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Special Issue on Plasticity in Postoperative Pain

Select Reports from the Journal-sponsored Symposium

IN this issue of the Journal, we present the third annual special issue. This special issue includes select peer-reviewed manuscripts of studies presented as poster abstracts at the 14th ANESTHESIOLOGY-sponsored symposium at the annual meeting of the American Society of Anesthesiologists, October 2005. We feature six original research reports and a Clinical Concepts and Commentary article related to the topic of the symposium, "Plasticity in Postoperative Pain." The Journal Editorial Board considered this topic to be timely because we are in the midst of the Decade of Pain Control and Research. This "decade," declared by the U.S. Congress in the fall of 2000, is aimed at stimulating further progress in research, education, and clinical management of pain in the new millennium. This is only the second congressionally declared medical decade and follows the Decade of the Brain in the 1990s.

Webster's defines *plasticity* as "the capability of being molded." In neuroscience, *plasticity* is the term used to denote the dynamic functional and/or anatomical changes occurring in the nervous system as a result of an injury or disease. Plasticity occurs not only in the neural pathways damaged directly, but also in undamaged pathways in the peripheral and central nervous systems[1,2] as part of a compensatory reorganization. With regard to postoperative pain, the relevant mechanisms are processes whereby tissue injury increases the responsiveness of the sensory system so that subsequent stimuli have an enhanced effect—a phenomenon termed *sensitization*. The Journal symposium examined the advances in our understanding of the plastic changes that occur in the peripheral and central nervous systems as a result of surgery, how these mechanisms may contribute to postoperative pain, and how anesthesia and acute perioperative pain management may influence this plasticity.

The major goals in optimizing postoperative pain management include achieving a pain-free state with minimal drug-related adverse effects, facilitating early rehabilitation and discharge from the hospital, identifying patients likely to develop chronic pain states, and establishing effective preventative therapies for this population. We now recognize that postoperative pain is not just a transient uncomfortable experience to the patient, but can have far-reaching long-term sequelae.[3] The development of animal models of incisional pain[4] has helped considerably in understanding the pathophysiological mechanisms of postoperative pain. A better understanding of these neural changes and their regulation is important in designing strategies to hasten and improve functional recovery in our patients and to minimize the development of chronic pain states after surgery.[5,6]

Challenges in the pain field include translation from animal models to identification of novel targets for drug development for humans and developing strategies that lead to improvements in patient care. Toward this goal, the symposium featured presentations that reviewed advances in the basic science and clinical arenas. Timothy Brennan, Ph.D., M.D. (Associate Professor of Anesthesia and Pharmacology, University of Iowa, Iowa City, Iowa), discussed the "Peripheral and Central Plasticity in an Animal Model of Incisional Pain" and Gary Strichartz, Ph.D. (Professor of Anesthesia, Pharmacology and Biophysics, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts), reviewed "Pharmacological Studies on Preventing or Modulating the Plastic Changes in Experimental Models of Incisional Pain." Additional presentations on "Clinical Evidence for Neural Plasticity in the Postoperative Period: Its Relevance and Modulation" and "Persistent Pain following Surgery: Neurobiological Mechanisms" were made by Troels Jensen, M.D., Ph.D. (Professor of Neurology, Aarhus University and Danish Pain Research Center, Aarhus, Denmark), and Henrik Kehlet, M.D., Ph.D. (Professor of Surgery, The Juliane Marie Center, Rigshospitalet, Copenhagen, Denmark), respectively. Dr. Brennan discussed the 11 poster abstracts selected for presentation at the symposium. All of these 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.

Authors of abstracts submitted to the symposium were encouraged to submit a manuscript for consideration in the special issue. Six of the submitted articles were selected for publication. The published articles describe factors predicting postoperative pain in patients, the sites of action and roles of cyclooxygenase products, and the synaptic physiology of incisions. A Clinical Concepts and Commentary on postthoracotomy pain was solic-

Additional material related to this article can be found on the ANESTHESIOLOGY Web site. Go to http://www.anesthesiology.org, click on Enhancements Index, and then scroll down to find the appropriate article and link. Supplementary material can also be accessed on the Web by clicking on the "ArticlePlus" link either in the Table of Contents or at the top of the HTML version of the article.

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ited. We deeply appreciate the help of our panel of reviewers for their expedited reviews of the manuscripts submitted for this special issue. We also thank Barbara Bewyer (Managing Editor, ANESTHESIOLOGY) and her editorial staff, who not only played a significant role in the planning and organizing of the Journal symposium, but also in the timely publication of this issue.

