■ CORRESPONDENCE

Pulsed Radiofrequency: A Neurobiologic and Clinical Reality

To the Editor:—First, I would like to congratulate Van Zundert *et al.*[1] for their efforts to elucidate one of the putative mechanisms associated with pulsed radiofrequency (PRF), which may help us to understand its analgesic effect in clinical settings. Unfortunately, the explicit and implicit critique in the editorial by Richebé *et al.*[2] about PRF in general may leave readers not familiar with this technique with a false impression that this modality is all but a speculative, experimental treatment.

The use of PRF is not taken lightly. Last year, more than 350 pain specialists from all over the world met on April 24–25, 2004, in Amsterdam for the First European Scientific meeting of the International Spinal Injection Society. During this 2-day meeting, we launched numerous multicenter clinical and basic science research protocols and created the European Collaborative Group for PRF research, while exchanging among us vast accumulated clinical experience. It is therefore that I read with some surprise the unsubstantiated remark that "there has been a mass migration to the use of pulsed radiofrequency with few data to support efficacy of this new technique."[2] I wish to clarify this statement.

In a simple, straightforward, systematic search in MEDLINE®, EMBASE, and Cochrane on PRF, one can generate 269 relevant reports in many fields, including pain medicine. Even by excluding all reports on electrical field research not directly relevant to the nervous system (such as biology, biochemistry, and physics), 38 reports remain available for critical reading. Of these, 1 is a prospective, randomized controlled trial (RCT);[3] 5 are prospective uncontrolled trials; 7 are case series and clinical audits; 18 are letters, comments, and editorials; 7 are neurobiologic reports; and more than 30 are abstracts from important scientific meetings, including my own presentation at the American Society of Anesthesiologists annual meeting on October 11–15, 2003 (A-1090). The accumulation of these data is impressive and shows unequivocally that PRF is a genuine neurobiologic and clinical phenomenon and is different when compared with continuous radiofrequency (also known as thermocoagulation).[4] Although the clinical advantages of this modality are not yet clear, what is clear is that PRF is not merely a whim of "wishful thinking" for those who practice it. Furthermore, exciting data on the effect of electrical fields on neural substrates suggests that PRF may have positive effects on synaptic strength and long-term potentiation,[5] and if indeed central sensitization and long-term potentiation share similar mechanisms, these findings are of great interest.[6]

My second comment regards the implicit critique "Neurobiology in Need of Clinical Trials,"[2] suggesting that clinical trials are indispensable to determine the utility of PRF and that neurobiology is only of intellectual and theoretical interest. Implying lack of knowledge and thus lack of value to any treatment in the presence of marked variation in response is not a trivial epistemological matter. Causality in conditions of uncertainty require a careful approach to data analysis, and even perfect data synthesis may create "statistical alchemy" devoid of logical thought, resulting in "mega-silliness."[7] Asking the question "Does PRF work, or does PRF cause pain relief in patients?" is like asking what caused the fire in a house that was burned down as a result of a lit candle, a piece of paper, an open window, a strong wind, and the fact that the house was wooden. This situation, known in philosophy as INUS (insufficient nonredundant component of unnecessary sufficient complex), means in lay terms that by analyzing each component, none of them is a single sufficient cause, but their conjunction gives origin to an overall sufficient result.[8] That is, assuming a hierarchy of causes that can be proved by a hierarchy of evidences, as evidence-based medicine (EBM) pretends, in conditions of uncertainty is at best misleading and at worst simply incorrect.

Current knowledge is fallible, EBM is limited by its probabilistic nature, and knowledge and evidence are not interchangeable terms. RCTs may sometimes be difficult or unattainable for methodologic or ethical reasons, and one must not forget that the decision to "downgrade" other forms of knowledge, as suggested by the editors in the spirit of EBM (such as clinical audits and basic science experiments), is a decision, not a truism. Systematic reviews may as well be victim to publication bias sullied by commercial influence, sponsorship pressures, and forces beyond control of reviewers. Reviews may suffer from poor delineation of references, simplistic concepts of pathophysiology, and the thought that stand-alone therapies (such as PRF) can be the cause of pain relief. Therefore, I argue that just as "basic scientific studies in the neurobiology of pain models and analgesic techniques are not a substitute for randomized controlled clinical trials,"[2] RCTs are not a substitute for knowledge. EBM is only a methodologic solution to clinical epistemology, and it is blind to and disinterested in mechanisms of explanation and causation. EBM does not test causal hypotheses but merely establishes correlations or contributes to probability kinematics of various degrees of belief.[9]

Finally, science is about discovering, recognizing, and changing paradigms, and that is the beauty of the PRF story that I think should be told. For years, heat has been thought to be the cause of pain relief in radiofrequency lesioning, until the ingenuity of Professor Sluijter and others suggested that perhaps it is only an epi-phoneme, and it is the electrical fields that are responsible for the analgesic effect. Saying (again) that we need to perform RCTs is too easy, and perhaps methodologic modesty is the order of the day.

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(Accepted for publication May 17, 2005.)

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A Comment on the History of the Pulsed Radiofrequency Technique for Pain Therapy

To the Editor:—As one of the inventors of the pulsed radiofrequency technique for pain therapy, I disagree with the Editorial View of the history of this technique.[1] The authors state that the history was based on a "personal written communication" from William Rittman, M.S. (Principal, RF Medical Devices, Middleton, MA). The editorial stated that there was a chance meeting at a 1995 scientific conference in Austria between Mr. Rittman and Menno Sluijter, M.D., Ph.D. (Professor Emeritus, Department of Anesthesia, Maastricht University, Maastricht, Netherlands), and a Soviet-bloc scientist, and

> this scientist challenged the conventional belief that pain relief after radiofrequency treatment was a result of tissue destruction, suggesting that pain relief could result from the strong magnetic fields induced by voltage fluctuations in the area of treatment. Mr. Rittman returned to the bench and quickly devised a means of creating the same high-voltage fluctuations without any heating at the tip of the needle by using pulses of electrical current rather that continuous current. Dr. Sluijter immediately introduced the technique into clinical practice . . .

In my opinion, Mr. Rittman's view of the history of pulsed radiofrequency, as described in the editorial, is factually incorrect and misleading, and ignores the roles that Dr. Sluijter and I played in it. I give my view of the history here.

