Anesthesiology 2008; 108:538

Epiduroscopy and Epidural Steroid Injections

To the Editor:—We read with interest the two case reports by Dr. Heavner *et al.*[1] in which the introduction of an epiduroscope for placement of hyaluronidase, local anesthetic, and steroids in the lower lumbar epidural space led to the apparent disruption of venous wall integrity. Unintended vascular uptake of dye was documented on fluoroscopy. The case reports raise several concerns about the value of using an epiduroscope to place medication in this manner.

The evidence in the literature does not support the practice of using an epiduroscope to perform a caudal injection as a means to improve outcome, when compared with a fluoroscopically guided injection *via* a catheter or needle.[2]

As these case reports portray, use of an epiduroscope clearly offers no protection against vascular trauma. Indeed, the view through the scope gave no indication in either case that vascular wall integrity had been broached. It was fluoroscopic imaging in conjunction with dye administration that diagnosed the inadvertent injection.

Rather than protecting against trauma, it is reasonable to assume that the larger instrument (the epiduroscope is blunt, rigid, and 2.8 mm in diameter; a 20-gauge epidural catheter is softer and less than 0.9 mm in diameter) would be more likely to cause trauma. Indeed, Heavner *et al.* suggest that it is the lack of a low-pressure alternative route for the injectate to escape around the vessel that drives injectate into the vein. An epidural catheter, taking up less space, would allow more avenues of egress for the injectate and would be less likely to traumatize the vessel (smaller and softer) or lead to a high-pressure environment that would distend the vessel breach and induce this unwanted vascular ingress of medication.

The cost and charge to the patient of the fluoroscopically guided epiduroscope-based epidural injection is higher than a fluoroscopically guided needle or catheter injection.

Because a catheter is as effective, is less expensive, is less traumatic, and uses the only imaging technique (fluoroscopy) that provides safety in this injection, we must ask: Where is the value in using an epiduroscope to inject medication into the lumbar epidural canal?

The concept of introducing a flexible fiberoptic scope into the epidural space to directly visualize structures is appealing. Ideally, we could accomplish this safely, be able to clearly define normal and abnormal anatomy, and use the anatomical information to improve treatment by providing directed therapy. These goals have been elusive, despite the availability of this technique for more than 20 yr.[3] The current case reports[1] are a clear reminder that the risks and benefits of this technique have yet to be clearly established. We believe that safety and cost dictate that the routine use of epiduroscopy to "guide" caudal injection not be used until evidence generated by randomized controlled trials proves that it provides benefit sufficient to warrant the additional trauma, risk, and cost it obviously incurs.

Douglas G. Merrill, M.D.,* James P. Rathmell, M.D., Richard W. Rosenquist, M.D. *The University of Iowa, Iowa City, Iowa. douglas-merrill@uiowa.edu

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In Reply:—We thank Merrill *et al.* for their comments concerning our article.[1] We did not intend to present epiduroscopy as an alternative to using a catheter, where indicated, for targeted drug delivery. Dr. Merrill *et al.* used our case reports to take a stand against such practice. That being the case, we totally agree with them.

Blinded by catheters, look through an epiduroscope, see, and be enlightened!

James E. Heavner, D.V.M., Ph.D., F.I.P.P. (HON),* Hemmo A. Bosscher, M.D., F.I.P.P. *Texas Tech University School of Medicine, Lubbock, Texas. james.heavner@ttuhsc.edu

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Nitrous Oxide and Evidence-based Medicine: Here We Go Again

To the Editor:—We read with great interest the article by Myles *et al.*,[1] "Avoidance of Nitrous Oxide for Patients Undergoing Major Surgery," and the accompanying editorial.[2] We commend the extraordinary efforts by the authors in the execution of this large multicenter trial. As neuroanesthesiologists, we were particularly intrigued by the evaluation of this anesthetic gas, because it remains in common use in our specialty area and the safety and efficacy of nitrous oxide are periodically debated at national meetings and within the literature. Our concerns are directed at how this study, given the limitations of the trial, may inappropriately impact clinical practice.

Several specific negative impressions regarding the use of nitrous oxide that are conveyed but not substantiated by the study include the following:

The above letter was sent to the author of the referenced editorial. The author did not feel that a response was required.—James C. Eisenach, M.D., Editor-in-Chief.

