

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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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

practice.”³ In our opinion, this statement expresses appropriate and adequate express caution regarding the application of these data to clinical practice.

We would also like to comment regarding the statistical analysis and presentation in the article by Kalkman *et al.*,² as questioned by Dr. Raghunathan *et al.* Their study focused on effect sizes and not on statistical significance judgments. This was a prudent choice because of the pilot nature and goals of the effort. This clear focus on effect sizes is made abundantly clear by the fact that in the article by Kalkman *et al.*² there is not a single *P* value reported. Instead, Kalkman *et al.*² referenced the size of the observed effects throughout. For a properly powered study, making a claim about an effect that is not statistically significant is, indeed, anathema. However, in this clearly defined pilot study, reminding a reader that an observed effect size did not reach statistical significance is actually a responsible practice. The uncovered effect sizes in a pilot study are estimates of their population values, but as Kalkman *et al.*² overtly stated, these estimates are in the context of very wide confidence intervals.

We strongly believe that there is a place for small *n* research in ANESTHESIOLOGY. Small *n* research is tricky to report. We have a sophisticated community of researchers (mostly bench scientists) who successfully add to our knowledge base while using studies that are not optimally powered. Again, this reinforces the importance of clear effect size reporting (as in the two mentioned studies), *a priori* power analyses to overtly report assumptions, and exact *P* value reporting to arm a reader with enough information to properly interpret experimental effects.

Regarding their statement on *post hoc* power analyses, Raghunathan *et al.* are to be concerned about power calculations that are based on observed *P* values. We agree with this sentiment, articulately voiced by Hoenig and Heisey,⁴ and for that reason actively discourage such

power calculations. The provided power calculation, though, was clearly presented as the primary aim of the study, and posits that the observed risks are the population values, and to reject a null hypothesis of no added risk (under a traditional set of inference assumptions), a future prospective study would need to study 2,268 children (thus making it similar to power analyses conducted throughout the research world; this one is simply in print). There is a difference between stating “These differences would be statistically significant with *n* patients” *versus* “If these differences are population values, we need *n* patients to reject a null hypothesis in our next study.” In that regard, Kalkman *et al.*² have succeeded in providing a context for interpreting their study.

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“Innocent Prattle” and the Quality of Scientific Discourse

To the Editor:—We read with interest the editorial titled “Innocent Prattle” by Dr. Lagasse¹ that accompanied our article on anesthesia mortality.² As we described, the recent 10th revision of the *International Classification of Diseases* (ICD-10) codes now includes extensive data on anesthesia complications. Its adoption by the United States to classify death certificate data offers both the opportunity and the obligation for researchers to engage in thoughtful analyses of these data. Our study was the first to accept that challenge. As stated in our article,² our objectives were “to develop a comprehensive set of anesthesia safety indicators based on the latest version of the ICD and to apply these indicators to a national data system for understanding the epidemiology of anesthesia-related mortality.” By any measure, we have achieved these objectives despite Dr. Lagasse’s critique. It is well recognized and extensively discussed in our article that administrative data, such as those from ICD-coded, multiple-cause-of-death files, may underestimate the true incidence of adverse outcomes of medical care. It has been estimated, for example, that adverse drug effects reported to the US Food and Drug Administration account for substantially less (< 20%) than the true incidence.³ However, such data can and have been crucial in detecting trends, identifying safety problems, and defining strategies to improve drug safety. In addition, thoughtful analyses will allow further granularity to be either detected from the current data or built into future ICD editions. Dr. Lagasse seems to disagree with our view that the opportunity should not be lost to

analyze the ICD-10-coded mortality data as presented in our article and seems to view such analyses as “innocent prattle.”

Although vigorous argument, discussion, and even disagreement are essential and useful parts of the scientific process, derogatory comments about colleagues’ work are not. It would be a pity if learned publications fall into the trap of adopting the headline style of some popular tabloid newspapers. A deeper reading of the message of Hans Christian Andersen might be that substance and reality (read: scientific data) trump posturing and belief regardless of one’s perceived status. We will look forward to the application and validation by the scientific community of the techniques described in our article to monitor anesthesia safety and improve patient outcomes in the future.

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