

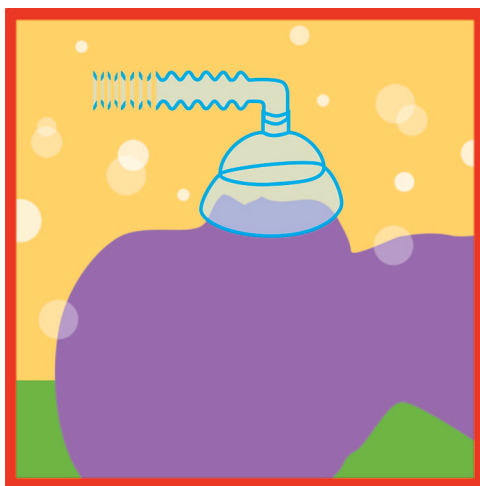
# Neurotoxicity and the Need for Anesthesia in the Newborn

## *Does the Emperor Have No Clothes?*

**I**N 2011 nearly half the pediatric papers in ANESTHESIOLOGY were related to neurotoxicity of general anesthetics to the developing brain. There is continued debate about the clinical relevance of the animal data, and the interpretation of human cohort studies. In this issue Shih *et al.* present a paper that moves us a significant step closer to translating the animal data to clinical situations.<sup>1</sup> But, as we slowly unravel the question of whether or not general anesthetics cause any clinically significant effect on brain development, we should perhaps address some wider-related issues that sometimes go unsaid.

Shih *et al.* provides further evidence that several hours of anesthesia exposure is associated with neuronal injury and subsequent neurobehavioural change in a rodent. At a mechanistic level it is difficult to argue that apoptosis would be triggered by sevoflurane in rodents but not in humans. The big question has always been how to translate this to human practice. Is it relevant clinically? This study helps address two important issues in translation: the effect of tissue injury, and the relative effect of anesthesia on neurobehavioural outcome when compared with other events that might influence outcome.

The study found that tissue injury neither worsens nor mitigates the effect. Rats with tail-clamp injury had the same histologic change and the same neurobehavioral changes compared with rats with no injury. This is interesting as previous animal studies have often been criticized as being invalid because they have no surgical stimulus. It had been argued that surgery provides an intense stimulus that would override any “use it or lose it” mechanism where apoptosis is due to neuronal traffic quiescence. In this respect findings



***“... regardless of whether or not sevoflurane causes any clinically relevant toxicity, is it time to question the mantra that all babies need a hypnotic agent such as sevoflurane?”***

from this study imply that previous studies are indeed a valid model whether there is a surgical stimulus or not. It has also been argued that the increased risk of poor outcome found in some human cohort studies is because of the inflammation and stress associated with the surgery rather than the anesthetic. Shih *et al.*'s study provides some indication that the surgery itself may not be a contributor to poor outcome; however, the degree of surgical stimulus in clinical practice varies considerably, and it is still possible that the stress of a major laparotomy or cardiac surgery has a greater chance of measurable impact on neurodevelopment than a tail clamp.

Another aspect of Shih *et al.*'s study looked at whether or not the injured rats could be “treated” with environmental enrichment. They found that environmental enrichment did indeed reverse the effect of anesthetic, resulting in performance similar to environmentally enriched controls and superior to unenriched control and anesthesia-exposed animals. This is important for translation, perhaps not as a viable treatment modality (it is difficult to see how we could practically further enrich the environment for the average infant in the 21st century), but the finding is very important as it highlights that neurobehavioural outcome is dependent on multiple factors. A common criticism when translating animal to human data is that there are a multitude of influences on outcome in humans and that an anesthesia exposure may only be one minor insult compared with many other more significant events in childhood. Shih *et al.*'s findings might provide some hint that the