The topic of the next Journal symposium at the annual meeting of the Society at Chicago in October 2006 will be "Postoperative Cognitive Dysfunction," organized by Michael M. Todd, M.D. (Editor-in-Chief, ANESTHESIOLOGY; Head, Department of Anesthesia, The University of Iowa, Iowa City, Iowa), and Mervyn Maze, M.B., Ch.B. (Editor, ANESTHESIOLOGY; Professor, Sir Ivan Magill Department of Anesthetics, Chelsea and Westminster Hospital, London, England, United Kingdom). We invite you all to participate in the symposium and to submit your work related to the topic to be considered for inclusion in the symposium at the next annual meeting of the American Society of Anesthesiologists. The Journal hopes to continue this tradition of publishing a special issue dedicated to the subject of the symposium.

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Obesity and Diabetes

Evidence of Increased Perioperative Risk?

WE are in the midst of an epidemic of obesity.[1] Its prevalence has more than doubled over the past 15 years. A consequence of this is the progressive increase in the number of patients undergoing surgery related to medical complications of obesity—in particular weight loss (bariatric), cardiac, and orthopaedic surgery.[2] Although an emerging body of evidence details the practical perioperative management of morbidly obese patients,[3] we have little epidemiologic data with which to assess perioperative risk and few available risk-reduction interventions. In the area of cardiac surgery, one large cohort study reported increased perioperative risk in obese patients undergoing coronary artery bypass surgery,[4] whereas another study found different conclusions.[5] Therefore, the question remains unanswered.

Obese patients are frequently diabetic. Diabetes itself has been associated with increased perioperative risk in cardiac surgery.[6,7] Poor glycemic control further worsens risk.[8] Importantly, there has been increased attention to the importance of glycemic control in cardiac surgery patients. This may be one means of modifying perioperative risk.[9] In this issue of the Journal, Wei Pan and colleagues used a retrospective analysis of nearly 10,000 patients at Texas Heart Institute over a 10-year period to study the interaction between obesity and diabetes.[10] Patients were subdivided on the basis of body mass index into overweight-obese and normal weight, and into diabetic and nondiabetic. Obese patients were significantly younger than normal-weight patients at the time of surgery, in line with previous similar studies. The diagnosis of diabetes was based on admission data or therapy. Obesity or diabetes, individually, did not confer additional risk to patients. In contrast, obesity and diabetes (type 1 or type 2) in combination were associated with an elevated risk of postoperative respiratory failure, atrial and ventricular arrhythmias, renal insufficiency, and leg wound infections.

With any retrospective database analysis, it is important to determine if the question being asked (and the association being investigated) has biologic plausibility. Obesity is a heterogeneous disorder characterized by excessive energy intake. There seem to be two separate subsets of obese individuals. One group has been termed *the metabolically healthy, but obese*.[11] Of greater interest

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are the metabolically obese. These individuals may be of normal weight or obese but are linked by the presence of a constellation of abnormalities that has been termed the *metabolic syndrome*. This is characterized by hyperglycemia with insulin resistance (including type 2 diabetes), hypertension, central/visceral obesity, and dyslipidemia characterized by high triglycerides and low high-density lipoproteins. This patient population is known to be at elevated risk for long-term cardiovascular events.[12–14]

Adipose tissue, and in particular visceral fat, is an endocrine, paracrine, and immunologic organ. Obesity is a state of chronic inflammation.[15] Insulin is an antiinflammatory hormone. Increased circulating free fatty acids, derived from highly metabolic visceral fat, can cause insulin resistance and promote hepatic steatosis. Tissue macrophages invade adipose tissue and release tumor necrosis factor α. This, in turn, causes the release of interleukin 1, interleukin 6, and other cytokines. There is an alteration in the relative concentrations of adipose-derived hormones, collectively known as *adipokines*. Leptin, the first adipokine described, is involved in the control of satiety and is markedly proinflammatory. Leptin levels are raised in patients with the metabolic syndrome. Conversely adiponectin, which is thought to be antiinflammatory and enhances insulin sensitivity, is reduced in these patients. Resistin, an adipokine that antagonizes insulin, is elevated in the metabolic syndrome. Hence, the metabolic syndrome produces an inflammatory picture analogous to low-grade sepsis. Interestingly, there are preliminary data that this adipokine picture is associated with an increase in the risk of myocardial ischemia.[16] Recent studies have highlighted the contribution of inflammation to myocardial ischemia and infarction.[17,18] One would anticipate that the combination of inflammation, the metabolic syndrome, and perioperative stress would have a significant impact on perioperative morbidity and mortality. Long-term therapy for metabolic syndrome includes lifestyle modification, weight loss, tight control of hypertension and diabetes, β blockade, statin, and perhaps fibrate administration, nicotinic acid, and thiazolidinedione (insulin sensitizer) therapy.[19,20]

What of the perioperative care of patients with metabolic syndrome? There are surprisingly few available data in this setting. One would presume that, as in the general population, patients with this cluster of risk factors would be at increased risk. The absence of such data relates to the low level of recognition of the metabolic syndrome, confusion regarding diagnostic criteria, and ongoing controversy about the validity of the disorder itself.