I was the scientific director of all radiofrequency generators and radiofrequency electrodes built at Radionics since 1970, including the first pulsed radiofrequency unit in 1995. I was also the overall director of Radionics. Mr. Rittman reported to me, and I was aware of all research he was doing. I was the main contact at Radionics with Dr. Sluijter, with whom I had worked closely since 1977. Therefore, I know the history well.

After the meeting with the Soviet-bloc scientist, Dr. Sluijter and Mr. Rittman were intrigued by his magnetic field idea and discussed it with me. I made quantitative estimates that magnetic field effects are negligible for our parameter range and that only the electrical field could possibly produce biologic effects to reduce pain, outside of the known radiofrequency heating effects. To test the magnetic field hypothesis, Mr. Rittman suggested disconnecting the reference electrode to isolate the magnetic effect and eliminate electric effects. I again argued that pain relief effects when the reference electrode was disconnected could only arise from either a transient electric field pulse when the radiofrequency is turned on or from capacitively induced radiofrequency electric fields. Dr. Sluijter tried this suggestion on a few patients, and some of them experienced pain relief. However, the percentage of success was not high enough to be convincing.

Dr. Sluijter then called me and suggested making a stream of pulses that might work better than a transient electric field pulse that I had postulated earlier. I liked his idea. Intense discussions followed among Sluijter, Rittman, and myself on an appropriate pulsed radiofrequency waveform that would be practically adaptable to the existing Radionics RFG −3C RF Lesion Generator. Careful attention had to be given to what was possible and safe related to the existing generator's circuits, software, and signal outputs. This led to the specification for the first pulsed radiofrequency generator. The actual design and bench work to build the first pulsed radiofrequency unit in 1995 was not done by Mr. Rittman at all. It was done by two other Radionics engineers: Raymond Fredricks and Jack Thomasian. The unit was sent to Dr. Sluijter, and he did a small patient series with the unit in early 1996. The results were encouraging. At that time, I performed more detailed calculations to prove that the magnetic field near our electrode at our radiofrequency voltages and frequencies is about 1 gauss, approximately equal to the earth's magnetic field. Therefore, the magnetic field is irrelevant. I also calculated that the electric fields and currents are very large, in biologic terms, and are the likely agents to produce the clinical effect observed.

Sluijter, Cosman, Rittman, and van Kleef published the world's first article on pulsed radiofrequency, which included the above work, in *The Pain Clinic* in 1998.[2] A U.S. patent on pulsed radiofrequency for pain therapy was first applied for in June 1996 with the proper inventors: Sluijter, Rittman, and Cosman.[3] Four U.S. patents were eventually issued stemming from that initial patent application.

The discovery of the pulsed radiofrequency technique for pain therapy involved many events, exchanges of ideas among the inventors, and well-thought-out implementations. It was certainly not a quick, solo performance by Mr. Rittman as the editorial portrays.

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(Accepted for publication May 17, 2005.)

Pulsed Radiofrequency

To the Editor:—I read your editorial view on pulsed radiofrequency[1] with great interest. I wish to point out that the narration of the history of pulsed radiofrequency is incorrect.

I remember this period quite clearly. During the meeting in Austria, Professor Sinerik Ayrapetyan, Ph.D., from Yerevan, Armenia, suggested that the clinical effect of radiofrequency could be due to exposure to magnetic fields. In your editorial, it sounds as if this assumption might be right. It is not. The magnetic field at 500,000 Hz is negligible. William Rittman, M.S. (Principal, RF Medical Devices, Middleton, MA), and I did not realize this at that time, but it gave us the idea that the role of heat might be disputable. Mr. Rittman then suggested applying radiofrequency without using a ground lead, thus breaking the circuit. In retrospect, this could only cause a minor biologic effect, but I have tried it. It had an effect in a minority of patients, certainly not enough to follow that road any further.

There was a deadlock then, lasting until approximately 6 months after the Austria meeting. The suggestion that "Mr. Rittman returned to the bench and quickly devised a means . . ." is therefore fantasy. It was a period of intensive interaction about the subject between Professor Eric Cosman, Ph.D. (then director of Radionics [Burlington, MA]), Mr. Rittman, and myself, but we did not find a workable solution, and no

action was taken. Finally, it was my idea to pulse the output of the radiofrequency generator, and it was only then that the deadlock was broken, during the autumn of 1995. An RFG 3C was then adapted to generate the appropriate output. Anecdotally, this museum piece is still in use to treat pain in horses, in a veterinary clinic in Niederlenz, Switzerland. The first clinical application of pulsed radiofrequency was in my practice in Amsterdam, on February 1, 1996.

I read that your information was based on a personal written communication by Mr. Rittman. To put it mildly, I find that an unconventional way to gather information for an editorial in a prestigious journal such as yours. There is nothing against that, provided that the facts are checked. This would have been easy in this case, and it would have prevented you from printing inaccurate information.

Menno E. Sluijter, M.D., Ph.D., Maastricht University, Maastricht, The Netherlands, and Swiss Paraplegic Center, Nottwil, Switzerland. sluijterm@aol.com

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In Reply:—We thank Dr. Cahana for his comments regarding our editorial on pulsed radiofrequency (PRF) treatment.[1] Certainly, basic scientific experiments may help us to understand the analgesic effects of PRF. The caution is in the interpretation of the experiments; that is, PRF does affect sensory pathways in rats. Fos expression induced by PRF does not demonstrate how or whether this procedure may relieve persistent pain in patients. The study does not yet help us to understand its mechanism or justify its use in patients.

In a recent editorial, Rathmell and Carr[2] discussed the difficulties of applying evidence-based medicine in the pain clinic:

> The field of evidence-based medicine endeavors to educate practitioners about how to frame specific questions based on the clinical problems they are faced with every day. The idea is to get the best information available to the practicing clinician. It describes the best available evidence and if there is no good evidence it says so. In pain medicine, we are faced with an expanding array of treatment options that strike us as logical developments that *should* provide pain relief for our patients. However, there is a dearth of clinical evidence to guide rational choice and application of the majority of emerging treatments [such as pulsed radiofrequency]. The evidence-based medicine movement gives little guidance to practitioners whose tools are still under development. They simply remind us that no evidence regarding many of our techniques exists.

