40% oxygen in the study of Felderhoff-Mueser *et al.*[10] in which injury was not observed. The available data indicate, therefore, that in experimental models, the toxicity produced by anesthetic exposure is not due to oxygen administration but due to anesthetics.

There is a remote possibility that there might be a *relative* increase in brain tissue partial pressure of oxygen (PO_2) during anesthesia, even with the administration of air. Anesthetics decrease the cerebral metabolic rate for oxygen substantially and, depending on the inspired concentration of inhaled agents, cerebral blood flow may increase. Whether this relative increase in tissue PO_2 is detrimental in the developing brain is not clear. However, it is not outside of the realm of possibility that relative tissue hyperoxia might reduce the antioxidant defenses of neurons[16] and thereby make them more vulnerable to anesthetic neurotoxicity. This question will have to be addressed experimentally. We therefore invite Dr. Kopp to join us in our efforts to more definitely characterize anesthetic (and oxygen) toxicity in the developing brain and to develop the means and practices by which this toxicity can be prevented. This would, to paraphrase Kopp, allow us to bring more balance to the discussion.

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In Reply:—We are gratified by the interest generated by the publication of our recent article.[1] The accompanying letters raise important issues and questions relevant to our article and to the question of anesthetic neurotoxicity as it applies to children. The concerns expressed by the various authors can be categorized as follows: (1) The observed effect may reflect comorbidity or other unidentified factors rather than the effects of anesthesia *per se* (Arul and Thies, Pysyk *et al.*, Taylor); (2) the definitions for learning disability (LD) were inappropriate (Pysyk *et al.*, Tolpin and Collard); (3) hypoxia or hyperoxia may be responsible for the observed effects (Coté, Mitchell, Kopp); and (4) the underlying relevant animal data are flawed (Taylor). As to number 4, we did not participate in the many animal studies, and given that the animal data have been recently reviewed by Loepke and others,[2–7] we will simply refer the reader to those studies, reviews, and editorials.

Clearly, we share the concern expressed by several of the authors for the need to control or adjust for comorbidity. However, we also recognize the difficulty of doing so in retrospective studies (or even in prospective studies) involving children. Arul and Thies suggest that comorbidity is the "elephant in the room." We completely agree and extensively discussed this clear limitation of our data in our article. A cautionary sentence appears in the abstract, and this limitation is discussed at length in the body of the article, most clearly as follows: "These data cannot reveal whether exposure to anesthesia itself may contribute to the pathogenesis of LD, or whether the need for anesthesia is a marker for other unidentified confounding factors that contribute to LD." We also chose not to include the positive findings in the article's title.

We appreciate similar concerns expressed by Pysyk *et al.* regarding the difficulty of determining whether the effect observed in our study was the result of the surgical indication rather than the exposure to anesthesia *per se*. In our cohort, as would be true in any community-based sample, otolaryngologic procedures are the majority of the total, and children requiring myringotomy or tonsillectomy may indeed be predisposed to the adverse effects of sleep disturbance and/or hearing deficiency on learning. However, if surgical treatment of these conditions is efficacious and results in catch-up growth and development in those undergoing surgery, and if not all children receive surgical treatment, those *not* undergoing the procedure may be at greatest risk for the neurocognitive and speech problems described by Pysyk *et al.*,[8,9] which would bias against the observed effect of multiple surgeries on learning abilities. Also, the relation between this (and many other) condition(s) and the development of learning disabilities is not always clear. Arul and Thies cite a 1983 article that suggests that minor conditions such as otitis media are known to be associated with educational delay. The cited review of the existing literature of that time concluded that, "children who have been medically managed [with otitis media] have minimal deficits." A subsequent article failed to demonstrate an increase in LD among children who were surgically managed for recurrent otitis media.[10] A recent Cochrane review suggests that it is uncertain that otitis media represents a risk for language or speech delay, and as a consequence, surgical treatment is of unclear benefit. Other studies have demonstrated that among children with language delay of unclear etiology, the only factors of significance were those controlled for in our analysis, *e.g.*, hearing abnormalities were not found to be predictive.[11]

