

Taking the Lead in Research into Postoperative Cognitive Dysfunction

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IN this issue of the Journal, Dr. Monk *et al.*^{1,2} explore the effects of surgery and anesthesia on cognitive function in both the short and medium-term postoperative period; these articles follow up investigations conducted previously by the International Study Group on Postoperative Cognitive Dysfunction (ISPOCD).³ Using the ISPOCD measures of outcome, Monk *et al.* have confirmed the risk factors for the development of postoperative cognitive dysfunction (POCD) that had been previously identified (age, low educational level). Interestingly, they also found that asymptomatic patients with a history of stroke had a higher incidence of POCD. Strikingly, they add critical insights into the overall significance of POCD by defining a relationship to mortality.

Regarding risk factors, the evidence garnered by these and other studies¹⁻³ may be considered as a reduction in cognitive reserve that provides the milieu for the development of POCD. Stern⁴ refers to passive and active models of cognitive reserve; in the passive model, reserve is represented by increased brain size and/or number of synapses available. Within this model, any cognitive deterioration consequent to a brain injury can be compensated for by means of neuronal pathway substitution. The active model features an improved processing of the available information by exploitation of pre-existent redundant neuronal networks. This theory of

synaptic enrichment provides a convenient explanation for the observation that high levels of intelligence and educational attainment are good predictors of brain resistance to injuries before cognitive dysfunction is manifest.⁵ Conversely, it clarifies the role of previous stroke (even though there was no neurologic deficit) as an exacerbating factor. Aging, one of the aforementioned risk factors for POCD, causes several structural and morphologic changes to brain tissue, which are likely to be correlated with a reduction in cognitive reserve. These include reduced brain weight and volume⁶ as well as loss of cellular bodies and myelinated fibers in several brain regions⁷ including the hippocampus,⁸ an area of the brain that is critical for memory. Subcellular changes are documented as a reduction in synaptic density,⁹ rarefaction of cerebral microvasculature,¹⁰ and alterations to DNA repair systems including the mechanisms for removal of neurons with damaged nuclear DNA¹¹ among others. Oxidative stress has been cited as a likely cause of age-related neurodegeneration.¹² Within the aging brain, there is a proinflammatory phenotype with up-regulation of markers, such as interleukin 6 and C-reactive protein, which have been correlated with cognitive decline in a study of elderly patients.¹³

Is the deterioration of cognitive function seen in elderly postoperative patients after surgery (POCD) initiated by an exacerbation of processes already active during the aging process? If so, does surgery or anesthesia accelerate the mechanisms leading to age-related cognitive decline? There is now compelling evidence to suggest that inflammation occurs in the brain after nonneurologic, noncardiac surgery as evidenced by increased levels of proinflammatory cytokines in cerebrospinal fluid. Buvanendran *et al.*¹⁴ found that hip replacement surgery was associated with postoperative up-regulation of interleukin 6, and prostaglandin E₂, in the cerebrospinal fluid. Others observed increased concentrations of interleukin 6 in the cerebrospinal fluid during and immediately after off pump coronary artery bypass surgery.¹⁵ In addition, studies performed in animals after abdominal¹⁶ and orthopedic surgery¹⁷ have demonstrated inflammation in hippocampal tissue during the postoperative period; inflammatory changes in these brain regions are capable of adversely affecting learning and memory as well as other cognitive domains.¹⁸ However, neither the findings of the preclinical nor clinical studies of POCD can be causally attributed to these alterations in inflammatory markers; also, it is unclear whether the neuroinflammation is pathogenically linked to surgery, anesthesia, or other patient factors. Although

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◆ This Editorial View accompanies the following two articles: Price CC, Garvan CW, Monk TG: Type and severity of cognitive decline in older adults after noncardiac surgery. ANESTHESIOLOGY 2008; 108:8-17; Monk TG, Weldon BC, Garvan CW, Dede DE, Van Der Aa MT, Heilman KM, Gravenstein JS: Predictors of cognitive dysfunction after major noncardiac surgery. ANESTHESIOLOGY 2008; 108:18-30.

