

12. Aasvang EK, Bay-Nielsen M, Kehlet H: Pain and functional impairment 6 years after inguinal herniorrhaphy. *Hernia* 2006; 10:316–21

(Accepted for publication July 27, 2010.)

In Reply:

We thank you for Dr. Mohammadhosseini's comments to our article on predictive risk factors for persistent postherniotomy pain.¹ We will emphasize that the main purpose of the study was to identify relevant preoperative risk factors together with detailed neurophysiological data from open versus laparoscopic groin hernia surgery. We used high ligation and cutting of the hernia sac in indirect hernia, which was the case in 60% of patients. We believe that the literature on the role of sack ligation is not conclusive and at least not quantitatively important for persistent pain. Regarding type of mesh, this was reported in our article, and we agree that the heavyweight mesh used in the Lichtenstein repair may—although the literature again is not conclusive—result in more postoperative discomfort and potentially persistent pain problems.² However, this again does not invalidate our study, where the methodology otherwise is well explained. The point on nerve identification is well taken—although again the literature is not finally conclusive. The ilioinguinal and iliohypogastric nerves were identified in about 95% of cases, but in only about 20% could the genitofemoral nerve be identified; 2.2% of nerves were cut on purpose to allow sufficient position in suturing of the mesh. We do not agree that the quoted study by Caliskan *et al.*³ is conclusive on prophylactic neurectomy compared with other studies in the literature, also because the study included only 54 patients, which in our opinion is insufficient to provide useful answers on persistent pain problems.

Since our large two-center study was planned, a better understanding of some surgical risk factors has become available, such as those raised by Dr. Mohammadhosseini. However, although such modifications of surgical technique may alter the risk of persistent pain, we believe that our well described study, including preoperative characterization as well as 6 months follow-up with neurophysiological assessment, provides unique information and better understanding of the mechanisms of persistent postherniotomy pain and the potential to reduce this burden.

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References

1. Aasvang EK, Gmaehle E, Hansen JB, Gmaehle B, Forman JL, Schwarz J, Bittner R, Kehlet H: Predictive risk factors for persistent postherniotomy pain. *ANESTHESIOLOGY* 2010; 112: 957–69
2. Kehlet H: Chronic pain after groin hernia repair. *Br J Surg* 2008; 95:135–6
3. Caliskan K, Nursal TZ, Caliskan E, Parlakgumus A, Yildirim

S, Noyan T: A method for the reduction of chronic pain after tension-free repair of inguinal hernia: Iliohypogastric neurectomy and subcutaneous transposition of the spermatic cord. *Hernia* 2010; 14:51–5

(Accepted for publication July 27, 2010.)

Neurotoxicity of Anesthetic Agents and the Developing Brain in Rodents and Primates: The Time Has Come to Focus on Human Beings

To the Editor:

In a recent experimental animal study, Bambrink *et al.*¹ have shown that 5 h of isoflurane anesthesia (0.7–1.5 vol%) in 6-day old primates (Rhesus macaque) caused a large increase in neuronal apoptosis in several brain regions 3 h later. This study adds to a plethora of studies published the last decade showing that exposure of infant animals—primarily rodents—to anesthetic agents, whether *N*-methyl-D-aspartate receptor antagonist or γ -aminobutyric acid receptor agonist, triggers widespread apoptotic death of neuronal cells in the developing brain. Background information about these studies can be found in a recent review article.² Indeed, these studies have been a subject of intense speculation and debate in the pediatric anesthetic community.³ Unfortunately, although human studies are being mounted, they are still scarce, and the results of animal studies and laboratory investigations cannot easily be translated into the human clinical environment because of, for example, pharmacokinetic and pharmacodynamic differences.³

However, at this point, there is solid animal evidence that anesthetic drugs induce acute apoptotic neurodegeneration in the developing animal brain. In our opinion, there is no need for any more animal studies of this kind. These will only add to the current confusion rather than contribute to a move forward. From now on, experimental animal research on this topic should be focused on the long-term morphological and, in particular, the neurocognitive consequences of these findings (if any), as well as a safer use of our anesthetic drugs, including possibly protective strategies. For instance, why did the authors not wait several months or even years before harvesting the brains of the monkeys used in the present study? Apoptosis can be elicited by physiologic and pathologic stimuli. The number of supernumerary neurons disappearing due to physiologic apoptosis during normal brain development has been estimated in human beings and rodents to be 50–70% of the entire neuronal cell population. Therefore, one could expect significant recovery of function because the pathologic process occurs at a time of great neuroplasticity.

Researchers should now focus on human beings and neurocognitive function after exposure to anesthetic agents in infancy and early childhood in various clinical situations; there is no need or reason to sacrifice more animals.