Despite Dr. Cahana's blanket condemnation that the knowledge provided through evidence-based medicine is fallible, we are entrenched in the scientific method and will not be fooled by lack of evidence.

The conceptual appeal of a minimally invasive, nondestructive technique such as PRF that can successfully treat any type of chronic pain is compelling.[1] We hope that PRF will be shown to help patients with persistent pain problems through randomized controlled trials. However, there have been many procedures in medicine that were ac-

cepted as helping patients that we no longer perform because placebo-controlled, randomized, controlled trials demonstrated that there was no benefit. Certainly, ligating the internal mammary artery looked as though it relieved angina,[3,4] and arthroscopy for degenerative arthritis of the knee seemed to decrease knee pain.[5] We no longer perform the procedures because placebo-controlled, randomized, controlled trials demonstrated no difference than a sham (incomplete) operation.[6–8] Despite the wealth of anecdotal and uncontrolled evidence available that suggests that PRF is a useful treatment modality, it is up to our specialty and others using the treatment to assume that the procedure may not be truly effective (*e.g.*, perhaps a placebo effect) and to demonstrate using placebo-controlled, randomized, controlled trials that it is beneficial. If it works, its mechanisms should continue to be explored using basic science pain models. Our editorial was written in an effort to help readers understand the state of our knowledge regarding PRF, to suggest that the basic science findings to date in no way support or refute the link between PRF treatment and reduction in pain, and to urge clinical researchers to move on to much-needed controlled trials. Our editorial should not be taken as a blanket condemnation of this technique or the significant efforts of clinical investigators to date to describe their experience with PRF.

For the letters from Drs. Cosman and Sluijter, we are grateful. We thank them for clarifying the history of development of the technique of pulsed radiofrequency, and we apologize for omitting the details they have provided. One of us (J. P. R.) had extensive conversations with Mr. Rittman by telephone and *via* e-mail over a period of several months. I knew I was talking directly to one of the principals involved in developing PRF, and on this fact, all seem to agree. I assumed that all of the patent holders would tell a similar history, and it seems that they do. In closely reading the additional details provided by both Drs. Cosman and Sluijter, it seems I was lacking in detail, but I made no factual errors in my recounting of the history. It was my attempt at brevity that led to the statement "Mr. Rittman returned to the bench

and quickly devised a means . . .”; this was not meant to imply that Mr. Rittman acted alone without many others involved nor that this process did not evolve over time, and Drs. Cosman and Sluijter have filled in these details and given credit to some of the others involved. As to the strong magnetic field *versus* the electrical field being responsible for the biologic effects of PRF, their comments clarify how the original concept was modified based on experimental observation. In the end, my brief account of correspondence with Mr. Rittman and the additional details provided by Drs. Sluijter and Cosman form a seldom-told story about how these innovators were involved in the origins of pulsed radiofrequency treatment that will be of interest to all who are familiar with the technique and historical value as this technique emerges.

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Graphical Display of Data Could Reveal Errors in Statistical Tests

To the Editor:—I read with interest the article about intraoperative remifentanil infusion by Lee *et al.*[1] I have major concerns regarding the nonsignificance of chi-square tests for the behavioral pain score during the first 15 min in the recovery room. The bar representation in their figure 1 is appropriate for expressing these results and clearly shows a different comportment of patients in the two groups. After redoing the analysis by extrapolated number of patients according to bar height, it seems that, as expected, significant activity for chi-square tests is very high at all times studied (table 1). Calculations were made with JMP 5.1 (SAS Institute, Cary, NC). The comment in the text says that 60% of patients in the remifentanil group *versus* 40% in the nitrous oxide group have a behavioral pain score of 0. That does not match the figure in the article. Furthermore, the percentage of total patients exceeds 100% at T5 for the remifentanil group.

If these results are not type errors, we could have question about the morphine titration. In our study,[2] the morphine titration was based essentially on behavioral scale during the first 15 min after extubation, because of the difficulty to have correct pain assessment just based only on the visual analog pain scale score at this moment. Another difference with our study is the use of fentanyl at induction and morphine at skin incision. The time to first dose of morphine does not appear in the results. The authors' conclusion could be right, but the discrepancies in the presented data may alter this finding. Opioid tolerance is not always clinically significant because of patient variability, surgery duration, opioid dosage, or concomitant medication. Graphics can help us to show clinical evidence, and statistical tests are used to confirm and valid ideas revealed by data.[3] The high publication pressure should not deserve statistical review.[4] Analysis and criticism are the guaranties of medical research.

Table 1. Numbers of Patients Classified by Behavioral Pain Scores

Time	T0			T5			T10			T15		
Pain score	0	1	2	0	1	2	0	1	2	0	1	2
N_2O, n	20	5	5	15	9	6	10	14	6	8	20	2
Remifentanil, n	2	13	15	6	10	20	1	4	25	0	8	22
Chi-square	26.1			11.4			26.9			29.2		
P value	< 0.0001			0.003			< 0.0001			< 0.0001		

Pearson chi-square tests ($df = 2$) are calculated at 0, 5, 10, and 15 min after arrival in the recovery room. Pain score: 0 = calm patients with no verbal or behavioral expression of pain; 1 = moderate verbal or behavioral expression of pain; 2 = intense verbal or behavioral expression of pain.

N_2O = nitrous oxide.

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In Reply:—We thank Dr. Guignard for his comments and interest in our article.[1] We have checked figure 1 as presented in the text and found that there was an error in the graphical presentation of this figure. There were higher behavioral pain scores in the first 10 min in patients who had received remifentanil but not at 15 min and, as Dr. Guignard correctly points out, this has not been made clear in the text. For completeness, the tabular data are presented below (table 1), with our statistical analysis using the continuity adjusted chi-square test to analyze the behavioral pain score (statistical software: SAS System for Windows Release 8.02; SAS Institute Inc., Cary, NC).

There was no difference by 15 min and no difference in visual analog pain scale scores. We believe that these differences in the first 10 min relate to pharmacokinetic differences between remifentanil, nitrous oxide, and the titration of drugs at the end of the case because the scores rapidly equilibrated and they are of little significance compared with the main outcome measures of this study. In retrospect, a narrow scoring system such as this may also have limitations in discriminating differences.