Accepted for publication September 17, 2007. Dr. Maze is a paid consultant for Air Products, Allentown, Pennsylvania, which is involved, together with Air Liquide Sante, in the commercial exploitation of xenon for postoperative cognitive dysfunction after cardiac surgery. If xenon is marketed and sold for this application, Dr. Maze is eligible to receive royalties at a rate of approximately 1% of sales.

plausible arguments can be made for each of these factors, further research is needed to establish the mechanisms for the associations that have been noted.

In their companion article, Monk *et al.* suggest that different types of cognitive impairment may develop after surgery. This has been explored by separating the results of tests that assess the primary attention domain (often referred to as executive function) from that assessing the memory cognitive domain. Executive tasks (*e.g.*, the Wisconsin Card Sorting Test) explore the activity of prefrontal cortices, thalamus, and white matter fibers. The successful accomplishment of these tests is associated with normal functioning in middle-aged and older individuals.¹⁹ Difficulty in completing the tasks implies an impairment (either functional or morphologic) of these structures in the brain of POCD patients. A dysfunction of memory domains, as referred to by the authors, can be accounted for by an impairment of hippocampus, entorhinal cortex, thalamus, and basal forebrain. Because different cognitive domains depend on different brain regions, it may be considered more likely that a common pathogenic mechanism (such as inflammation) impairs each of these structures concurrently, rather than separate mechanisms affecting them individually. Differences in the degree of postoperative cognitive impairment observed between individuals and between different regions of the brain may reflect site-specific variability in cognitive reserve.

Despite limitations of the studies by Monk *et al.* (including use of age-matched [not disease-matched] controls, exclusion of patients with preexisting cognitive impairments, and the use of an unrestricted anesthetic protocol), the finding that cognitive loss is correlated with longer-term (1-yr) mortality is remarkable but unsurprising because longitudinal studies had previously demonstrated the relation between cognitive decline and mortality rate in nonsurgical settings.²⁰ Although a causal relation between POCD and death cannot be strictly deduced, investigators in this field of inquiry will be better prepared to address the “so what” comment when seeking funding from relevant agencies. The call to seek a more meaningful overall global outcome measure of cognition that the everyday practitioner can apply and easily understand will continue but is not reason to ignore the results of other forms of testing when an association with mortality has been found. The mortality relationship that was noted must be corroborated, ideally in a multicenter fashion, to strengthen its broader applicability; also, it would be helpful to obtain further insight into the role of anesthetic techniques by standardizing these.

Amelioration of POCD can be seen as part of a quest to control the processes of aging and the postponement of

cognitive decline. Those involved in the care of elderly patients scheduled to undergo surgery must identify the pathogenic mechanisms and orchestrate appropriate protective and therapeutic interventions to target the pathogenic processes that produce POCD. Although the anesthesiologist may not have all the necessary tools to undertake this quest, who is better placed to lead the response to this perioperative challenge?

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Liars, Damn Liars, and Propensity Scores

PROPENSITY score methods are being used increasingly to reduce the impact of treatment-selection bias when using observational data to estimate causal treatment effects.¹ In the article by Vincent *et al.*,² 821 pairs of patients were matched according to a propensity score. The data in the study of Vincent *et al.* were derived from a previous study called the Sepsis Occurrence in Acutely Ill Patients Study, which was a multicenter, observational study that included all adult patients admitted to 198 European intensive care units.³ The authors demonstrated that the 30-day survival rate was higher in those patients who received a transfusion compared with those who did not. These results contradict those of Hebert *et al.*,⁴ who demonstrated that a restrictive strategy of erythrocyte transfusion was at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients in a multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. The use of propensity score analysis is not without controversy, because occasionally its use has resulted in some disputed conclusions.⁵ So what is propensity score analysis, and what strengths, weaknesses, and biases are inherent to the analysis?