First, the time to emergence recorded in the study calls into question one of the major benefits of nitrous oxide as an anesthetic. Its ability to facilitate a brisk and timely emergence has been well documented[3] and remains an attractive property to neuroanesthesiologists and others. Therefore, we were surprised by the 11-min time to eye-opening in the nitrous oxide group, which was both longer than expected and equal to that of the nitrous oxide–free group. We are accustomed to the very dependable less-than-3-min time to emergence that is largely independent of the duration of the surgical procedure and shorter than that observed with volatile agents alone. We suspect that the lack of blinding of those actually delivering the anesthetic and the use of Bispectral Index monitoring may have contributed to the similarity of the groups. Bispectral Index monitoring was more frequently used in the nitrous oxide–free group, but no data regarding Bispectral Index targets, use of muscle relaxants, or frequency of spontaneous ventilation were presented.

Second, in the introduction, the authors allude to the inactivation of vitamin B_{12} and elevation of homocysteine by nitrous oxide as major concerns, despite millions of uncomplicated anesthetics and literature that has never substantiated a causal relation. For example, in the cited study by Deleu *et al.*,[4] the investigators in their analysis noted no change in cobalamin or red cell folate levels between nitrous oxide and nitrous oxide–free patients. The three patients with postoperative neurologic symptoms had documented folate deficiency preoperatively, and no preoperative neurologic examination had been performed to establish a perioperative etiology for their condition.

Third, in the Discussion, the authors linked the use of nitrous oxide to a greater risk of myocardial infarction and death without statistical support. It is disconcerting to read that a causal association exists between an independent variable and outcome, but that it "lacked statistical significance." Either a finding is significant or the null hypothesis must carry the day.

Fourth, in the introduction, the authors expressed concern about the detrimental effects of nitrous oxide on cerebral blood flow but failed to report any evidence to substantiate this claim in the Results or Discussion. In their study, no neurologic complications were ascribed to nitrous oxide use, although 15% of all cases were neurosurgical procedures. The use of nitrous oxide in neurosurgery has been criticized before, fueled by experimental studies suggesting a worsening of infarction in ischemic rat models. Such data have been elegantly countered by more recent work, demonstrating that the previous findings were likely a matter of experimental methodology rather than a distinct toxic effect of the gas.[5] Recently, the *N*-methyl-D-aspartic acid antagonist action of nitrous oxide has been shown to be neuroprotective in a number of models, similar in potency to xenon.[6] Hence, the neurotoxic claims on nitrous oxide seem to have been countered.

Fifth, the authors focus much of their attention on the topic of postoperative nausea and vomiting (PONV). In fact, the principal outcome data (fig. 4) prominently displays PONV outcomes first, highlighting the meaningful odds ratio. The data, however, are not new, surprising, or of much consequence. The literature generally supports that nitrous oxide and volatile anesthetics have a similar risk for PONV, whereas total intravenous anesthesia is associated with a reduced incidence.[7] As important, prophylactic therapy has been shown to greatly decrease the incidence of PONV. In the current study, only one third of the patients received prophylaxis; hence, the investigators' priority to minimize PONV was low. Therefore, the data on PONV become less interesting. We subscribe, with excellent results, to the International Anesthesia Research Society Consensus Guidelines whereby patients with a 10% risk of emesis deserve cost-effective prophylaxis.[8]

More generally, we must emphasize the importance of interpreting data clearly if we are to improve on evidence-based practice. In the above article, a significant finding in favor of the avoidance of nitrous oxide as part of a balanced anesthetic was the predominant claim. The clinical trial, however, prospectively defined the primary outcome measure as "duration of hospital stay." Presumably this metric was a collective endpoint serving to capture the variety of "ill effects" from the use of the gas and their net impact on hospital stay. The clinical results for this primary endpoint satisfied the null hypothesis between the nitrous oxide and nitrous oxide–free groups. Although this was chiefly a negative study, both the abstract and Discussion present the principal outcome as a minor result after presentation of the secondary data, thereby minimizing the significance of this null effect. It could be argued this criticism is but a minor point. But all who manage spinal cord injury patients know very well that anesthesiologists, emergency physicians, and intensivists continue fighting to correct the false conclusion proliferated 16 yr ago when a prominent medical journal published trial results regarding infusion steroid therapy.[9] That trial was fundamentally negative (no clinical outcome difference between methylprednisolone *vs.* placebo), but that point was obscured by the manner in which the article was published. Secondary, statistically flawed *post hoc* analysis in that trial led the authors to further argue for a meager, functionally meaningless effect. Since then, thousands of patients have been treated with a therapy that, although not overtly toxic, is not benign. Worse yet, the treatment may have led to complacency by some acute care physicians, believing they had "done all they could" by administering steroids while possibly not being compulsive about spinal cord perfusion and other management strategies that do offer medical benefit. Although the results of that trial have been successfully refuted,[10] this treatment continues to have a life of its own. More recently, the controversy over tight glucose control for perioperative and intensive care unit patients rages, and numerous studies have recently been published, many with poorly designed methodology, with improperly drawn conclusions, and without appropriately emphasizing the risks of such therapy. In these studies, there was also a relative failure to properly recognize the numerous trials that have demonstrated toxicity without overt benefit.[11,12]

