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Special Issue on Postoperative Cognitive Dysfunction

Selected Reports from the Journal-sponsored Symposium

ALTHOUGH described more than 50 yr ago,[1] postoperative cognitive dysfunction (POCD) remains an enigma. The subject of a Rovenstine Lecture in 2003 and numerous panels at international meetings, POCD was again featured prominently at the American Society of Anesthesiologists Annual Meeting in October 2006 as the topic for the Journal's sponsored symposium. Each of the keynote speakers graciously agreed to be recorded and to provide their slides, and we are pleased to offer their presentations as a Web Enhancement to this month's issue of ANESTHESIOLOGY. Also in this issue of the Journal are POCD-related review articles,[2,3] as well as articles that have evolved from posters presented at the symposium.[4–6]

Opening up proceedings at the Journal's sponsored symposium was Lars S. Rasmussen, M.D., Ph.D., Associate Professor, Department of Anesthesia, Centre of Head and Orthopaedics, Copenhagen University Hospital, Copenhagen, Denmark. Also the highly regarded leader of the International Study of Postoperative Cognitive Dysfunction (ISPOCD) group, he was tasked with addressing four questions: (1) Does POCD exist after noncardiac surgery? (2) If so, what is the incidence? (3) Which risk factors have been identified? and (4) Is the incidence affected by the choice of the anesthetic technique (general *vs.* regional)? The existence of POCD has been challenged; the hypothesis that the care associated with a surgical intervention produces a greater decline in cognitive performance than could have been expected to occur had these surgically scheduled patients not undergone surgery has never been formally tested. Absent a control group of surgical patients randomized to nonsurgical care, investigators have sought a variety of less appropriate alternatives, including age-matched healthy controls, or disease-matched patients who do not undergo the surgical procedure because of the choice of the patient or the surgeon. At the poster session that accompanied the Journal-sponsored symposium, Saager *et al.*[7] reported their preliminary findings obtained from the Alzheimer's Disease Research Centre's database. The annual rate of cognitive decline was accelerated in an aged population after a major noncardiac surgical intervention when compared with a similar cohort, prospectively followed for at least 3 yr, who did not require a surgical intervention. Epidemiologic studies of this type are likely to shed light on the question of whether cognitive decline in surgical settings differs from the apparent decline experienced by aged patients receiving care for major medical illnesses.

Stanton Newman, D.Phil., Professor and Director, Center for Behavioral and Social Science in Medicine, Royal Free and University College of London Medical School, London, England, addressed methodologic aspects in the diagnosis of POCD. Coming from the doyen of behavioral psychologists in this field, Dr. Newman identified problems in the realm of testing and analysis of the neurocognitive data sets. These are further elaborated in a review article by Newman *et al.*[2] in this issue of the Journal.

Mark Newman, M.D., Merel H. Harmel Professor of Anesthesiology, Chief, Division of Anesthesiology Cardiac Service, Chair, Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, is a pioneer in the field of POCD after cardiac surgery. He suggested that the distinction between cardiac and noncardiac POCD may be more apparent than real and raised the likelihood that these two artificially separated conditions may be governed by similar etiologic factors and pathogenic mechanisms. Previously, Newman *et al.*[8] had provided data that demonstrate the independent adverse effect that POCD has on long-term morbidity and mortality. More recently, Newman's group has reported on the deterioration in quality-of-life indices that occurs in patients with POCD.[9]

The panelists agreed that POCD does indeed exist as an often subtle persistent deterioration in cognitive performance (including one or more of memory, attention, and speed of information processing) after a surgical intervention; its assessment requires neuropsychological testing, and it is diagnosed by applying firm criteria to yield a dichotomous result. Thereafter, there was lively debate regarding when the change in cognitive performance between two time points separated by a surgical intervention constitutes POCD. Specific issues addressing the degree of change, together with the timing, type, and analysis of the neurocognitive battery of tests, were explored in depth without reaching a consensus view.

