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EDITORIAL

Restoring Order to Postoperative Neurocognitive Disorders

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Through the ages, anesthesiologists have had a Pollyannaish view that general anesthesia was an instantaneously reversible condition that left no trace after emergence, despite remarkable alterations in consciousness and similarly dramatic changes in other organ systems. Over the last 2 decades, that myth has been exposed by contravening evidence, which has left the discipline scrambling for answers about the neurotoxicity that anesthesia and the accompanying surgical interventions wreak on vulnerable patients, particularly those at the extremes of life. In the current issue of *JAMA Neurology*, Evered et al¹ report on surrogate biomarkers that may portend neurological injury that can result in postoperative cognitive decline (PCD) in elderly surgical patients. The clinical manifestations of postoperative cognitive decline run the gamut from delirium (there are listed criteria in the *Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition] for this form of “acute brain failure”²) to a more indolent, diagnostically imprecise form of cognitive disorder. Both ends of the spectrum can result in long-term consequences, such as dementia and increased mortality.^{3,4} Under recently proposed updates to the nomenclature, conditions related to postoperative cognitive decline are referred to collectively as perioperative neurocognitive disorders (PNCD).⁵



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In parsing the pathogenic roles played by anesthetic agents vs the aseptic trauma of surgery, investigators have encountered an ethical constraint, because the effects of surgery alone cannot be directly studied. It has seemed to some researchers that general anesthetics had been exonerated, because the incidence of PNCD is no different if a patient is randomized to receive general vs regional anesthesia⁶; however, trials focused on establishing this equivalence have generally not been appropriately powered,⁶ and regional anesthetic techniques are often supplemented with general anesthetics,⁶ albeit at somewhat lower doses, which thereby contaminated the randomized groups. Animal models have suggested that disordered cognition is owing to a neuroinflammatory response⁷ that may become exaggerated and persistent in circumstances that are becoming more prevalent as a result of aging populations of surgical patients and increasing burdens of lifestyle-related diseases.⁸

These findings have led to the quest for identifying neuroimaging and other biomarkers of perioperative brain injury, which is now taking shape through the creation of large consortia in Europe (via a study cohort named Biomarker Development for Postoperative Cognitive Impairment in the Elderly, or BIOCOP), North America (via the Successful Aging after Elective Surgery, or SAGES, study, and the Trajectory of

Recovery in the Elderly, or TORIE, study) and countries in the Southern Hemisphere (via study cohorts called Cerebrospinal Fluid And Preclinical Alzheimer Cognitive Trajectory, or CAPACITY, and the Assessment And Review Of Cognition, Alzheimer Disease, And Inflammation In Elderly Patients After Hospital Intervention, or ARCADIAN). Findings from the CAPACITY and ARCADIAN trials precipitated this commentary.¹

In the course of associating biomarkers with careful phenotyping, Evered et al¹ provide an intriguing preliminary finding that 2 plasma markers of brain injury, namely tau and neurofilament light, rise significantly in surgical patients 60 years and older who are anesthetized with either sevoflurane or propofol; levels then return to baseline within 3 days. The high precision and sensitive analyses of these samples were performed in batches by their Swedish coauthors using single molecule array technology (Simoa). It is notable that the baseline values differ remarkably between the batch assays from the 2 separate trials, which leads the investigators to focus on the incremental, rather than absolute, changes in these levels over time. At this juncture, the authors do not report a corresponding behavioral phenotype to which these changes can be linked; therefore, it remains an open question whether these changes are relevant to the development of PNCD. While it does appear that the analytes were upregulated in each surgical patient (as displayed in Figure 2 of the report by Evered et al¹), it would be extremely unusual for all study participants to have developed perioperative neurocognitive disorders. Therefore, if there is a relationship between the incremental changes in tau and neurofilament light and postoperative cognitive decline, it must begin above a currently unknown threshold. At the time that the cognitive changes are documented, it will be necessary to explore the relationship with receiver operating characteristic curves. The authors draw attention to the fact that these same biomarkers have been noted to increase *pari passu* with traumatic brain injury.^{9,10} While the pathogenesis of PNCD is not fully understood, there is a lack of biologic plausibility that injury was produced by the combination of peripheral surgery and anesthesia, resembling traumatic brain injury and resulting in similar biomarkers.