Ideally, extensive information regarding comorbid conditions would be available in a sample of children large enough to allow the subanalysis suggested by Pysyk *et al.* Realistically, however, controlling for comorbidity is much more difficult than may be appreciated. Unfortunately, no uniformly recognized measure of burden of illness exists for children, requiring that we rely on measures such as the American Society of Anesthesiologists (ASA) physical status (PS) score. Arul and Thies point out that many of those children with multiple exposures had comorbid conditions that may predispose them to LD. LD was not, however, clustered among those with the greatest burden of illness as measured by the ASA PS. In fact, among the 144 children with multiple exposures, only 11% (2 of 19) with an ASA PS of greater than 2 had LD, whereas among those with an ASA PS of 2 or less, 34% (43 of 125) had LD. Therefore, it is by no means clear that the burden of comorbidity, as reflected by ASA PS, is associated with an increased risk of LD. Like Taylor, we also recognize the problems associated with the use of the ASA PS in this setting but also appreciate that no alternative measure is available. Similarly, we could not, as she suggests, control for comorbidity in the exposed group and not do so in the comparison group. To do so would have required that we individually abstract the complete medical records of more than 5,000 children. In an ongoing analysis using the same cohort, we, in partnership with the U.S. Food and Drug Administration, are in the process of examining, in a case–control design, the comorbid conditions of both cases and controls in an attempt to better control for both medical and surgical diagnosis. We hope that this will provide more insight into the concerns expressed.

The definitions used to determine LD in the birth cohort were those used for the original incidence (not prevalence) studies performed using the Rochester Epidemiology Project. Those studies used four methods to determine the incidence of various types of LD. For the study by Wilder *et al.*, one method (Shayvitz) was eliminated because it was deemed to be redundant. The rates quoted by Tolpin and Collard from our group's previous publications are for the incidence of the individual types of LD (math, reading, *etc.*). The higher rate that we reported was because our outcome was the development of one or more types of LD. As described in the article, we chose this as an outcome because (1) we had no data to suggest that one type of LD (math, reading, *etc.*) is more likely in this setting and (2) to examine a single type of LD would have dramatically reduced the statistical power of the study. For the same reason, we were not able to perform subanalyses to determine whether the observed effect was concentrated in one or more types of LD, but agree that this would be a fruitful topic for future investigations of sufficient power to conduct this analysis. In addition, LD as determined by the National Health Interview Survey and the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*, are measures of prevalence rather than incidence and therefore cannot be directly compared with the incidence rates found in the Rochester Schools. Furthermore, the definition of prevalence found in the National Health Interview Survey is based on questionnaire responses to "Ever told sample child had a learning disability" rather than specific testing as was used in our cohort. The observation by Pysyk *et al.* regarding our use of a cutoff of 1.75 SDs rather than the conventional 2 SDs is correct. This was chosen because it was the criterion in use by the state of Minnesota at that time.

Mitchell and Coté raise an issue that we did not discuss, positing unrecognized hypoxia as an explanation for the increase in LD observed in our cohort. The studies by Coté do not address the issue of cognitive impairment but do suggest that unrecognized hypoxia frequently occurred before the widespread adoption of pulse oximetry. Likewise, the presence of brief modest hypocapnia (a finding that occurred in only 9 of 260 total events and may have been as brief as 60 s in his study) is suggested as a potential confounder.[12] To our knowledge, brief hypocapnia has not been linked to subsequent deficits in learning, although among preterm neonates sustained profound hypocapnia has been suggested as a cause of periventricular leukomalacia, a pathology that is highly unlikely to have contributed to our findings. Interestingly, studies of hyperoxia in neonates have examined the effect of the prolonged oxygen saturations as low as 70% on the incidence and severity of retinopathy of prematurity. Those studies have failed to show an adverse neurocognitive effect in follow up as long as 18 months,[13,14] suggesting that even prolonged periods of hypoxia may be relatively well tolerated in children. Conversely, Kopp suggests that hyperoxia could lead to LD, observing that virtually all children in our cohort received a 30:70 mixture of oxygen and nitrous oxide. The degree of hyperoxia that could result from this mixture is modest. Furthermore, we are not aware of studies that link LD to oxygen exposure in young children, nor were studies cited that associate hyperoxia with abnormalities in memory, cognition, and learning in animals. The studies previously mentioned examining hyperoxia and its relation to retinopathy of prematurity do not show an increase in cerebral palsy or cognitive dysfunction. Therefore, although oxygenation state and hypocapnia are factors that could conceivably contribute to LD after anesthesia, experimental support for this possibility is not robust, although future animal studies could evaluate this possibility.