In a fascinating mechanistic study, Wan *et al.*[4] subjected anesthetized rats to splenectomies and demonstrated that there was a brief period of cognitive dys-

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Accepted for publication January 3, 2007. Dr. Maze is a consultant to Air Products, who are exploiting the possible neuroprotective effects of xenon in settings that include postoperative cognitive dysfunction after coronary artery bypass graft surgery.

function, as assessed with a Y-maze, and that this was associated with biochemical markers of glial activation and inflammation (interleukin-1β and tumor necrosis factor-α messenger RNA) in the hippocampus. Of particular note was that anesthetized animals that had not undergone surgery showed none of these changes, reinforcing the concept that the observed changes were not related to anesthesia *per se*.

Interestingly, in most of the earlier clinical trials addressing the prevalence and risk factors associated with POCD, patients with existing cognitive impairment were excluded (*e.g.*, see ISPOCD1).[10] In two articles resulting from this Journal-sponsored symposium, both prospective[5] and retrospective[6] analyses were used to redress this deficiency.

Hudetz *et al.*[5] prospectively examined the independent effect of self-reported alcohol abuse on the development of POCD and demonstrated what others had intuitively suspected,[11] that with less "cognitive reserve" (lower baseline scores), patients are more likely to develop POCD. There are several caveats that need to be considered in this relatively small study (*i.e.*, only 14 patients in each of four groups). The surgical alcoholic group included two patients who developed postoperative complications, each of which has been independently shown to increase the risk of POCD[10]; therefore, the influence of alcohol abuse on the subsequent development of POCD is brought into question. Furthermore, the alcoholic surgical patients were more likely to require postoperative admission to the intensive care unit, where sleep deprivation is likely to occur[12] and can result in postoperative confusional states including delirium.[13] The fact that patients were assessed relatively soon after the surgical procedure (within 2 weeks) makes this a distinct possibility.

Silverstein *et al.* from ISPOCD have retrospectively reviewed their data from the first trial[10] to determine whether particular cognitive domains are more severely affected by a surgical intervention in patients in whom preoperative cognitive impairment can already be detected. As can be expected from their original inclusion criteria ($>$ 23 on the Mini-Mental State Examination), only 74 patients (of a total of 1,185 patients) met their definition of preoperative impairment (visual verbal learning test score that is 1.5 SD below that of healthy age-corresponding controls; this definition was selected to resemble the amnestic minimally cognitively impaired cohort). Of the four cognitive domains (memory, information processing, planning, and attention) that the ISPOCD neurocognitive battery tests, Silverstein *et al.* noted that postoperative deterioration in memory was *less* likely in the preoperative cognitive impairment group.[10] However, this may be due to the phenomenon of "regression to the mean" in which a low score is not capable of dropping as much in absolute terms as a higher score. This becomes particularly problematic when use is made of the "change in score" (referred to as a "floor effect" by Silverstein *et al.*). Residualized change scores is a method of measuring change that could have avoided the problem that Silverstein *et al.*[3] seem to have encountered. In this calculation, the postoperative score is regressed at a "normal" rate of decline to yield a preoperative score, and the difference from this predicted value and the observed value provides the "unexpected change."

While Hudetz *et al.*[5] concentrate on the cognitive effects of alcohol abuse and Silverstein *et al.* purport to address the intermediate state between normal aging and Alzheimer's Disease,[14] both groups have ventured into what should become fertile territory. It will be necessary to comprehensively examine the effects of a surgical intervention on the slope of cognitive decline in those already cognitively impaired in order for these patients to be fully apprised of the possible cognitive consequences of a surgical intervention before providing consent for a non–life-preserving surgical intervention.

Although the original four Koch's postulates referred to the causal relationship between an infective agent and a disease (*e.g.*, tuberculosis and anthrax),[15] at least two of the four can be used to establish the existence and to understand the etiology of other "new" diseases such as POCD in a preclinical laboratory setting. In this vein, one may wish to investigate what are the minimal features are that are exhibited by all patients with POCD and whether these can be transferred to a healthy organism to recreate the disease. Hypotheses testing, as well as the development of treatment strategies, can be explored in validated animal models; in particular, the role of possible causative (as well as protective) interventions that occur in the perioperative period, and the contribution of genetic polymorphisms can be investigated.