*Illustration: J. P. Rathmell, A. B. Johnson.*

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◆ This Editorial View accompanies the following article Shih J, May LdV, Gonzalez HE, Lee EW, Alvi RS, Sall JW, Rau V, Bickler PE, Lalchandani GR, Yusupova M, Woodward E, Kang H, Wilk AJ, Carlston CM, Mendoza MV, Guggenheim JN, Schaefer M, Rowe AM, Stratmann G: Delayed environmental enrichment reverses sevoflurane-induced memory impairment in rats. ANESTHESIOLOGY 2012; 116:586–602.

toxic effects of anesthesia are indeed relatively mild compared with other environmental influences. This leaves the clinician somewhat less concerned that the anesthesia has a significant effect. However, there are some limitations. First, one could be reassured that the effect of the injury is probably minor, but some might think any preventable injury should be avoided, even a minor one. Second, the issue of translation for the “treatment” is as pertinent as the issue of translation of the injury. How do we translate to humans the comparison of a rat that lives in a dull environment to a rat that lives in an enriched environment? Is it not surprising that such a huge change in environment dwarfs any effect of anesthesia? In humans, is this equivalent to a child living for years in a stimulus-free orphanage compared with a child in a stimulating family? Hence, is this really a valid reassurance that the injury is not significant?

The paper by Shih *et al.* is an important contribution, but there are perhaps wider-related issues that quietly emerge when discussing neurotoxicity of anesthesia in neonates. First, we must remember that some cohort studies do find that neonates having major surgery are at greater risk of poor neurobehavioral outcome. The anesthetic may, or may not, be the causative factor, but if anesthetic toxicity is ruled out this is not “mission accomplished.” We have not ruled out other factors in the perioperative period that might contribute to poor outcome and be under the control of the anesthesiologist, such as hemodynamic or respiratory changes or the humoral or inflammatory response to surgery. Shih *et al.*'s study is one of the few to explore the effect of surgery *per se*. They found no evidence of causation, but further studies with greater injury should be done.

The other question is, “Well, do neonates need a general anesthetic anyway?” Such a question is met with cries of heresy and cruelty, but there are subtle aspects of this that need at least some thought. A couple of decades ago neonates were often given nitrous oxide, morphine, and muscle relaxants for anesthesia. In the 1980s several studies demonstrated that this was inadequate. In 1987 Anand *et al.* compared nitrous oxide with nitrous oxide and fentanyl in neonates having a ductal ligation.<sup>2</sup> The fentanyl group had fewer cerebral hemorrhages, shorter ventilation, and less cardiovascular instability. Anand *et al.* also compared nitrous oxide with nitrous oxide and halothane and found neonates in the halothane group required less respiratory support and had less cardiovascular instability.<sup>3</sup> Lastly, the same author compared high-dose sufentanil with low-dose morphine and halothane in neonates having cardiac surgery and found that the sufentanil group had lower mortality.<sup>4</sup> Since then further studies have convincingly demonstrated that neonates have better outcomes with adequate analgesia for painful procedures. From these studies it was rightly concluded that neonates need adequate anesthesia for surgery. But the question of what is an adequate anesthetic for a neonate is still not entirely answered. Anand *et al.* found they need more than just nitrous oxide, and they certainly need good analgesia,

but if there is adequate analgesia, do they need a hypnotic agent? In 2001 Gruber *et al.* reported that adding midazolam to high-dose fentanyl made no difference to outcome in infants having cardiac surgery.<sup>5</sup>

The classic components of anesthesia are lack of movement, loss of consciousness, amnesia, and analgesia. Is this model really relevant to neonates? Neonates have no explicit memory so the amnesia is irrelevant. Certainly they need to be immobile and they need analgesia, but do they need to be unconscious? All agree that leaving a neonate awake and distressed is inhumane, but it is difficult to define and measure consciousness in a neonate, and hence we have no idea of how much hypnotic agent produces unconsciousness. Alternatively, provided the baby shows no signs of distress, does it really matter if some sensory information filters through to their consciousness? Thus the aim of anesthesia in neonates is more to prevent signs of distress. Do you need a hypnotic agent such as volatile anesthesia or propofol to do this, or can it be adequately achieved with opioids or other sedatives? In our institution we often anesthetize babies in the neonatal unit with just large doses of opioid and no volatile or intravenous general anesthetic agents. Others do the same.