We appreciate the opportunity to respond to the thoughtful concerns and criticism contained in the accompanying letters. Each of the authors has provided additional food for thought as this issue moves forward. What unifies all is the clear need for larger, more extensive prospective and retrospective studies that would allow for the control of comorbidity and variations in anesthetic management, the examination of effects according to surgical procedure, the determination of effect by LD type, and more comprehensive measures of academic achievement, cognitive/memory functions, and quality of life. This study represents an initial attempt at unraveling this complex and difficult issue. Other studies planned and currently under way will, no doubt, add to the slowly accumulating body of clinical data that we hope will help to resolve this important and difficult issue.

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Anesthesiology 2009; 111:1386

The Need for Perspective

To the Editor:—We were disappointed that ANESTHESIOLOGY chose to publish the articles by Kalkman *et al.*[1] and Wilder *et al.*[2] without an accompanying cautionary editorial. Kalkman *et al.*[1] state, “children undergoing urologic surgery at age less than 24 months showed more behavioral disturbances . . . although the results were not statistically significant.” We disagree with this statement; namely, because statistical significance was not achieved, more behavioral disturbances were *not* observed. Furthermore, they go on to perform a sample size calculation to determine the number of patients that would be required to detect a statistically significant effect of the effect size they found. Their estimate for such a potential association between anesthesia and behavioral problems could be explained by chance alone, and using such an estimate to guide future studies is misleading. Wilder *et al.*[2] were unable to separate out the effects of multiple anesthetics from the effects of the underlying clinical problems requiring multiple procedures. By publishing these two studies as part of a larger series including several animal models, ANESTHESIOLOGY seems to send the message that two independent teams reported similar findings in humans. At a minimum, a cautionary editorial putting these studies into context was warranted. Studies such as these, reported on by the lay media, may cause an already wary public much alarm and put pediatric anesthesiologists in an impossible position. Parental concerns regarding the possible deleterious effects of anesthesia will not be assuaged by statistical explanations. ANESTHESIOLOGY has an obligation beyond merely reporting interesting studies. We are sure that, like us, other readers are looking for perspective.

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In Reply:—We thank Dr. Raghunathan *et al.* for their letter regarding their disappointment that we did not publish a cautionary editorial regarding the reports by Wilder *et al.*[1] and Kalkman *et al.*[2] in the April issue of ANESTHESIOLOGY. These clinical articles, which were published with laboratory work presented at the ANESTHESIOLOGY/Foundation for Anesthesia Education and Research session at the 2008 Annual Meeting of the American Society of Anesthesiologists, were accompanied by an editorial by Drs. Patel and Sun,[3] thought leaders in research regarding the mechanisms and clinical relevance of neurodevelopment after exposure to anesthetics. Regarding the clinical article, they concluded in their editorial, “Although two retrospective studies herein suggest that a correlation between anesthetic exposure early in life is associated with learning and behavioral abnormalities later in life, the data cannot be considered to be evidence of the existence of anesthetic neurotoxicity in humans. The absence of rigorously conducted prospective randomized trials precludes recommendations on clinical