So how does the current study add to the growing body of literature on the perioperative risk of both diabetes and obesity? Caution must be taken by clinicians in embracing these data. The study is a retrospective analysis of cumulative data over 10 years. During this period, there were considerable changes in the type of patient undergoing cardiac surgery, the nature of the cardiac disease, and the quality and organization of postoperative care. Moreover, the diagnosis of diabetes was based on chart data, not rigorous evaluation. Type 1 and type 2 diabetes were treated as a single disorder. Undoubtedly, the nonobese group contained undiagnosed diabetics and normal-weight, metabolically obese patients. The authors do not inform us of their criteria for diagnosing respiratory failure or renal insufficiency; indeed, there is little consensus on the criteria for these diagnoses in the literature.

We note that data are presented comparing nondiabetic obese patients with normal-weight patients and comparing diabetic obese patients with normal-weight diabetics. No data are presented comparing diabetic obese and diabetic nonobese patients. Without this comparison, it is difficult to draw conclusions regarding the cause of increased risk.

No large prospective study of perioperative risk in obese patients or in those with metabolic syndrome has been performed. Smaller studies of both obesity and cardiac surgery have failed to demonstrate adverse outcomes.[5,21–23] In the absence of blinding or standardization of anesthesia techniques, as in studies that have failed to demonstrate increased difficulty with intubation in this patient population, it is impossible to discount Hawthorne effects.

Where does this lead? Proponents of tight glycemic control will suggest rigorous control of blood sugar with insulin in this patient population.[24] Insulin has significant antiinflammatory properties.[25] Insulin seems to be cardioprotective in the presence of ischemia.[9,26] Insulin therapy in perioperative and, in particular, cardiothoracic surgical patients was associated with a significant reduction in the risk of death.[27] Enthusiasm for insulin therapy, rather than glycemic control, must be tempered by the knowledge that increased insulin administration is positively associated with death in the intensive care unit regardless of the prevailing blood glucose level.[28] In addition, it remains unclear whether these data may be applicable in other clinical situations.

The combination of obesity and diabetes is associated with increased perioperative risk. We would like to see future epidemiologic studies that differentiate patients, obese and nonobese, with the metabolic syndrome from those without. We would like to see studies that differentiate those with type 1 diabetes from those with type 2 diabetes. We would like to see prospective studies of perioperative care of patients with the metabolic syndrome randomized, for example, to receive antiadrenergic therapy, statins, tight glycemic control, or insulin sensitizers. However, if this relationship holds true, then the importance of one nonmodifiable risk factor (obesity) may be mitigated if tighter glycemic control in diabetic patients does modify perioperative risk.

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Anesthesia in Silico

THE rapid pace of advancement in understanding anesthetic mechanisms of action—from the molecular level to macroscopic measures of human brain function—have coalesced this month in a paper using molecular level anesthetic effects to drive a mathematical model of cortical neuron responses.[1] This model nicely replicates human electroencephalograph patterns produced by volatile anesthetics, even when mixed with intravenous agents. We hope that this advance from the Steyn-Ross group will encourage further use of computational models in studies of anesthetic mechanisms and cortical brain states.

A wide range of neural network models have been developed to simulate brain function, and some models have been particularly successful in modeling cortical level processing in the visual and auditory systems. Many of these models consist of large-scale networks with complex structures that require a great deal of computing time using large-scale computers, and often the output is difficult to interpret.[2–5] In contrast, mean-field models using coarse-grained time equations were created to approximate neuronal function, to minimize the complexity of cortical simulations, and to reduce computational time.[6] These models allow more tractable simulations of specific features of a network, and the output can be as simple as a simulated electroencepha-

This Editorial View accompanies the following article: Wilson MT, Sleigh JW, Steyn-Ross DA, Steyn-Ross ML: General anesthetic-induced seizures can be explained by a mean-field model of cortical dynamics. ANESTHESIOLOGY 2006; 104:588–93.

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logram signal. These reduced models, like the one used by the Steyn-Ross group, seem to offer powerful and directed simulations of specific aspects of cortical function, including neural responses to pharmacological manipulation.