There was no difference in the total morphine consumption or the time to the first dose of morphine during the stay in the recovery room. The two groups had similar total morphine consumption in the first 24 h and visual analog pain scale scores at rest and movement. The reported incidence of postoperative nausea and vomiting was 10% in both groups. There was no difference in the sedation scores.

Our main objective was to determine whether the substitution of remifentanil for nitrous oxide, an increasingly common clinical practice, results in acute opioid tolerance. To more tightly control this study, we had to substitute remifentanil for nitrous oxide, as far as possible, while otherwise maintaining a normal standard of care. At our institution, that involves fentanyl coinduction and morphine before skin incision. This is why this occurs in both groups.

Table 1. Numbers of Patients Classified by Behavioral Pain Scores

Time	T0			T5			T10			T15		
Behavioral pain score	0	1	2	0	1	2	0	1	2	0	1	2
N_2O, n	20	5	5	15	9	6	10	14	6	8	20	2
Remifentanil, n	13	14	3	10	20	0	4	25	1	8	21	1
Continuity adjusted chi-square	5.93			10.14			8.55			0.27		
P value	0.052			0.006			0.014			0.87		

N_2O = nitrous oxide.

We apologize for this oversight in the behavioral pain score data presentation but are confident that this does not detract from the principal conclusions of the study.

Libby H. Y. Lee, M.B.B.S., F.H.K.C.A., F.H.K.A.M., Michael G. Irwin, M.B.Ch.B., M.D., F.R.C.A., F.H.K.C.A., F.H.K.A.M.* *University of Hong Kong, Hong Kong. mgirwin@hkucc.hku.hk

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(Accepted for publication June 7, 2005.)

Some Points Regarding Anesthesia for Patients with Congenital Long QT Syndrome

To The Editor:—I read with great interest the article by Kies *et al.*[1] in the January 2005 issue of ANESTHESIOLOGY entitled "Anesthesia for Patients with Congenital Long QT Syndrome." The article is a good review of the subject, but it omits a number of important points regarding the perioperative care of patients with this disease. First, it should be noted that no studies exist comparing the safety of anesthetic agents in long QT syndrome (LQTS). The recommendations are therefore extrapolated from case reports and studies from healthy volunteers. Although isoflurane may indeed shorten the QT interval more than other agents, significant arrhythmias in LQTS patients anesthetized with isoflurane have been reported.[2] A number of reports on this subject[3,4] have noted that the most prevalent factor associated with significant arrhythmias during surgery and anesthesia is the lack of control of symptoms before surgery. Although halothane and ketamine should probably be avoided, patients whose arrhythmias are well controlled before surgery rarely have arrhythmias during surgery, regardless of the anesthetic technique chosen.

Second, Kies *et al.* do acknowledge that different genetic subtypes of LQTS are known to exist. However, optimal treatments of the various subtypes differ in important and significant ways. LQTS types 1 and 2 (LQT-1 and LQT-2) are defects on chromosomes 11 and 7,

respectively, both encoding for potassium transmission. The standard treatment for both has been β-blockade. β-Blockade may, however, be contraindicated in LQT-3 (a defect in sodium transmission), because bradycardia in these patients can further prolong the QT interval and lead to ventricular arrhythmias.[5] In 1991, Moss *et al.*[6] showed that cardiac pacing at a rate sufficient to shorten the QT interval could prove useful in LQTS. This article was written before the genetic subtypes of the condition were known, and the data of Schwartz *et al.*[5] suggest that cardiac pacing might be particularly useful in LQT-3.

Kies *et al.* do mention the possibility of droperidol prolonging the QT interval. However, numerous drugs do the same and should probably be avoided in patients with LQTS. Those likely to be encountered in the operating room include amiodarone, disopyramide, chlorpromazine, dolasetron, haloperidol, tamoxifen, and many others.*

Although genetic testing is still not easily obtainable, it should be noted that it is often possible to distinguish among the various subtypes of LQTS by the electrocardiographic pattern.[7] LQT-1 has a prolonged QT interval with a normal to high T-wave amplitude, a broad-based T wave, and an indistinct T-wave onset. LQT-2 is characterized by a prolonged QT interval, low-amplitude T waves, and bifid T waves in more than 60% of cases. LQT-3 shows a prolonged QT interval with late onset, peaked T waves, and a long, isoelectric ST segment.

Last, despite all efforts, arrhythmic episodes, particularly torsade de pointes, are common in LQTS patients. Kies *et al.* do not give specific recommendations for dealing with such arrhythmias when they occur, but intravenous magnesium; intravenous lidocaine; rapid-acting β-block-

David C. Warltier, M.D., Ph.D., acted as Handling Editor for this exchange.

* A comprehensive listing of such drugs is available at: http://www.torsades.org/druglist.cfm. Accessed January 31, 2005.

ing medications, such as esmolol in LQT-1 and -2; and, in LQT-3 patients, cardiac pacing may be effective, and in all cases, the equipment for emergency electrical defibrillation should be present.

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(Accepted for publication June 14, 2005.)

Volatile Anesthetics and the Long QT Syndrome

To The Editor:—With much interest we read the article by Susan J. Kies *et al.*[1] regarding patients with congenital long QT syndrome (LQTS). We congratulate the authors on their excellent review but would like to discuss several aspects. As stated in the introduction, patients with LQTS often show a "delayed cellular repolarization and heterogeneity in dispersion of repolarization, which . . . can lead to early after-depolarization, further dispersion of repolarization, and the formation of reentry circuits."