The accepted standard for demonstrating that a treatment produces a certain outcome is a prospective, randomized, blinded (controlled if appropriate) trial. This is the case because random assignment of patients to treatment groups balances both known and unknown patient characteristics that may affect outcome and reduces the likelihood that there will be differences in the patient characteristics between study arms. Unfortunately, many therapies cannot be randomized for ethical, economical, or practical reasons, and on these occasions, observational studies can provide valuable information about treatment effectiveness. However, because of the very nature of the study design, the interpretation of observational studies is fraught with difficulty.

An inherent problem in the methodology of observational studies is that the investigators do not have control over the treatments given to participants. As in the study of Vincent *et al.*,² patients are often "assigned" to a treatment condition based on a conglomeration of char-

acteristics that make it very likely/unlikely that they will experience the outcome under study. Unlike random assignment, where the groups systematically differ on only the treatment intervention, the treatment groups in observational studies are likely to differ on both the treatment intervention and also a myriad of other variables that may independently affect outcome (called covariates). As a result of differences in treatment groups, investigators must rely on statistical adjustments to control for the confounding effect of the observed covariates when estimating the unique effect due to treatment. Often, there are large amounts of data on potential cofounders available for analysis, but the large volume and complexity of this data does not guarantee reliable and accurate analysis. It is for the improvement of such analyses that propensity methodology was created.

Propensity methodology was first proposed in 1983 as a novel strategy for statistical control in observational studies.⁶ The method first focuses on the relation between baseline patient characteristics and the primary treatment variable of interest, such as receiving erythrocyte transfusion *versus* not. Conceptually, the propensity score is the conditional probability that an individual study participant would have been treated based on that individual's observed pretreatment variables. Statistically, propensity score methods require a two-step process in which a logistic regression model is first built to predict the probability ("propensity") of exposure to treatment condition (treatment model). A second model incorporating the information on the propensity score is then constructed to evaluate the exposure-outcome association (outcome model). Statistical adjustments using the estimated propensity score have the advantageous property of balancing observed covariates that were used to construct the score, thus producing a situation closer to actual randomization. The propensity score can also be used outside of a model-based approach to compare patients with similar characteristics. The three most common methods for using the estimated propensity score are matching,⁷ regression adjustment,⁸ and weighting (stratification).⁹ Regardless of the technique, the propensity score is calculated the same way.

Patient matching by propensity score is one technique for addressing baseline characteristics. In this method, a propensity score summarizes all measured confounders in a single score, and subjects are then matched by the propensity score. This greatly simplifies the matching of subjects, because patients would otherwise have to be independently matched on all of the covariates, an endeavor whose complexity increases with each considered covariate. In regression adjustment based on propensity scores, the propensity score is entered into the

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model as the only confounding variable, in addition to the exposure to treatment, to better estimate the unique effect of the treatment exposure on outcome. Vincent *et al.*² used regression adjustment based on the propensity score in their study. Finally, in weighting or stratification by propensity score, patients are stratified based on their propensity score. Predetermined strata (*e.g.*, quintiles) are used to directly compare treatment and control patients in the same strata. Although each propensity score technique has its own unique advantages, in general they all share the same limitations.

The first and most important limitation of all methods of confounder control such as multivariable logistic regression and propensity score methods is that although they can balance observed baseline covariates between groups, they do nothing to balance *unmeasured* characteristics and confounders. As a result, unlike randomized control trials, propensity score analyses have the limitation that remaining unmeasured confounding variables may still be present, thus leading to biased results. Another limitation of propensity score methods is that the analysis does not “fix” other potential methodologic biases that may exist. For example, in the study by Vincent *et al.*,² patients who received a blood transfusion at any time were matched, based on propensity score, with patients who did not receive a blood transfusion. Because blood transfusions could have occurred at any time, the design could have taken into account the fact that transfusions are a time-dependent variable. For example, consider two patients, one who died on postoperative day 1 without receiving transfused blood and one who received an initial blood transfusion on postoperative day 4 and subsequently died within hours after the transfusion. If these patients were selected as a matched pair for the proportional hazards regression analysis, when evaluating this matched set it would seem that transfusing blood improved survival because the patient who received a blood transfusion survived 4 days, whereas the patient who did not only survived 1 day. To overcome this potential bias, the matched control for each case would have necessarily been selected from the pool of nontransfused patients who survived at least until the day at which the transfused patient received his or her first blood transfusion. Other problems with propensity score analysis have been identified, in-