Thus, if hypnotics, such as propofol or volatile anesthetics, do cause an injury that is clinically relevant, then it is indeed possible to construct an argument that we could do without them in neonates. Of course this would only be so if the alternative opioids and sedative agents were not neurotoxic, and if the alternative anesthetic techniques didn't introduce other risks. If, on the other hand, general anesthetics were found not to be clinically neurotoxic, then we still have the problem that infants having major surgery have an increased risk of poor outcome. The question remains as to what type of anesthetic could reduce this risk. Which is better at providing hemodynamic stability or reducing nociception, and the humoral and inflammatory responses? Giving an anesthetic to address these issues may be more important than aiming to guarantee unconsciousness. Again, the role of volatile and other hypnotic agents may be marginal.

“The Emperor's New Clothes” by Hans Christian Andersen is a story about two mischievous weavers who promise an emperor a new set of clothes that is invisible to those who are unfit for their positions.<sup>6</sup> Neither the emperor nor his advisers or subjects see the clothes, but they are afraid to say the emperor is naked because this would imply they are unfit for their positions. Eventually a child points out that the emperor has no clothes on. Shih *et al.*'s study provides some evidence that sevoflurane causes apoptosis but some reassurance that any injury may be relatively minor compared with other influences. This study helps translate the animal data to humans, but regardless of whether or not sevoflurane causes any clinically relevant toxicity, is it time to question the mantra that all babies need a hypnotic agent such as sevoflurane? All agree that neonates need effective analgesia, but it is still unpopular to suggest that neonates do not always need a hypnotic agent. Perhaps the emperor indeed has no clothes

and the adult-derived paradigm of the general anesthesia triad is not completely relevant to neonates. Whatever the outcome of the neurotoxicity studies, we should not be afraid to rethink what anesthetic technique provides the best outcome in neonates.

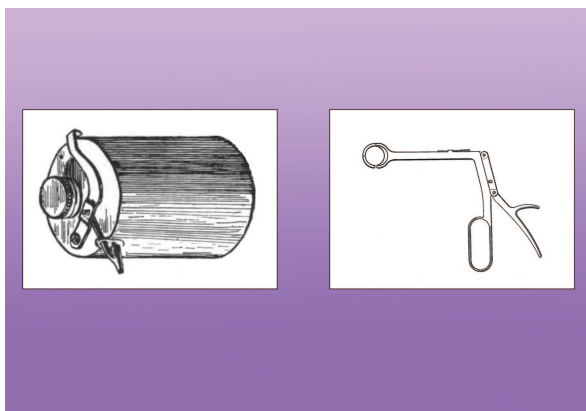
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## ANESTHESIOLOGY REFLECTIONS

### The Rohrig Dropper Device for Ether or Chloroform



Practicing later as an eye-ear-nose-throat, or EENT, surgeon, John George Rohrig (1883–1933) received his medical doctorate from the University of Iowa in 1909. That same year, he reported his design for a dropper can (*left*) for ether or chloroform. The large-diameter screw cap allowed rapid reloading of the can with liquid anesthetic. A conical valve permitted finger-control of continuous drop by drop administration of ether or chloroform from the vented can. Dr. Rohrig touted his dropper can as safer than the traditional “flooding” of a gauze-covered wireframe mask surface—a practice he criticized as alternately exposing the patient to “pure ether vapor” or “pure air.” Better known for the Rohrig tonsil enucleator (*right*) that he patented a decade later, EENT surgeon Rohrig would pass away at the tender age of 50 years, just four days after emergency surgery for his perforated gastric ulcer. History did not record whether or not Dr. Rohrig was anesthetized with his namesake ether dropper. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at [www.anesthesiology.org](http://www.anesthesiology.org).)

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