It becomes increasingly apparent that the QT interval prolongation *per se* is not the crucial pathology in LQTS. The delayed cellular repolarization in LQTS represents either impaired rapid or slow delayed rectifier potassium currents (i_{Kr} or i_{Ks}) or inappropriately inactivated sodium currents (i_{Na}).[2] The main arrhythmogenic substrate resulting from these altered ion currents is an increase in transmural repolarization heterogeneity. This heterogeneity favors the development of torsade de pointes, which is triggered by early after-depolarizations.[3] More than 300 mutations in six genes encoding cardiac ion channel subunits[4] and ankyrin B[5] have been identified in patients with LQTS. According to the affected ion channel subunit, LQTS is classified into six subtypes with partially different clinical courses and triggers of torsade de pointes. Hence, the clinical and electrophysiologic presentations of the syndrome are considerably heterogeneous, and the effects of different drugs may be unpredictable.[6]

The QT interval obtained by a 12-lead electrocardiogram is only a rough measure of the repolarization time. Diagnosis based solely on summation vectors projected to the body surface is therefore neither sensitive nor specific.[7] Accordingly, studies that only focus on drug effects on the QT interval may produce premature conclusions regarding potential safety or risk of these drugs in LQTS. This explains the contradicting results of numerous investigations, which report different effects of drugs on QT interval. Kies *et al.* recommend isoflurane as volatile anesthetic of choice in LQTS patients. In our opinion, to date, such recommendation cannot be supported. The reported effects of volatile anesthetics on QT interval are inconsistent or even conflicting. Only few studies have focused on QT heterogeneity or ion channel physiology, and it seems that all volatile anesthetics—including isoflurane—interact directly with cardiac delayed rectifier potassium channels.[8–11] We therefore propose to avoid this class of anesthetics and would prefer propofol as the anesthetic of choice until more informa-

tion is available from pharmacologic studies that focus on ion channel physiology and transmural heterogeneity of repolarization. These studies should ideally differentiate between LQTS subtypes.

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(Accepted for publication June 14, 2005.)

In Reply:—We appreciate the commentary and the excellent points raised by Dr. Katz. We apologize for the omission of his excellent case report from our extensive though limited bibliography.[1] It is true, as it

states both in the original article and in Dr. Katz' letter, that our information about anesthetic management of long QT syndrome (LQTS) is derived primarily from case reports and anecdotal data. We

agree thoroughly that preoperative control allows for the optimal intraoperative and postoperative management.

Second, Dr. Katz opines that genetic testing may not be routinely available but that electrocardiogram analysis may offer insight into the genetic subtype. We agree that it is important to elucidate the genetic subtype for treatment purposes. Since the birth of cardiac channelopathies in 1995, LQTS genetic testing has been performed in a few specialized research laboratories. However, clinical genetic testing for LQTS has been available for nearly a year now. Except for perhaps a few expert T-wave morphologists, great caution should be exercised in attempting to genotype based on inspection of the electrocardiogram.

In response to the correspondence from Drs. Rasche and Hübler, we agree that the heterogeneity of repolarization is the prominent feature of LQTS and that the QT interval only relays general information about the effect of anesthetic medications. Although the effect of isoflurane on delayed rectifier potassium ion channels has been shown to be inhibitory at supratherapeutic concentrations and nonphysiologic temperatures, we do not believe that these data warrant the exclusion of isoflurane as an inhaled anesthetic; however, we respect the assertion that a total intravenous anesthetic may be a more conservative approach to use in patients with LQTS.

Susan J. Kies, M.D., Christina M. Pabelick, M.D., Heather A. Hurley, Pharm.D., Roger D. White, M.D., Michael J. Ackerman, M.D., Ph.D.* *Mayo Clinic College of Medicine, Rochester, Minnesota. ackerman.michael@mayo.edu

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(Accepted for publication June 14, 2005.)

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On the Origin of Critical Care Units: A Clarification

To the Editor:—In delivering the 43rd Rovenstine Lecture, "Assessing the Past and Shaping the Future of Anesthesiology," which was reprinted in the May 2005 issue of ANESTHESIOLOGY, Jerome H. Modell, M.D., D.Sc. (Hon) (Professor Emeritus of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida), pays tribute to his many American mentors, friends, and colleagues.[1] Certainly, the credits could be well merited, but in the case of Dr. Thorkild Andersen, they are misplaced. Dr. Modell is correct when he states that "Critical care medicine also is primarily an outgrowth of anesthesiology" but incorrect when he states that it was "Dr. Thorkild Andersen and his colleagues in Copenhagen, Denmark, [who] demonstrated that polio victims could be kept alive if they were intubated and hand ventilated by an anesthesiologist at the bedside." The honor for demonstrating that polio victims were succumbing considerably more frequently from respiratory insufficiency than from overwhelming virus encephalitis belongs solely to another Danish anesthesiologist: Dr. Bjørn Ibsen.[2,3] During the 1952 poliomyelitis epidemic in Denmark, it was he who showed that polio victims, with paralysis of the respiratory or bulbar muscles, could often be kept alive if they were treated as Dr. Modell describes in his Rovenstine lecture. Ibsen's account of events is available, in his own words.[4]

In the short term, the contribution of Bjørn Ibsen was of fundamental importance for the victims of polio. But it was the well-deserved credit he gained from his achievements in the great struggle of the polio epidemic that made it possible for Ibsen to open the first multidisciplinary intensive care unit in the world at the Kommune Hospital in Copenhagen, Denmark, on December 21, 1953.[5]

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(Accepted for publication August 31, 2005.)

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In Reply:—I thank Drs. Berthelsen and Trubuhovich for their input regarding an item that I mentioned in the 2004 Rovenstine Lecture.[1] In that lecture, I was recounting a number of persons that I personally have had the opportunity of working with who were among the pioneers in critical care medicine. I mentioned Dr. Thorkild Andersen, who immigrated to the United States from Copenhagen and who, on multiple occasions, reported to me that in the early 1950s, they treated polio victims with tracheal intubation and hand ventilation because mechanical ventilators were scarce and not readily available to them. My comment was not meant to imply that Dr. Andersen was the first person ever to do this in Denmark or in the United States. I appreciate Drs. Berthelsen and Trubuhovich's pointing out that actually a number of Danish physicians and students used this technique, but it was Dr. Bjørn Ibsen who first described it and is thought to deserve the credit for its introduction. Unfortunately, Dr. Andersen passed away several years ago, so it is not possible for me to go back and find out exactly what his involvement was with the technique. However, clearly, the Danes were pioneers in this field.

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(Accepted for publication August 31, 2005.)