cluding the performance of the technique under certain conditions, such as when there are seven or fewer events per confounding variable.¹⁰ As a result, it is unclear which adjustment method is most preferable for each given situation. This, coupled with perceived opacity of the statistical process, results in propensity score analysis having a very “black box” feeling about it.

Evidence-based medicine has been established as a cornerstone of good medical practice and as a method to improve patient care. Ideally, evidence-based medicine should be based on prospective, randomized, blinded trials. Frequently, these trials are not available and we must use observational trial data that has been modified by statistical analysis such as propensity analysis. It is imperative that we understand the strengths and weakness of these statistical techniques to improve the care of our patients. Therefore, the limitations discussed above suggest that the results reported by Vincent *et al.*² must be interpreted with caution.

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Radicular Low Back Pain

What Have We Learned from Recent Animal Research?

BACK pain affects 50–80% of adults at some point in their lives; the cause is unknown in approximately 85% of the cases.¹ However, mechanical deformation of the dorsal root ganglion (DRG) and its nerve roots is a possible consequence of certain disorders, such as spinal stenosis, disc herniation, degenerative disorder, spinal injury, or tumors.² Recently, it was discovered that radicular pain behaviors such as thermal hyperalgesia and mechanical allodynia develop in rats after a chronic compression injury of the ipsilateral DRG (chronic compression model [CCD]) produced by the implantation of a metal rod in the intervertebral foramen.^{3,4} Ectopic discharges originating in the compressed ganglion were electrophysiologically recorded from dorsal root fibers and from the somata of the DRG neurons.³⁻⁵ This suggests that anatomic abnormalities are an important factor in the development of radicular back pain. In the current issue of ANESTHESIOLOGY, Gu *et al.*⁶ describe a modified CCD model created by compressing the DRG with SURGIFLO™ (Johnson & Johnson, Somerville, NJ), a hemostatic gelatin matrix. SURGIFLO™ hardens within a minute or two after injection and has been extensively and safely used in surgical operations. Rats subjected to DRG compression with SURGIFLO™ develop thermal hyperalgesia and mechanical allodynia that last more than 30 days. The benefit of using the biologically degradable SURGIFLO™ as compared with a metal rod is that the texture of the SURGIFLO™ is similar to that of herniated disc and thus it can better mimic some clinical conditions.

Inflammatory responses in the compressed DRG play key roles in the development of radicular pain. In their study, Gu *et al.* demonstrated that the level of an inflammatory marker ($\text{I}\kappa\beta\text{-}\alpha$) was up-regulated in both the compressed DRG and the adjacent spinal cord. Epidural administration of the corticosteroid triamcinolone effectively reduced the increased cutaneous sensitivity in the SURGIFLO™ CCD rats, suggesting an important role of inflammation in the development of the painful behaviors in this model. Consistent with findings from the study of Gu *et al.*, Homma *et*

*al.*⁷ reported previously in a modified CCD model that DRG compression-induced mechanical allodynia can be partially blocked by simultaneous local administration of soluble tumor necrosis factor- α receptors to the compressed DRG. Local application of inflammatory cytokine, tumor necrosis factor α , to a normal DRG, on the other hand, induced mechanical allodynia similar to that of CCD rats. In another study, White *et al.*⁸ demonstrated increased expression of a chemokine, monocyte chemoattractant protein 1 and its receptor, chemokine (c-c motif) receptor 2, in the compressed DRG. Application of monocyte chemoattractant protein 1 to the cell bodies of the intact formerly compressed DRG produced potent excitatory effects not observed in control ganglia.