With the aging of their populations, it is predicted that cognitive decline will constitute an increasing healthcare problem in the developed countries of the world, causing despair to patients and their providers alike while consuming a growing fraction of available healthcare resources. The latter should provide the "business case" to fund the type of studies that are required to address the genesis of this health problem and, in particular, the contribution of what role a surgical intervention plays in cognitive dysfunction. Were postoperative cognitive decline shown to be no different from that which occurs in the elderly confronted by any cause of failing health, it still requires the perioperative practitioner to understand this condition more fully because, uniquely, the elective surgical setting provides an opportunity to test preemptive therapies. Falling between several stools, a clinical discipline needs to take "ownership" of this putative perioperative problem, and in our view, this needs to reside within our specialty. The major large-scale clinical trials defining some of the issues involved

have been led by the eminent keynote speakers at the Journal's sponsored symposium.[8,10] Although the existing data seem to rule out a putative anesthetic causative factor,[16] we can be at the forefront, hunting for and implementing solutions with the same success that has seen our discipline pioneer strategies to prevent and treat ischemic–reperfusion organ injury both in and outside the operating room.

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"A Razor May Be Sharper Than an Ax, but It Cannot Cut Wood"

> "A razor may be sharper than an ax, but it cannot cut wood."
>
> —Annang proverb

IT would be an understatement to say that molecular biology has revolutionized medicine by increasing our understanding of the pathophysiologic mechanisms of disease and ability to assess genetic risk. Since the completion of the Human Genome Project in 2003, we have witnessed the use of genomics for the rapid identification of newly discovered pathogens, such as that involved in the severe acute respiratory syndrome; the use of gene-expression profiling to assess cancer prognosis and guide therapy; the use of genotyping to stratify patients according to the risk of a disease, such as prolonged QT interval syndrome or myocardial infarction; the use of genotyping to increase our understanding of drug pharmacokinetics and pharmacodynamics; and the use of genetics for tissue engineering and the cloning of several different species.[1,2] However, we have been slow to apply many of these novel, cutting-edge molecular techniques within our own discipline.

In this issue of ANESTHESIOLOGY, Lucchinetti *et al.*[3] use a GeneChip microarray (Affymetrix, Santa Clara, CA) to perform myocardial genetic expression profiling of patients receiving intravenous *versus* inhalational anesthetics during off-pump coronary artery bypass graft surgery. Microarray technology is a powerful and elegant tool for genetic research that uses nucleic acid hybridization techniques and recent advancements in computing technology to evaluate the messenger RNA (mRNA) expression profile of thousands of genes within a single exper-

◆ This Editorial View accompanies the following article: Lucchinetti E, Hofer C, Bestmann L, Hersberger M, Feng J, Zhu M, Furrer L, Schaub MC, Tavakoli R, Genoni M, Zollinger A, Zaugg M: Gene regulatory control of myocardial energy metabolism predicts postoperative cardiac function in patients undergoing off-pump coronary artery bypass graft surgery: Inhalational *versus* intravenous anesthetics. ANESTHESIOLOGY 2007; 106:444–57.

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iment. Labeled complementary DNA or complementary RNA targets derived from the mRNA of an experimental sample are hybridized to nucleic acid probes (*i.e.*, gene fragments) attached to a solid support (*i.e.*, a "chip"). By monitoring the amount of label associated with each DNA location, it is possible to infer the amount of each mRNA species represented. In addition to analyzing gene expression on a genome-wide scale, other important microarray applications include genomic resequencing, genotyping, genome-wide exon analysis, and transcript mapping.[4] Moreover, microarray technology offers the unprecedented opportunity to measure gene expression in relation to physiologic and environmental factors, and has great potential for clinical and pharmacologic applications.[4]

