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# Editorial

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Over 35 million people worldwide are reported to suffer from Alzheimer's disease (AD). With healthcare advances and marked increase in life expectancy, there is an ever-increasing incidence of AD. Longevity and the continuous improvement of peri-operative medicine, reducing mortality and morbidity, have led to an exponential increment in surgery and, as a consequence, a larger number of aged patients are undergoing surgery. While anesthetics are indispensable clinical tools and generally considered safe and effective, in some situations there is a growing concern about the potential neurotoxicity of these agents. Particularly among the elderly, a number of cases of post-operative cognitive decline (POCD), both short-term and long-term, have been globally reported. It is argued, and justifiably so (with regard to cardiac surgery in particular, having several risk factors which could result in cognitive decline), that it is not possible to dissociate the effects of surgery and anesthesia. However, significant reports of cognitive decline on follow up of patients undergoing non-cardiac, prolonged surgical procedures under general anesthesia have resulted in several scientific groups focusing greater attention on the possible neurotoxic effect of anesthetics in POCD.

The overwhelming response to the call for articles for this supplemental issue is proof enough of the common note of concern and urgency shared by the scientific community to scrutinize the possible toxic effects (if any) of anesthesia in POCD (the long-term form simulating the clinical and molecular mechanisms involved in AD), particularly in the aged population. Scientists, anesthesiologists, neurologists, neuropsychologists and surgeons have expressed their expert views on various aspects of the pathophysiology of AD, and the role of anesthetics as a possible risk factor. These efforts, when viewed as a whole, will inevitably stimulate rethinking on the subject.

The introductory article by Dr. Finder provides a panoramic view of the classic and recent literature on the complex cellular and molecular mechanisms underlying AD, supported by subsequent articles which focus on the more recent observations in specific areas of molecular research. Amyloid-$\beta$ (A$\beta$) plaques were considered the pathogenic species in AD; however, accumulating evidence suggests that plaques could represent final waste deposits, with the oligomeric intermediates representing the key toxic players since the severity of cognitive deficits in AD correlates with the level of oligomers in the brain but not with the total A$\beta$ burden. The proposed neurotoxic effects of A$\beta$ oligomers are synaptic failure, membrane disruption with $Ca^{2+}$ influx, mitochondrial failure and oxidative stress, and recruitment of cellular factors or activation of cellular processes such as apoptosis and inflammation.

A$\beta$ has a natural role in many functions of the nervous system. There is evidence that A$\beta$ is part of the innate immune system of the brain and natural antibodies against oligomeric, fibrillar A$\beta$ and plaques have been identified. However, with the aging process, there is a decrease in the level of these antibodies that could account for the reduced efficiency of the immune system, leading to decreased A$\beta$ plaque clearance. An imbalance between production and clearance causes A$\beta$ to accumulate and this may lead to AD. The elaborate review on anesthetics promoting *in vitro* A$\beta$PP metabolism and A$\beta$ toxicity, by Dr. Barbara Eckel and colleagues, provides convincing evidence for the possible role of anesthetics in AD pathophysiology, while acknowledging the limitations of such *in vitro* studies. Dr. Gong and his team members stated in their article that inhaled anesthetic-induced hyperphosphorylation of tau protein is also a significant observation in animal model studies.

Systematic biophysical studies by Dr. Mandal and colleagues, using state-of-the-art NMR technique for A$\beta$ peptide interactions with a range of varying sized anesthetics, have led to the conclusion that only smaller sized (e.g., isoflurane, desflurane, etc.) anesthetics (many of which are widely used in anesthesia today) can access the cavity containing critical amino acid

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residues (G29, A30, and I31) whose perturbation leads to A$\beta$ peptide aggregation (oligomerization). This observation emphasizes the association of the size factor of anesthetics and their profound role in A$\beta$ peptide aggregation. Based on this *in vitro* research, the thought-provoking novel concept put forward to the scientific community and the pharmaceutical industry is that it may be crucial to focus efforts on the development of new larger sized ($\sim$191 Å$^3$) inhaled anesthetics. The novel NMR technique can be used to screen new generation anesthetic molecules.