The "mean-field" model used by the Steyn-Ross group was based on realistic neuronal parameters—reasonable values for resting membrane potentials, synaptic connections among inhibitory and excitatory cortical neurons, as well as anesthetic concentration-dependent effects on molecular and cellular drug targets. The output from this model is an electroencephalogram-like signal that appears to be similar to those seen in normal humans.[7] When the model is anesthetized with volatile anesthetics, a concentration-dependent profile of effects are seen, and this study specifically addressed seizure-like effects produced by the ethers isoflurane and especially enflurane. The model was anesthetized by changing neuronal input parameters based on data from quantitative measures of anesthetic effects on γ-aminobutyric acid and *N*-methyl-D-aspartate synapses. With only these limited changes, the model was able to reproduce accurately ether-induced seizure electroencephalogram responses and even predicted the greater efficacy of enflurane *versus* isoflurane for burst activity observed during anesthesia. Thus, this model has confirmed earlier hypotheses about enflurane's propensity for producing seizures that were based on neurophysiological findings.[8,9]

Of course, the scope of the model is limited, and there is room for improvement in the output behavior. The electroencephalogram signals generated by the model agree in general with brain recordings, but lack subtle features evident in real signals.[7,10,11] For example, at low anesthetic concentrations, the model correctly produces an increased amplitude of electroencephalogram responses, but fails to replicate some of the frequency slowing that occurs in actual recordings of anesthetic effects. At higher concentrations, the seizure electroencephalogram patterns generated by the model are highly simplified and stereotypic compared with complex patterns of burst-suppression and seizure discharge seen in real electroencephalogram recordings. However, the robustness with which the model reproduces major anesthetic-induced electroencephalogram transitions is encouraging. No doubt, some of the more subtle anesthetic effects on output will emerge when additional anesthetic sites of action are included in the model.

What additional anesthetic sites of action could we add to improve this model? If you ask 10 anesthesia researchers this question, you will likely receive more than 20 sites that need to be considered; however, there are three key neurophysiological processes that, if included in the model, would help to generate more realistic anesthetic-induced electroencephalogram output responses. First, a mechanism to trigger bursts using the well-documented buildup of excitatory synaptic inputs should be addressed.[10,11] This could include dynamic changes in inhibitory interactions among inhibitory interneurons, which lead to disinhibition of cortical circuits. Anesthetic-enhanced γ-aminobutyric acid inhibition of connected pairs of inhibitory interneurons[12] may help drive the barrages of excitatory postsynaptic potentials that initiate synchronized burst discharges in cortical neurons. A second important element to emphasize further in the model is the prolongation of both γ-aminobutyric acid receptor type A slow and fast inhibitory postsynaptic potential, because these have been shown to contribute to a slowing of electroencephalogram frequencies.[13] This would result in the large amplitude slow wave (δ 0.5–3.0 Hz) activity that is produced by many anesthetics—a much stronger effect than the model output currently exhibits. Finally, the present model needs to incorporate shunting of both excitatory and inhibitory synaptic inputs throughout the cortical circuitry. At present, inhibition is modeled as a change in membrane potential (hyperpolarization); however, a good deal of enhanced inhibition (*i.e.*, *via* tonic γ-aminobutyric acid-mediated chloride[14] and two pore-gated potassium conductances[15]) involves membrane resistance decreases that shunt dendritic synaptic inputs with little change in membrane potential. Shunting conductances seem to play important roles in anesthetic inhibition and for terminating burst discharges in cortical neurons.[10,11] Many other important sites of anesthetic action have not yet been incorporated into the mean-field model, such as presynaptic effects to increase γ-aminobutyric acid or to depress glutamate release from nerve terminals,[16–18] and effects on ascending modulatory systems[19,20] and subcortical inputs[21] to the cortical model will need to be explored. Thus, we can expect considerable improvement in the near term from including anesthetic effects on targets that have already been well characterized, to say nothing of improvements to the model that will result from the inclusion of yet undiscovered, perhaps even more important, anesthetic effects on cortical neurons.

A major advantage of this mean-field model is that it provides tools needed to incorporate new data into a mathematical framework that can be used to test hypotheses about anesthetic actions on electroencephalogram responses. The true test of its usefulness will come when predictions based on the model guide experimentalists to fruitful avenues of research. Care must be exercised with this, and all models in their early and incomplete stages, because, in the words of pioneering anesthesiologist John Severinghaus, as relayed to us by Ted Eger II: "To every problem there is a solution; neat, plausible and wrong." To ensure that we have the right solution from the mean-field model, it will be necessary to compare findings using more complex, biologically realistic multisite anesthetic actions.

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