Extended-release Epidural Morphine Formulation Data
Far from Clear

To the Editor:—The article by Viscusi *et al.*[1] describing a novel, extended-release epidural morphine formulation is very informative. However, Dr. Viscusi and his coinvestigators have stacked the deck in favor of their study drug by the way they designed their study and presented the data. Their study calls for patients undergoing hip arthroplasty to receive either general or spinal anesthesia; furthermore, median times to first postoperative use of patient-controlled analgesia (PCA) fentanyl were compared. Without knowing who received spinal anesthesia and the duration of the spinal blockade, median times to first postoperative use of PCA fentanyl cannot be interpreted, and neither can the total narcotics use in 24 or 48 h. The study also limited intraoperative use of intravenous fentanyl to 250 μg per patient, clearly an inadequate dose for a hip arthroplasty in the general anesthesia group, and disallowed the use of any other pain medication. By artificially prohibiting the control group from receiving adequate amounts of analgesics, it is no surprise that both surgeons and patients were more satisfied if the study drug, the extended-release epidural morphine, was also administered. Figure 3 of the article shows some patients needing as much as 2,500 μg fentanyl in the first 24 h. Programming intravenous PCA fentanyl, a narcotic not commonly used for postoperative pain control after hip arthroplasty, and limiting the doses at 10–20 μg with a lockout interval of 6 min then can be interpreted as some patients almost constantly pressing their PCA buttons and never achieving adequate pain relief. Extended-release epidural morphine is an interesting formulation; however, it has a higher side effect as demonstrated by 12.5% of patients needing opioid antagonist in the study group *versus* 0% in the control group. Moreover, it is far from clear from the presented data that it is superior to the present-day pain management of post–hip arthroplasty patients with adequate doses of intravenous PCA morphine plus or minus conventional epidural.

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In Reply:—Dr. Roboubi's comments reflect a number of common misconceptions regarding clinical trials of new therapeutics. Our study was a placebo-controlled, randomized, double-blind study, which is considered the gold standard for assessing the safety and efficacy of a new single-therapeutic agent such as extended-release epidural morphine (EREM; DepoDur™; Endo Pharmaceuticals Inc., Chadds Ford, PA).[1] Several other features of the trial are also intrinsic to the drug development process: the dose-finding nature of the study (including doses that may never be approved) and the requirement that EREM demonstrate efficacy as a single agent.

Therefore, Dr. Roboubi's comment regarding differences in general or regional anesthesia reflects a lack of understanding regarding patient randomization. The patient randomization was stratified such that the number of patients receiving general and regional anesthesia was evenly distributed across treatment groups. Had there been differences between patients receiving these two techniques, the effects of randomization would control for such differences, as would be true for other patient variables (*e.g.*, sex, age). However, there were no meaningful differences in the amounts of intravenous patient-controlled analgesia (PCA) used by patients receiving general or regional anesthesia: The amounts were 971.9 *versus* 836.1 μg, respectively (a 16% difference). Moreover, the amounts were also similar between the subsets of placebo patients who received general or regional anesthesia: 2,027.4 and 2,176.8 μg, respectively. It is precisely because of randomization and the robust nature of the data that the conclusions regarding median time to first fentanyl and total opioid use are valid, as stated in the article.

I also disagree with Dr. Roboubi's statements on the uses of fentanyl in pain management and whether patients had access to adequate analgesia. Intraoperative intravenous fentanyl administered at 250 μg is a reasonable dose for pain control in hip arthroplasty, and PCA fentanyl is widely used for postoperative pain management. At my institution, which is one of the highest volume joint replacement centers in the United States, intravenous PCA fentanyl has been the standard for many years because of its favorable metabolite profile. At equipotent analgesic doses, fentanyl produces analgesia similar to that of other opioids. Although the clinical study protocol provided guidelines for the use of PCA fentanyl, it was at the discretion of the physician to ascertain the individual needs of the patient. Patients could have been given bolus doses of fentanyl, and/or the PCA lockout interval could have been modified to address the needs of each patient.

Although the data were not presented, I also note that the study included a pharmacokinetic analysis of EREM. This would not have been possible if morphine were used for PCA instead of fentanyl; PCA morphine would have interfered with the pharmacokinetic analysis of EREM and its metabolites, whereas fentanyl did not.

Dr. Roboubi also takes issue with the number of patients receiving opioid antagonists (12.5% [17 EREM-treated patients]), but this again reflects a failure to understand the nature of a dose-finding clinical study and the inherent limitation of a study designed to focus on the safety and efficacy of a single agent. Dose-finding studies are designed knowing that some of the doses used may fall outside the range that is ultimately approved by the U.S. Food and Drug Administration, and this proved to be true in our study for the 25-mg dose and for the 20-mg dose in older patients. Therefore, it is critical for physicians to read the product label to understand the approved doses and uses.

It is also important to note that although the randomized nature of the clinical trial provides scientific validity, the environment is artificial and represents a worst-case scenario because patients are randomly assigned to the treatment drug and dosed without benefit of clinical judgment. In clinical practice, patient needs, comorbid medical conditions, and/or overall health as well as clinical practice guidelines are considered in determining an appropriate drug treatment. For example, in our study among the patients who received the Food and Drug Administration–approved doses (15 and 20 mg), three patients (< 4%) were treated for respiratory depression. Of these three patients, one was aged 75 yr and another was morbidly obese. In clinical practice, the overall health and preexisting medical conditions of these two patients would have been considered before selecting a drug treatment and dose.

It is also important to recognize that the clinical trial of EREM did not permit the use of multimodal analgesia. In clinical practice, the multimodal approach for pain management in postoperative patients is common practice and has proven quite effective for pain management. As shown by a recent meta-analysis, the use of nonsteroidal antiinflammatory drugs can reduce morphine consumption substantially and significantly decrease the rates of adverse events.[2] In my clinical practice, patients generally receive lower doses of EREM ($\leq$ 10 mg) in conjunction with other modalities. Under these conditions, patients frequently transition to oral medications without intravenous PCA. Regular monitoring for adverse events is performed, but the time required for monitoring is more than compensated for by the time saved on PCA setup, monitoring, and maintenance.