Because microarray experiments literally involve the comparison of thousands of data points, the scientific community has grappled with identifying specific guidelines for the conductance, statistical analysis, and interpretation of microarray experiments due to the significant potential for false positives (*i.e.*, type I error). To this end, the Microarray Gene Expression Data Society, an international organization of molecular biologists, computer scientists, and data analysts, developed standards known as the Minimum Information About a Microarray Experiment (MIAME), which outlines the minimum information that should be reported about a microarray experiment to enable its unambiguous interpretation and reproduction.[5*] In addition adhering to the MIAME guidelines, Lucchinetti *et al.* analyzed their microarray data using a highly sophisticated technique known as gene set enrichment analysis. Gene set enrichment analysis is a computational method that determines whether an *a priori* defined *set* of genes (as opposed to individual genes) shows statistically significant, concordant differences between two biologic states (*e.g.*, phenotypes).[6] Gene set enrichment analysis involves three steps: (1) calculation of an enrichment score, (2) estimation of the enrichment score significance level, and (3) adjustment for multiple hypothesis testing. This last step involves controlling for the proportion of false positives by calculating the false discovery rate (FDR) corresponding to each normalized enrichment score.[6] This is very important because gene set enrichment analysis involves the comparison of hundreds, if not thousands, of gene sets (547 gene sets were compared in the analysis by Lucchinetti *et al.*). Indeed, most major journals are now requiring that the FDR for each gene set be determined and that gene sets with an FDR > 0.25 be excluded from the final analysis. Alternatively, instead of simply fixing a level at which to control the FDR, one may calculate the FDR q value, which is defined to be the FDR analog of the *P* value.[7] Specifically, the FDR q value for a particular feature is the expected proportion of false positives incurred when calling that feature significant.[7]

In the study by Lucchinetti *et al.*, the authors conclude that their microarray data suggests that the proliferator-activated receptor γ coactivator-1α and granulocyte colony-stimulating factor survival pathways play key roles in perioperative myocardial protection. As opposed to specifying a specific FDR cutoff for gene set exclusion in the study methods section, Lucchinetti *et al.* instead calculated the FDR q value for each gene set. This is important because the proliferator-activated receptor γ coactivator-1α pathway was used as an indicator of preoperative "myocardial background energy metabolism" in their multivariate analysis despite the fact that this pathway had an FDR q value of 0.26. That is, 0.26 is the expected proportion of false positives incurred when we call the proliferator-activated receptor γ coactivator-1α pathway significant.[7]

Similarly, these authors also conclude that their data suggest that sevoflurane reduces the transcriptional activity of genes involved in fatty acid oxidation (FDR q value = 0.33) and DNA-damage signaling (FDR q value = 0.11) while increasing the transcriptional activity of genes in the granulocyte colony-stimulating factor survival pathway (FDR q value = 0.10) compared with patients receiving propofol. Again, the FDR q value for a particular feature is the expected proportion of false positives incurred when calling that feature significant.[7]

Does this mean the conclusions by Lucchinetti *et al.* are incorrect? No, but it does suggest the potential for a high proportion of false positives in the data on which their conclusions are based. In fact, genetic statisticians have yet to determine whether and what cutoff value should be used for the FDR q value (although many would argue for a FDR q value < 0.10).[7] But it does highlight the significant statistical problems of handling genomic data that involve thousands of multiple comparisons. Guarding against any single false positive occurring is often much too strict and will lead to many missed findings. The goal is therefore to identify as many significant features in the microarray data as possible while incurring a relatively low proportion of false positives.[7]

In summary, Lucchinetti *et al.* are to be commended for taking advantage of and applying such cutting-edge molecular techniques as gene microarray screening to our discipline. Furthermore, publication of such microarray data should not only adhere to MIAME standards, but should also involve careful controls for the FDR (*i.e.*, type I error). Without such blunt statistical instruments as the FDR controlling for the large number of genetic comparisons, it is going to be difficult to see the forest for the trees.

* Available at: www.mged.org/miame. Accessed December 1, 2006.

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