Clinically, the severity of pain may not correlate with the degree of disc herniation or mechanical deformation of the DRG. There is a subgroup of patients with lumbar radiculopathy who have minimal abnormality of the external morphology of the annulus and yet present with leg pain, paresthesias, and signs of dural irritation. Corticosteroids may have a dramatic effect on the pain of patients with either major or minor morphologic disc abnormalities, but no structural changes accompany their clinical improvement.⁹ Therefore, inflammatory irritation *per se* (i.e., in the absence of mechanical compression) is sufficient to cause radicular back pain. In laboratory animals, radiculopathy can occur when the DRGs are inflamed by mere exposure to materials released from the nucleus pulposus,¹⁰ which is known to possess immunogenic and chemogenic capacities.¹¹ To examine inflammation as the cause of radiculopathy, Xie *et al.*¹² recently developed a rat model of radicular pain by local inflammatory irritation of the DRG (localized inflammation model). The localized inflammation model involves depositing a drop of the immune activator zymosan over a single DRG. This results in a robust, prolonged state of mechanical allodynia, generation of ectopic discharges, extensive sympathetic sprouting, and elevation of inflammatory cytokines in the inflamed DRG.

Gu *et al.* also demonstrated an up-regulation of the *N*-methyl-D-aspartate receptor, NR1, in compressed ganglia and the adjacent spinal dorsal horn. *N*-methyl-D-aspartate receptors are known to play important roles in various pathologic pain states resulting from peripheral nerve injury, because of their involvement in central sensitization. Results from the current study demonstrated for the first time that *N*-methyl-D-aspartate receptors in the spinal cord and the injured DRG may be a contributing factor in radicular pain, although further study is necessary to prove that increased NR1 expression is related to the pain behaviors.

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In summary, laboratory and clinical studies have suggested that both mechanical deformation and inflammatory irritation of sensory ganglia are involved in radicular low back pain. Gu *et al.* have developed a modified CCD model that may help in studying radicular back pain. In addition, they have provided new evidence supporting a major role of inflammatory responses in the development of radicular pain. Further studies are needed to explore the exact mechanism of radicular pain in disc herniation and CCD models.

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Paradoxical Effects of Midazolam in the Very Young

MIDAZOLAM is a ubiquitously used benzodiazepine in hospital settings. It is an effective premedicant producing anxiolysis and anterograde amnesia. Although used in infants and children widely, new scientific understanding of the developing central nervous system prompts reevaluation of use of midazolam in the very young. This month's *ANESTHESIOLOGY* highlights ongoing work examining the response of the developing brain to midazolam. In contrast to the well-described effects of midazolam in the adult, Koch *et al.*¹ report that "midazolam dose-dependently decreased mechanical thresholds and increased mechanical and thermal reflex magnitudes" in neonatal rats. The experimental design permitted the conclusion that the differences seen in neonatal rats were mediated supraspinally, and very young rats demonstrated no sedation to midazolam as assessed by latency of the righting reflex.

In their article, Koch *et al.* examined the effect of midazolam (a positive allosteric modulator of the γ -aminobutyric acid

type A [GABA_A] receptor) administered to rats in a wide dose range and over an age range from immediate newborn to postnatal day 40, the equivalent in age of an adolescent human. The animals were tested for mechanical withdrawal thresholds, mechanical and thermal reflex threshold size, and level of sedation. In the youngest animals, midazolam elicited a reduced mechanical threshold (greater sensitivity to touch and possibly pain). In the older animals, midazolam had no effect on withdrawal thresholds. The investigators also tested animals using the righting reflex to evaluate the sedative properties of midazolam. The youngest animals (postnatal day 3) were able to right themselves as quickly after midazolam as they did before treatment; however, older animals demonstrated an increased latency to right themselves after midazolam. The youngest animals were not sedated, whereas older animals were as expected.

