Tom G. Hansen, Ph.D.,* Steen W. Henneberg, Ph.D. *Odense University Hospital, Odense, Denmark. tomghansen@dadlnet.dk

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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.

Jean Xavier Mazoit, M.D., Ph.D.,* Philippe Roulleau, M.D., Catherine Baujard, M.D. *Hôpital Bicêtre, Le Kremlin-Bicêtre, France. jean-xavier.mazoit@u-psud.fr

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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 nonhuman 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