Animal studies, conducted by Dr. Mena and her team, as well as many other investigators, show that plaque formation due to exposure to isoflurane is of significance. The exact mechanism(s) underlying AD are under great research scrutiny at the molecular and cellular level but continue(s) to evade total scientific understanding. This knowledge gap, if filled, could facilitate early intervention, better preventive measures, and more effective drug formulations to stem the progress of AD. The role of A$\beta$, tau, and S100$\beta$ as biomarkers of cognitive decline is being currently evaluated.

Cardiac anesthesiologists have been perturbed by the reported cases of long-term POCD and procedures ensuring optimal perfusion, neuroprotective methods and stricter anesthetic protocol to mitigate this have not been as successful as desired. It is of interest to note that off-pump CABG has not significantly reduced the occurrence of POCD compared to on-pump. The clinical research report, by Dr. Karen Ritchie and her team, with close attention to study design, statistical and analytic procedures, on the long-term effects of anesthesia on cognitive functioning after orthopedic surgery in a large number of elderly patients, stresses the observation that POCD is not confined to cardiac surgery. As highlighted by Dr. Tripati and colleague, from a neurological diagnostic point of view, clinical awareness of the emerging metabolic, nutritional, endocrinal, toxic, autoimmune, cerebrovascular, genetic, infectious, and hemorheological factors need to be kept in mind in the differential diagnosis of dementia, to add to the already established causes of dementia, which require consideration when faced with POCD.

A review by Dr. Rasmussen and co-workers, with general considerations concerning geriatric patients and specific features of perioperatively used drugs and anesthetics which might have an impact on patients with AD, covers the whole range of strictly-followed procedural details. These also include the legal aspects of obtaining informed consent in the demented patient, decisions on the use of premedication, choice of anesthetics, the depth of anesthesia and how to monitor it with precision, and the management of postoperative pain.

In this scenario of incomplete knowledge about what triggers AD on one hand and an incriminating finger pointing to the possible role of anesthetics on the other, abundant caution in the choice of anesthetics and the procedure is perhaps the key to avoid adding yet another factor to the armamentarium of risk factors for AD. A consistent part of funding for research in AD is currently aimed at delaying the clinical manifestations of the disease; however, during the past half-century, the inhaled anesthetics, suspected of potentially accelerating the AD onset, are the agents of choice in general anesthesia. Surprisingly, faced with this situation, whether anesthesia influences the development or even causes AD, is rarely evaluated and enmeshed in controversy. The medical field needs to adopt a more rigorous approach to codify the frequency and extent of early and delayed POCD against data on the anesthetic employed.

This supplemental issue sees the convergence of evidence from various groups on the possible neurotoxicity of anesthetics, especially in the elderly, even as our understanding of the pathomechanism of AD increases. We thank the Editors and contributors to the issue and Dr. Subbulakshmi Natarajan, MBBS, Ph.D and Dr. Poonam Malhotra, MD for suggestions which gave us unique opportunity to put together the many pieces of the jigsaw puzzle to present a comprehensive picture. We wish to express our appreciation to Dr. John P. Williams, MD, Safar Professor and Chair Anesthesiology, University of Pittsburgh, USA for discussion. It must be noted that this is no attempt to raise a 'fear of anesthesia', but an earnest quest for the 'safe anesthetic' for the elderly. It is most heartening that the contributors for this issue have joined efforts in this crusade against AD, and in pursuing the dialogue on anesthetics as a possible risk factor for AD. It is hoped that this special issue of the Journal of Alzheimer's Disease sends out a message to the scientific community to give a serious rethinking on the topic 'Anesthetics and AD' and add new knowledge and value to this emerging area of research.