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References

1. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW: Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *ANESTHESIOLOGY* 2010; 112:834–41
2. Creeley CE, Olney JW: The young: Neuroapoptosis induced by anesthetics and what to do about it. *Anesth Analg* 2010; 110:442–8
3. Hansen TG, Danish Registry Study Group, Flick R, Mayo Clinic Pediatric Anesthesia and Learning Disabilities Study Group: Anesthetic effects on the developing brain: Insights from epidemiology. *ANESTHESIOLOGY* 2009; 110:1–3

(Accepted for publication July 28, 2010.)

Isoflurane-induced Neuroapoptosis in the Neonatal Rhesus Macaque Brain: Isoflurane or Ischemia-Reperfusion?

To the Editor:

We read with great interest the article by Brambrink and colleagues.¹ We want to raise a major point concerning their methodology and the ensuing interpretation of their results. The authors did not measure blood pressure in either the control group or at baseline in the treated animals. If we speculate that mean arterial pressure (MAP) measured at recovery time in their infant monkeys reflects MAP at baseline, a 35% decrease in MAP occurred during the entire procedure (see table 1 in their article). In infant animals as in infant humans, loss of autoregulation in preserved organs such as the central nervous system may rapidly occur, even when blood pressure moderately decreases. In a previous study, we observed that spinal cord blood flow was markedly decreased by epidural lidocaine in infant rabbits compared with adults and that the decrease in blood flow was correlated with a decrease in MAP.² Also, another study from our group performed in former premature infants showed that spinal anesthesia was accompanied by a decrease in cerebral blood flow parallel to the decrease in peripheral blood pressure.³ Then, it can not be ruled out that the neurodegeneration observed by the authors was simply related to the decrease in MAP observed during the 5-hour procedure.

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References

1. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW: Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *ANESTHESIOLOGY* 2010; 112:834–41
2. Bouaziz H, Okubo N, Malinovsky JM, Benhamou D, Samii K, Mazoit JX: The age-related effects of epidural lidocaine, with and without epinephrine, on spinal cord blood flow in anesthetized rabbits. *Anesth Analg* 1999; 88:1302–7
3. Bonnet MP, Larousse E, Asehnoun K, Benhamou D: Spinal

anesthesia with bupivacaine decreases cerebral blood flow in former preterm infants. *Anesth Analg* 2004; 98:1280–3

(Accepted for publication July 28, 2010.)

In Reply:

We thank Drs. Hansen and Henneberg as well as Drs. Mazoit, Roulleau, and Baujard for expressing interest in our recent publication on neuroapoptosis in the developing non-human primate brain after isoflurane anesthesia.¹ We appreciate the opportunity to discuss their valuable suggestions and concerns.

Before addressing Drs. Hansen and Henneberg's suggestions for the direction of future research, we would like to comment on their statement that 50–70% of all neurons die by natural apoptosis during development. As we have explained in a recent publication, this is a misconception.² Natural apoptosis deletes a high (but unknown) percentage of neuronal (and glial) precursor cells. However, after precursor cells differentiate into neurons and begin the synaptogenesis process, very few die by natural apoptosis, unless synaptogenesis is disrupted by some unnatural circumstance. Exposure to anesthetic drugs is an unnatural circumstance that disrupts synaptogenesis and deletes many neurons that would otherwise have survived and made a positive contribution to functions of the brain.

Drs. Hansen and Henneberg argue that further animal studies can serve no useful purpose, because there is no satisfactory way of extrapolating experimental findings from animals to humans. They express concern that more animal data will not clarify and may further confuse the issue of human susceptibility. Therefore, to move the field forward, they suggest that the research focus should now be on human research aimed at clarifying whether exposure of the developing human brain to anesthetic drugs is associated with long-term neurocognitive disturbances.

We agree that there is an urgent need for well designed human studies, but it does not logically follow that animal research is futile or should be halted. Rodent data served the very valuable purpose of alerting the medical profession and regulatory authorities to a neurotoxic action of anesthetic drugs. If it can be proven beyond reasonable doubt that anesthetic drugs, at clinically relevant doses, exert this neurotoxic action in the developing human brain, and that this results in neurodevelopmental disabilities, this would be a public health problem of considerable magnitude. Demonstrating that the nonhuman primate brain is susceptible to this neurotoxic action of anesthetic drugs when applied at clinically relevant doses does not provide definitive proof of human susceptibility, but it helps to close the translational gap and contributes new insight into the apparent species generality of this neurotoxic phenomenon.

A major benefit of the animal studies that have been performed is that they have spurred clinical researchers to conduct human studies. Several independent groups have now