GAS, PANDA, and MASK: Comment

To the Editor:

In their recent Editorial, Drs. Vutskits and Culley discuss the General Anesthesia or Awake-regional Anesthesia in Infancy (GAS), Pediatric Anesthesia Neurodevelopment Assessment (PANDA), and Mayo Anesthesia Safety in Kids (MASK) studies.[1] These studies are similar in that they all prospectively tested children exposed to a single anesthetic at a young age using comprehensive batteries of neurodevelopmental assessments. While this Editorial interprets these studies as showing "No Evidence of Clinical Anesthetic Neurotoxicity!" with an emphatic exclamation point, we respectfully disagree for two reasons.

First, the Editorial suggests that the GAS study found no difference in "primary and secondary outcomes" and that the PANDA and MASK studies provide strong evidence of a lack of "detectable alterations in neurodevelopmental outcome."[2–4] This is largely true for the primary outcomes and most secondary outcomes. However, this was not true for parent reports of behavior/emotions and executive function (*i.e.,* guiding, directing, and managing cognitive abilities, as well as behavioral and emotional functioning). *All three studies reported significantly more problems* in at least one of these reports.[5] Although parent reports have definite limitations, they are an essential component of clinical neuropsychologic evaluations because children may exhibit different behavior in the laboratory environment *versus* other settings such as home or school. Interpreting these scores can be confusing because in contrast to other neuropsychologic tests, *higher* scores typically signify more problems. Four scores based on parent reports were reported in all studies: the Behavior Rating Inventory of Executive Function Global Executive Composite and the Child Behavior Checklist Internalizing Problems, Externalizing Problems, and Total Problems scores. Both the GAS and the MASK studies found significantly more problems with Executive Function as measured by the Behavior Rating Inventory of Executive Function. The PANDA study found that a higher proportion of children exposed to a single anesthetic for inguinal herniorraphy had clinically abnormal scores on the Child Behavior Checklist Internalizing Problems (*e.g.,* depression or anxiety) scale compared with their unexposed siblings. The MASK study found that a higher proportion of children exposed to a single anesthetic had clinically abnormal scores on the Child Behavior Checklist Externalizing Problems (*e.g.,* aggression or rule breaking behavior) scale compared with unexposed children. Furthermore, the observed effects (point estimates) were similar among all three studies, particularly for the Child Behavior Checklist outcomes. The clinical significance of these small differences in the absence of changes in other outcomes can be argued, but it is unjustified to conclude that there is "no evidence [!]" of an association between single exposures to anesthesia and any neurodevelopmental outcome.

Second, one criterion proposed for determining the biologic effect of exposure to a potential toxin is biologic gradient (*i.e.,* a dose–response relationship). The MASK study also examined children who received multiple exposures to anesthesia before age 3. Such exposures were associated with an approximate doubling of the risk of developing attention-deficit hyperactivity disorder or learning disabilities (reproducing an earlier study). Multiple exposures were also associated with modest deficits in fine motor skills and rapid automatic naming, a proxy for processing speed later in life in some children, without deficits in other neuropsychologic domains such as general intelligence and memory. Thus, the MASK study provides compelling evidence for a dose–response relationship between exposures to anesthesia and specific neurodevelopmental outcomes. Exposure to multiple anesthetics before age 3 is not uncommon. In the population-based cohort of children used to construct the MASK study cohort, 15% of children required general anesthesia before age 3. Of these, approximately 25% received multiple anesthetics before age 3. If extrapolated to the U.S. population, this would represent approximately 160,000 children each year. The associations noted in the MASK and other studies do not prove that anesthetics are causative agents—the potential for confounding by indication and other factors has been exhaustively discussed and is very real. Yet the finding of a specific pattern of differences may argue against this, as it is not clear what common underlying condition would produce such a specific pattern. If neurotoxicity occurs with multiple exposures, either it also occurs with single exposures (even if largely subclinical), or the first exposure primes the brain for later injury.