The authors' quest¹ for a biomarker for PNCD is welcomed. Validated biomarkers of enhanced susceptibility for the development of PNCD will facilitate customization of prehabilitation strategies for the vulnerable surgical patient, as well as providing a more realistic risk-benefit assessment prior to the patient's consenting to impending elective surgery. Biomarkers that can help diagnose PNCD in its preclinical manifestation may enable interventions that can successfully abort the full-fledged complication and its sequelae of increased morbidity and mortality.

The combination of surgery and anesthesia may also be responsible for the developmental neurotoxicity that has been well-documented in preclinical models, including in nonhuman primates, but is less well-established in clinical settings.¹¹ We anticipate that the current article¹ will spur the application of biomarkers of brain injury to anesthetic-induced developmental neurotoxicity, a lifelong complication that may be as devastating as PNCD and its sequelae.

The authors are to be applauded for uncovering this novel finding; however, without a defined link to cognitive disorders,

this observation is quite preliminary. Together with careful behavioral phenotyping we encourage future authors to limit confounders, such as the variety of anesthetic drugs used, the depth of anesthesia attained, the types of surgical procedures performed, the ages of the surgical patients, and comorbidities known to affect the prevalence of PNCD.¹² Nevertheless, with this report, Evered and colleagues¹ have begun to bring some order to the imprecise field of postoperative neurocognitive disorders.

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Conflict of Interest Disclosures: Dr Maze is a co-founder of a company, NeuroproteXeon, that intends to develop Xenex, a drug-device combination, for the treatment of acute ongoing neurological injury. In the future, it is possible that Xenex may be studied in the clinical settings that give rise to postoperative neurocognitive disorders and anesthetic-induced developmental neurotoxicity. Dr Maze is also supported by National Institutes of Health grant R01GM104194. No other disclosures are reported.

REFERENCES

1. Evered L, Silbert B, Scott D, Zetterberg H, Blennow K. Neurofilament light and tau are increased following anesthesia and surgery [published online February 19, 2018]. *JAMA Neurol*. doi:10.1001/jamaneurol.2017.4913.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
3. Berger M, Nadler JW, Browndyke J, et al. Postoperative cognitive dysfunction: minding the gaps in our knowledge of a common postoperative complication in the elderly. *Anesthesiol Clin*. 2015; 33(3):517-550.
4. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367(1):30-39.
5. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery. *BJA*. In Press.
6. Rasmussen LS, Johnson T, Kuipers HM, et al; ISPOCD2(International Study of Postoperative Cognitive Dysfunction) Investigators. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand*. 2003;47(3):260-266.
7. Terrando N, Eriksson LI, Ryu JK, et al. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol*. 2011;70(6):986-995.
8. Feng X, Valdearcos M, Uchida Y, Lutrin D, Maze M, Koliwad SK. Microglia mediate postoperative hippocampal inflammation and cognitive decline in mice. *JCI Insight*. 2017;2(7):e91229.
9. Shahim P, Gren M, Liman V, et al. Serum neurofilament light protein predicts clinical outcome in traumatic brain injury. *Sci Rep*. 2016;6: 36791.
10. Shahim P, Tegner Y, Wilson DH, et al. Blood biomarkers for brain injury in concussed professional ice hockey players. *JAMA Neurol*. 2014; 71(6):684-692.
11. Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity—clinical implications of animal models. *N Engl J Med*. 2015; 372(9):796-797.
12. Hudetz JA, Patterson KM, Amole O, Riley AV, Pagel PS. Postoperative cognitive dysfunction after noncardiac surgery: effects of metabolic syndrome. *J Anesth*. 2011;25(3):337-344.