The current article raises our level of understanding regarding the use of a common sedative (midazolam) in very young rodents. These animals demonstrated either insensitivity or paradoxical effects of midazolam in the youngest animals. These are not common observations (but have been anecdotally reported) in the clinical arena working with human infants. We routinely do see a sedative effect of midazolam even in young children. However, the doses prescribed to sedate a young child might be equal to or greater than what we routinely use in adults as a premedicant to anesthesia. Tolerance also seems to develop rapidly in young children, and dose escalations are common when used as continuous intravenous infusions in intensive care units. The

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current scientific report may help to explain these observations, which are not in our literature to any great degree.

The developing brain experiences significant and rapid growth and synaptogenesis in the first years of life. The balance of neurotransmitters in the developing brain is not similar to the more mature central nervous system. This period of increased central nervous system activity is associated with a higher propensity of seizure activity and of adaptive neuroplasticity after injury. The effect of any centrally acting drug in developing systems cannot necessarily be predicted by observations in the adult. Recently demonstrated developmental shift in the regulation of the chloride transporters in the rat central nervous system has been suggested to explain the excitatory effects of GABA and GABA-mimetic agents in early life.²

Parallel observations of differing age-associated sensitivity to the volatile anesthetics have been made. In children, minimum alveolar concentration of volatile anesthetics is consistently higher than reported values in adults. Although the volatile agents do not necessarily work by a uniform mechanism of action, the GABA_A receptor is likely involved. Is the observation of reduced sensitivity to volatile agents also due to developmental differences in the brain with excitatory activity of GABA_A receptors? Is synaptogenesis so robust, or is there a lack of inhibitory activity in the developing brain that underscores these observations? We may now have at least one well-established target to understanding developmental differences noted in our youngest patients.

Developmental pharmacology has been an important theme of scholarship and discussion in the journal over the past many decades. Clinically, doses of midazolam used in infants and children often exceed doses (mg/kg) used in adults, sometimes by many-fold. Infants and children have higher basal metabolic rates and cardiac indices as well as differences in pharmacokinetics for many agents when compared with adults. The application of observations made in adult patients or subjects does not always translate to an anticipated therapeutic effect when prescribing pharmaceuticals to younger patients. With new investigations evaluating agents in developmental models, we are discovering paradoxical effects in contrast to previous work in adult subjects. US National Institutes of Health-funded research applications are required to address issues of developmental and sex-related differences in the proposed research.

Regulatory requirements (US Food and Drug Administration) limit the description of a pharmaceutical agent to its demonstrated “safe and effective” applications. Therefore, when an agent has not been studied in a specific population, no recommendation can be made as to whether the drug may be safely used.

There have been increasing reports of “off-label” use of new, and not so new, pharmacologic agents in children

during anesthesia and sedation. These have significant implications for children with whom we work. For example, fentanyl is now used in many institutions *via* the intranasal route following its initial description.³ Many reports of the introduction of dexmedetomidine use in children were published in 2006. Although we take responsibility for prescribing these drugs and in reviewing the merit of clinical reports in the journal, off-label use is common but unregulated (except in clinical trials research).

The current article provides us with a well-designed trial examining multiple different effects of midazolam, including a generalized sedation evaluation, afferent sensitivity to mechanical stimulation, and integrated responses to mechanical and thermal stimulation. The rodent model poses a great opportunity for us to continue to advance our comprehension of developmental pharmacology. With recent work examining possible widespread neurodegeneration after common anesthetic exposure,⁴ more work is still necessary. Although clinically useful in isolated doses, should midazolam be evaluated for possibly hypersensitizing preterm and full-term newborns to stimuli? Does the magnitude of possible hypersensitivity increase with continuous use of midazolam as an intravenous sedative in intensive care units? Should midazolam be avoided in the very young? Does the rodent model predict actual responses in humans?

As we acquire new scientific information regarding our pharmaceuticals, we should expect some thoughtful introspection of our practice. Although we believe anesthesia and analgesia are meritorious in young infants, we should be willing to examine scientific information, propose new translational studies, and improve our clinical practice. Rodent and nonhuman primate models will certainly be important in developing new pharmaceuticals and identifying the possible benefits and hazards to our young population. This study is a welcome addition to our current knowledge in developmental pharmacology.

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