The possibility that general anesthetics might be neurotoxic in the developing brain has created huge concern and anxiety, and left anesthesia providers and parents with doubts as to whether it is safe and well-tolerated to use anesthesia in young children. While the animal data on the topic is indeed overwhelming and disturbing, human data are scarce and so far it has been difficult to demonstrate a human corollary to this phenomenon (1).

Given the paucity of human studies on neurotoxicity and the developing brain, it is maybe not so surprising that a multitude of review articles on this matter continues to get published each year in most anesthesiology journals worldwide. In this issue of *Acta Anaesthesiologica Belgica*, van Biesen and co-authors add yet another one to these (2). This gap between the number of review articles and the number of human studies on this subject also mirrors the gap between personal opinions and actual scientific facts.

van Biesen et al. describe some of the underlying and very disturbing animal data that have prompted and alerted the medical world about this issue. Additionally, they also include a paragraph about the potential underlying mechanisms leading to anesthetic-related injury, and - as many other authors before them - they mention GABA<sub>δ</sub> receptor stimulation and inhibition of NMDA receptors to be key in causing neuroapoptosis. However, the fact of the matter is that we actually don’t know the exact underlying mechanisms (1, 3). General anesthetics exert their mechanism of action through a variety of receptors and non-receptors. Recent data indicate that they might even exert direct effects on mitochondria which, in turn, could account for cell death and impaired synaptogenesis (4). Related to this issue, it is also very important to emphasize that there is currently no scientific evidence showing a causal link between neuroapoptosis and cognitive deficits following anesthesia exposure, and recent observations are even bringing new argument against this possibility. Additionally, anesthetics also cause neurodegeneration by non-neuroapoptotic means, as correctly emphasized by van Biesen et al.

van Biesen et al. also describe potential protective strategies that have been addressed in animal (rodent) studies, e.g. particularly α<sub>2</sub>-agonists (clonidine and dexmedetomidine) and xenon, but also e.g. melatonin, β-estradiol, lithium, L-carnitine, erythropoietin. They wisely refrain themselves from concluding anything from these studies so far. The protective properties of many of these agents in ameliorating or attenuating anesthesia-induced neurotoxicity are far from clear and unambiguous. Indeed, while, both α<sub>2</sub> agonist and Xenon have been proposed to offer protection, neurotoxic effects have also been reported with these agents (5-7).

To further increase the complexity of the issue, we should also emphasize that the majority of animal data on anesthesia neurotoxicity was obtained in the absence of surgery. This is a very important caveat to consider since surgery and the related inflammatory response can have a major role in regulating the context-dependent impact of anesthesia on brain development. In fact, a plausible possibility to be tested in the future is that general anesthetics might even play a protective role in the presence of surgery regarding neuronal network maturation.
HUMAN STUDIES

The authors also describe most of the relatively few human retrospective or follow-up cohort studies published so far and they address some of the (many) limitations inherent to these studies. In brief, some studies have suggested a link between exposure to anesthesia and surgery in early childhood and subsequently impaired neurobehavioral outcome whereas other similar studies have been unable to show any such association (1, 3, 4).

A major difficulty these studies are struggling with is that it is virtually impossible to separate the pharmacodynamic effects of general anesthetics per se from a multitude of other factors that might also cause neurological damage (see later).

Additionally most studies are single center studies focusing on relatively small sample sizes and multiple different surgeries and diagnosis. This is an important issue because specific surgeries and procedures independently impact neurocognitive function in later life (8). Van Biesen et al. correctly mention the confounding problem that e.g. a large proportion of children included in many of these cohort studies are ENT children known to suffer developmental delays and/or learning problems.

The problem with meaningful outcome measures and when and how to measure it is briefly discussed by Van Biesen et al. Should we search for developmental disorders in preschool, learning disabilities in elementary school, social disturbances in adolescence or psychiatric disorders in adulthood and what relevance has loss of various cognitive functions or early dementia in the elderly? How well does a single short-term interim measure performed in early childhood or adolescence adequately foresee outcome later in life? Assessment of academic performances has been criticized for lacking sufficient sensitivity to detect subtler neurocognitive impairment compared to individually administered cognitive tests (e.g. in language and speech). At this point, we do not know if individual cognitive testing is also meaningful human outcome measures. Many of these outcomes are interrelated. Further, studies employing comprehensive cognitive testing are laborious and expensive; therefore, the sample size in these studies will invariably be small. If this approach is used more widely in the future, a possible consequence is the accumulation of limited powered studies that might overestimate the effects we are looking for (type I error) or fail to detect a difference (type II error) based on limited sample size (9).

Although, the Bartels twin study (10) also suffers from limitations Van Biesen et al. do not acknowledge the inherent power of twin studies. Intra-pair analysis (with binomial distribution of parameters) inherently carries a tremendous statistical power. With a given specific a priori hypothesis only 6 twin pairs are required to reach a statistically significant result; e.g. if the exposed twin in all 6 twin pairs scored lowest the resulting p-value would be: \( p(n=6) = \left(\frac{1}{2}\right)^6 = 1/64 = 0.0156 < 0.05 \). Remember, in the Bartels study the intra-pair analysis comprised more than 70 twin pairs (10).

To date, no definite causal link between certain anesthetic drugs or techniques and poor neurological outcome in children has been established. Prospective studies are underway but will not be available for several years. However, they are also likely to be inconclusive. Many other perioperative factors impact neurocognitive outcome in young children exposed to surgery and anesthesia than merely anesthetic exposure, such as the stress of surgery, the reasons for surgery or impairment of physiological parameters because of inadequate anesthesia management (11).

In their conclusion Van Biesen et al. cite a recent NEJM commentary on this issue and state that elective surgery in children should be postponed until after the age of 3 years (12). The primary aim of this NEJM commentary was to encourage funding for future studies and it is of utmost importance to realize that no scientific evidence supports such statement. Accordingly, this conclusion has not been endorsed by any pediatric anesthetic societies. Any such recommendation carries the risk that our children do not receive appropriate and timely care and treatment. We concur with the BJA Salzburg statement: "...Given the fact that current clinical studies do not unequivocally demonstrate impairment of behavioral development, it is possible that more harm could be inflicted if necessary or timely treatment is withheld because of concerns regarding early life exposure to anesthesia......" (3).

References

5. Brosnan H., Bickler P. E., Xenon neurotoxicity in rat hippocampal slice cultures is similar to isoflurane and sevoflurane, Anesthesiology, 119, 335-44, 2013.