In summary, I thank Dr. Roboubi for providing me with an opportunity to dispel a number of common misconceptions regarding randomized clinical trials. Although such studies have limitations in describing how a drug may ultimately be used for effect in real clinical settings, the rigor of

randomized studies provides us with greater certainty regarding the study outcomes. No single study can capture the many important nuances of drug performance, and clinicians should always read the product label to ensure that they understand the approved drug doses and indications.

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(Accepted for publication August 31, 2005.)

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Anesthetics and Memory: On Memory at the Cognitive and Cellular Levels

To the Editor:—I read with interest the article by Naruo *et al.*[1] entitled "Sevoflurane Blocks Cholinergic Synaptic Transmission Postsynaptically but Does Not Affect Short-term Potentiation." I agree with the authors about the importance of studies at the cellular and molecular levels, which in conjunction with studies at the cognitive science level should provide a comprehensive account of effects of anesthetics on memory. However, my enthusiasm for the authors' excellent work was marred by the following points. It is not clear how the neurons used in the cell culture are relevant to memory processes. For example, in a similar aquatic invertebrate, *Aplysia*, the sensory and motor neurons of the gill withdrawal reflex are commonly used. The reflex in the intact animal can be classically conditioned and undergoes habituation and sensitization.[2] Does this occur with the neurons used in this report?

It is inaccurate to state that numerous studies found no effect of anesthesia on various types of memories. Anesthetics (in anesthetizing dosages) abolish both short- and long-term memories.[3] The authors cite as a reference,[4] an article that was presented at a symposium in 1995 where the authors sent a questionnaire to a number of consultants regarding their opinions about the existence of *implicit* learning and memory during anesthesia. However, such existence remains controversial, as best exemplified by the lack of replication of any positive findings (except for one recent work by Deeprose *et al.*).[5,6]

Although it is true that the anesthetized brain is able to process auditory information, this does not allow cognitive processing during adequate anesthesia. Looking at the auditory evoked responses,[7] the brainstem response is resistant to anesthetic effects. The early or midlatency responses that reflect neural transmission through the medical geniculate body in the thalamus to the primary auditory cortex disappear with deep anesthesia.[8] The late cortical responses that reflect transmission through cortical association areas, the frontal cortex and the hippocampus, and are engaged in cognitive processes are abolished with loss of consciousness. The authors give as a reference for persistence of cognitive processing during anesthesia a meta-anal-

ysis of studies of *implicit* memory before 1996.[9] More studies have been published since then, and as with any meta-analysis, the results are dependent on the quality of the reviewed articles. Finally, the authors state that cellular studies are important in resolving the issue of whether anesthetics affect learning and memory. Perhaps it would be more productive for investigators to start with the forgone conclusion that anesthetics do affect learning and memory and to elucidate the sites and mechanisms of this important interaction.

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(Accepted for publication September 9, 2005.)

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In Reply:—I appreciate the interest expressed by Dr. Ghoneim for my article.[1] I am pleased to have invoked a response from my clinician

counterpart *vis-à-vis* the need to understand fundamental mechanisms by which anesthetics may affect learning and memory.

To clarify how cultured neurons may be relevant to memory processes, I wish to point out that at both the cellular and the molecular level, most fundamental mechanisms underlying synaptic plasticity are preserved in a vast majority of *in vitro* (slices or cultured neurons) preparations. These plastic changes in synaptic activity, in turn, are thought to form the basis for learning and memory in most animals—ranging from worms, snails, and flies to humans. Therefore, it is highly appropriate and useful to take advantage of *in vitro* preparations for understanding complex processes such as learning and memory. Regarding the usefulness of the model system for studies on synaptic plasticity and learning and memory, I wish to point out that mine was the first laboratory to have reconstructed the entire respiratory network in cell culture.[2] I demonstrated that the *in vivo* reconstructed circuit, comprising behaviorally and functionally well-defined neurons, was sufficient to generate patterned respiratory rhythm in a manner similar to that seen *in vivo*. Both the Lukowiak (University of Calgary, Calgary, Alberta, Canada) and my laboratory have since demonstrated that the respiratory behavior in *Lymnaea* can be operantly conditioned[2–7] to exhibit short-, intermediate-, and long-term memory and have identified the locus for these memory related changes[7] at the level of a single neuron. By selectively removing a single cell in the intact animals, I have subsequently provided direct evidence regarding the storage site for learning and memory-related changes in individual neurons.[8–15] Moreover, using the cell culture model, I have not only defined the mechanisms that regulate synaptic efficacy[16,17] but also identified novel proteins[18] that can modulate synaptic strength *via* interactions with the glial cells. Therefore, I believe that the *Lymnaea* model is equally well suited for studies in synaptic plasticity and learning and memory—as has been the case in *Aplysia*.

Notwithstanding these strengths of my model and a clear demonstration in my article[1] that anesthetics do not affect short-term potentiation, I have still been very careful in drawing a generalized conclusion about the actions of sevoflurane on learning and memory. Specifically, I have explicitly stated in my article that "these data should be treated with caution as learning and memory involve a larger population of neurons, often requiring interplay between complex cognitive information processing mechanisms in the brain" (Discussion, first paragraph, page 924).

In the context of unresolved issues of whether anesthetics affect memory, the bottom line is that we still do not have the answer—notwithstanding Dr. Ghoneim's claim that anesthetics have been shown to block learning and memory. I believe that unequivocal evidence in this regard would still require a multidisciplinary approach and concerted efforts by both clinical investigators and basic scientists.

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(Accepted for publication September 9, 2005.)

Regular Clinical Use Bispectral Index Monitoring May Result in Lighter Depth of Anesthesia as Reflected in Average Higher Bispectral Index Values

To the Editor:—A recent study demonstrated that cumulative deep hypnotic time (Bispectral Index of the electroencephalogram [BIS] below 45) is a significant variable in postoperative outcomes.[1] The importance of anesthetic duration and depth is interesting and somewhat surprising, and emphasizes the need to more carefully evaluate the impact of intraoperative management strategies on outcome.[2] Anesthesiologists are now more concerned with assuring adequate depth of anesthesia for both clinical and professional liability reasons. We investigated whether the regular use of BIS monitoring could lead anesthesiologists to work with lighter levels of depth of anesthesia.