It may be useful to recognize that there are perhaps two separate questions here: one clinical and one scientific. The clinical question is "Should concerns about potential neurotoxic effects of anesthetic drugs prompt immediate changes in clinical practice?" In the case of single exposures, we and most others would agree that the answer to the latter is "no" based on the current evidence, with the caveat that for one in four children, a single exposure presages multiple exposures. Such multiple exposures could (if anesthesia proves causative for the observed associations) have more significant effects in some children. The scientific question is "Do anesthetic

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drugs produce long-term changes in the brains of children?" It is important to answer this question regardless of whether these changes produce clinically-relevant effects in most children. A confident exclamatory assertion of "no evidence [!]" may make us feel better as clinicians, but may not serve the pursuit of further knowledge in this important area.

Competing Interests

The authors declare no competing interests.

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GAS, PANDA, and MASK: Comment

To the Editor:

We read with great interest the recent editorial concerning anesthetic neurotoxicity by Drs. Vutskits and Culley.[1] We agree with their interpretation that it appears a short exposure to general anesthesia is unlikely to cause clinically significant neurocognitive deficits in our youngest patients. However, for our group, choosing a form of awake regional anesthesia for appropriate surgeries has never been about the theoretical risk of neurotoxicity. Rather, it involves a conscious choice to work as a joint surgical and anesthetic team to provide a technique that has a proven lower risk of hypotension, apnea, bradycardia and laryngospasm while producing lower pain scores in the postanesthesia care unit and shorter anesthesia control times.[2]

Although we are in alignment with most of the authors' main points, we must take exception to the overall picture of awake regional anesthesia in infants that the authors have portrayed. An awake infant with "no sedation, no mom or dad and instead a pediatric anesthesiologist providing sucrose on a pacifier to calm you" is not representative of our joint experience with 3,000 infants undergoing spinal anesthesia. Within 10 min of induction, most infants enter a state of sedation resembling phenotypically normal sleep. If necessary, we calm infants with stroking, soothing, and offer concentrated sucrose solution on a pacifier. If needed, we will administer small doses of intravenous sedation; however, this is required in less than 20% of cases, which is also representative of the experience of other investigators.[2] Awake regional anesthesia has numerous benefits and can be administered in a humane, patient-centered fashion while providing excellent surgical operating conditions.

Competing Interests

The authors declare no competing interests.

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GAS, PANDA, and MASK: Reply

In Reply:

We would like to thank both Ing *et al.*[1] and Drs. Williams and Sartorelli[2] for their thoughtful comments on our recent Editorial, "GAS, PANDA, and MASK: No Evidence of Clinical Anesthetic Neurotoxicity!"[3] We address their concerns in turn below.

Developmental anesthesia neurotoxicity is probably one of the most debated and controversial issues of the past 2 decades in pediatric perioperative care. The comments of Ing *et al.*[1] are a perfect demonstration of how interpretation of any data on this topic can vary even among those individuals who have been working on this field for a long time. The most plausible explanation for this strong divergence in opinions regarding the clinical implication of the already existing data stems from the important and probably unsolvable limitation of both experimental and clinical studies in this domain. In the following lines, we address the three lines of thoughts raised by Ing *et al.*

Our first comments go to the interpretation of secondary outcomes. We agree that a few among the multitude of secondary outcomes may suggest a statistical association between anesthesia exposure and neurodevelopmental outcome but associations do not imply a causal relationship. One must recognize that occasional results in subgroup analysis and secondary outcomes are difficult to interpret since these studies were neither specifically designed nor sufficiently powered to obtain reliable conclusions to these questions. While they may serve as food for thought, they definitely do not provide evidence of clinical anesthetic neurotoxicity.

Our second comment goes to the dose-response relationship of anesthesia exposure. We agree that there is a biologic rationale backed by animal experimental evidence in this regard. Human data are, however, controversial. While the Mayo Anesthesia Safety in Kids (MASK) study[4] raises the possibility that multiple anesthetic exposures and surgical episodes may lead to worse neurodevelopmental outcomes, other studies do not fully support this notion.[5,6] The large number of illnesses and confounders associated with pediatric populations necessitating repeated anesthesia and surgery at early life may explain these differences in the so-called biologic gradient.