Data collected during consecutive neurosurgical interventions (research committee approved and informed consent) with the same anesthesiologist were used in this study. Data were systematically collect on the same weekday in the same operating room during a whole year. Patients were submitted to general anesthesia using propofol (1% Fresenius; Fresenius Kabi Pharma Portugal Lda., Carnaxide, Portugal) and remifentanil (20 µg/ml Ultiva®; GlaxoSmithKline–Produtos Farmacêuticos Lda., Algés, Portugal). Patients with pathologies that
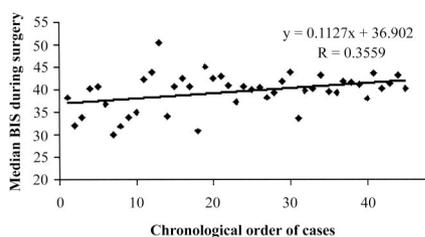
Fig. 1. Linear regression between the median Bispectral Index (BIS) during surgery and the chronological order of the case. Statistical significant correlation (P = 0.0148) and positive slope (P < 0.05).

Fig. 2. Linear regression between the average propofol dose (mg · kg^{-1} · min^{-1}) during surgery and the chronological order of the case. Statistical significant correlation (P = 0.006) and negative slope (P < 0.01).

could influence the results or showed obvious alteration of mental status were excluded. Patients were monitored with an A-2000XP BIS® monitor (Aspect Medical Systems, Newton, MA) using a BIS-Sensor® (Aspect Medical Systems) placed according to the instructions of the manufacturer and an AS3 Datex monitor (Datex–Engstrom, Helsinki, Finland) connected by an RS-232 interface to a personal computer using Rugloop II® software for data capture every 5 s. Rugloop II® was used to control *via* the RS-232 interface the remifentanil infusion pump (Asena Alaris TIVA; Alaris Medical Systems, San Diego, CA) and the propofol infusion pump (Asena Alaris GH, Alaris Medical Systems) using the pharmacokinetic–pharmacodynamic models of Minto *et al.*[3] and Schnider *et al.* [4] for remifentanil and propofol, respectively. Induction of anesthesia was performed with a propofol infusion (target-controlled infusion) with an initial effect site target of 5 μg/ml and a remifentanil infusion (target-controlled infusion) with an initial plasma target of 2.5 ηg/ml. Loss of consciousness was defined as loss of eye opening in response to a tap on the forehead and calling the patient's name. Rocuronium (10 mg/ml Esmeron®; Organon Portuguesa Lda., Lisboa, Portugal) was used for muscle relaxation. The drugs' target concentrations were manually controlled by the anesthesiologist during the entire surgery.

Data distribution is expressed as mean ± SD. Statistical correlation analysis, linear regression, and the Student t test were performed using MATLAB 6.5.1 (The Mathworks Inc., Natick, MA). P < 0.05 was considered significant. Average BIS and median BIS during the maintenance phase were calculated retrospectively from the anesthetic record and related to the chronological order of the case. The anesthesiologist was blind to the objective of this study.

Forty-five patients met the selection criteria. Patients were aged 49.8 ± 16.5 yr, weighed 67.8 ± 13.4 kg, and were 160.5 ± 8.8 cm tall. Thirty-three were female. The case duration was 287.3 ± 161.6 min.

During surgery, the average BIS value was 39.89 ± 4.04, and the median BIS value was 39.49 ± 4.1. The propofol average effect site and plasma concentrations were 3.01 ± 0.86 and 2.98 ± 0.84 μg/ml, respectively. The average propofol dose was 0.10 ± 0.03 mg · kg^{-1} · min^{-1}. The total amount of propofol was 1,940 ± 1,289 mg. The remifentanil average effect site and plasma concentrations were 3.13 ± 0.89 and 3.15 ± 0.9 ηg/ml, respectively. The average remifentanil dose was 0.11 ± 0.04 μg · kg^{-1} · min^{-1}. The total amount of remifentanil was 2,093 ± 1,355 μg.

There were significant positive correlations between the chronological order of the case and average BIS (P = 0.0164) and the chronological order of the case and median BIS (P = 0.0148; fig. 1). The average effect site propofol concentration decreased significantly over time (P = 0.0094), as did the plasma propofol concentration (P = 0.0112). Figure 2 shows the relation between the average propofol dose during surgery and the chronological order of the case (P = 0.006). There was no significant correlation between the remifentanil dose or concentration and time.
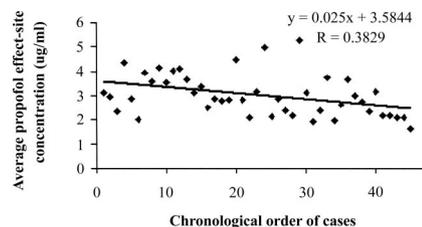
The possibility of observing the central nervous system response through BIS increased the anesthesiologist's confidence in the level of depth of anesthesia (learning trend) and improved the clinical management. The increasing trend in BIS values with clinical practice was accompanied by a decreasing trend in propofol consumption.

Anesthetic depth is often used as a tool to provide better control of hemodynamic variables.[2] However, hemodynamic depression is one of the major factors associated with perioperative coma and death.[5] A long duration of intraoperative systolic hypotension is also associated with increased risk of postoperative mortality.[1] By controlling depth of anesthesia using BIS, one can more easily control the associated hemodynamic variability (*e.g.*, using nonanesthetic drugs).

In our study, we observed that the regular use of BIS monitoring led to higher BIS values and, therefore, lower propofol consumption. This is in accord with the results of Guignard *et al.*,[6] who reported a reduced consumption of isoflurane when its titration was guided by BIS monitoring without higher incidence of light anesthesia.

In conclusion, the regular use of BIS monitoring by the anesthesiologist resulted in average higher BIS values. The increasing BIS trend with clinical practice also represented a trend toward safer BIS values (BIS between 45 and 60). This BIS trend was associated with a decrease over time of propofol average concentrations and consumption. Between the first and the last patients, there was an average decrease of 1,077 mg propofol per patient. The decrease in propofol consumption with time was a consequence of the experience with BIS monitoring acquired by the anesthesiologist (*i.e.*, trying to avoid excessive anesthesia), with potential benefits to the patients.

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(Accepted for publication September 8, 2005.)