Last but not least, Ing *et al.* argue to separate the clinical and the scientific questions. We respectfully disagree with this proposition since we believe that (substantial) changes in clinical practice should be driven by the results of appropriately planned clinical studies. At present, no such study convincingly supports the possibility of clinically relevant developmental anesthesia neurotoxicity. In fact, most studies, with the possible exception of the General Anesthesia Spinal (GAS) trial,[7] are not even designed to directly answer this question. Rather, and this is a fundamental difference from experimental studies, they tackle the impact of the perioperative period as a whole, on neurobehavioral outcome. Based on current clinical data, how can we truly expect to draw specific conclusion on drug-related effects in a highly complex environment when as yet unexplained interactions among perioperative stress and numerous surgical and anesthetic factors can result in a plethora of unanticipated effects?

We fully agree with Ing *et al.,* and we also pointed this out in our Editorial, that many unanswered questions remain. We also agree that many of these questions are intellectually stimulating. However, from a public health perspective, the elephant in the room remains the questionable feasibility of a study that would provide us with clinically relevant information on anesthetics neurotoxicity. Unfortunately, no clinical trial can ever be conducted that will conclusively prove that anesthetic neurotoxicity does not exist, because one cannot prove a negative. As said before by Dr. Ted Eger, one cannot disprove the existence of dragons.[8] The hypothetical relevance of such investigations should also be considered in the light of epidemiologic data showing that the hypothetical impact of exposure to "perioperative period(s)" on subsequent neurodevelopment appears to be much less important than parental socioeconomic status, sex, or even the period of the year when a child is born.

Therefore, the real question we should ask at the current state of our knowledge is whether we can still convincingly justify the need and research cost for expensive clinical studies aimed to find anesthetics neurotoxicity. Or are there more important and clinically relevant questions of pediatric perioperative care aimed to promote brain health? We are convinced about the latter.

We agree with Drs. Williams and Sartorelli that awake spinal anesthesia can be considered an attractive option for appropriate surgeries in small infants. In fact, the point we

wished to make in our Editorial is that the hypothetical risks of anesthetic neurotoxicity should not dictate our choice of regional *versus* general anesthesia. There is no evidence of the superiority of one approach over the other in terms of clinically relevant outcome. Therefore, the skills and expertise of the anesthesiologists and surgeons should be the main factors behind this strategic decision. In academic centers where teaching is a priority, the duration of even straightforward surgical procedures may often exceed the duration of a single spinal block. Given the importance of adequate analgesia during the entire procedure, general anesthesia, often in combination with a regional blockade, may have obvious advantages in these situations. As Drs. Williams and Sartorelli also point out, up to 20% of children with spinal anesthesia may need additional sedation even in experienced hands. While this situation can be easily handled by experienced pediatric anesthesiologists, failure of spinal anesthesia and the subsequent change in management plan may be more dangerous in less experienced hands. Again, it is the anesthesiologist and not the anesthetic that makes the difference.

Competing Interests

Dr. Vutskits is an Editor of Anesthesiology. He served as consultant for Primex (Zug, Switzerland) and Regeneron (Tarrytown, New York). Dr. Culley is an Executive Editor of Anesthesiology. She serves as a Director and Secretary for the American Board of Anesthesiology, Chair of the Academic Anesthesiology Committee for the American Society of Anesthesiology, *ex officio* Member of the Anesthesiology Review Committee for the Accreditation Council for Graduate Medical Education and as a member of the 3C Committee for American Board of Medical Specialities.

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Bacchus Listed for a Liver Transplant: Comment

To the Editor:

The American Society of Anesthesiologists' (Schaumberg, Illinois) Committee on Transplant Anesthesia is a voice for liver transplant anesthesiologists and is actively engaged in educational efforts related to both clinical and ethical approaches to donation after circulatory death. It was thus with surprise and some distress that we read a recent piece