In conclusion, studies that are largely negative in their primary outcome should not have a dramatic impact on practice. In this instance, more should be necessary before discarding the only anesthetic drug that has withstood the test of time. In contrast to the conclusion reached in the accompanying editorial, we view this study as additional evidence of the remarkable safety of nitrous oxide over the past 150 yr. Indeed, were nitrous oxide a new proprietary drug and marketed as a reliably short-acting, well-tolerated, inexpensive analgesic–anesthetic gas, it would be likely hailed as one of the most valuable adjuncts to the practice of anesthesiology.

Marek A. Mirski, M.D., Ph.D.,* Allan Gottschalk, M.D., Ph.D.,
*Johns Hopkins Medicine, Baltimore, Maryland. mmirski@jhmi.edu

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Nitrous Oxide or Nitrogen Effect

To the Editor:—We read with interest the recent publication by Myles *et al.*[1] on avoidance of nitrous oxide for patients undergoing major surgery. We are divided in our use of nitrous oxide as one of us routinely uses nitrous oxide (J.G.H.) and the other does not (J.S.D.).

We praise the authors for recruiting so many patients to their study, though we question why many of the variables for which this article will be criticized were not controlled more tightly, namely standardized use of antibiotics, antiemetics, and "propofol maintenance anesthesia." These three factors alone may well have been influential, in part, for some of the different outcomes observed between the two study groups.

We also note there was no standardization of the depth of anesthesia between the two groups. The nitrous oxide–free group had a median end-tidal volatile concentration of 0.87 minimum alveolar concentration (MAC) equivalents, whereas the nitrous oxide group had a median end-tidal volatile concentration of 0.67 MAC equivalents plus 0.64 MAC equivalents of nitrous oxide, 1.31 MAC equivalents in total, with no significant difference in use of other induction sedative drugs (midazolam or opiates) between the groups. The concept of prolonged deep hypnosis resulting in a poorer postoperative outcome has been suggested before,[2] and we question whether this too may have been a confounding factor in this study.

Finally, although the authors acknowledge the potential for the influence of the differing fractions of inspired oxygen between groups, they do not mention the possibility that the substantial differences in the fraction of inspired nitrogen gas may have affected postoperative pulmonary outcome. Humans have evolved in an atmosphere predominantly made up of nitrogen gas, and nitrogen is well known to splint the alveoli and limit atelectasis[3]; as little as 20% nitrogen in the anesthetic gas mixture has been shown to lessen atelectasis by nearly 10 times when compared with a pure oxygen mixture,[4] and one would expect similar findings in a nitrous oxide and oxygen anesthetic. Might many of the respiratory complications observed in this study and which favor the nitrous oxide–free anesthetic actually represent differences in nitrogen use between the two groups?

James S. Dawson, B.Sc., M.B., Ch.B.,* Jonathan G. Hardman, B.Med.Sci.(Hons), B.M., B.S., F.R.C.A., D.M. *University Department of Anaesthesia, Queen's Medical Centre, Nottingham, United Kingdom. james@dawson.me.uk

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Nitrous Oxide Remains a Valuable Adjuvant for Surgery

To the Editor:—Myles *et al.*[1] have presented the results of a large prospective multicenter trial evaluating the use of nitrous oxide in patients undergoing major surgery.[1] The study did not achieve its primary endpoint; therefore, the authors chose to emphasize the differences in the secondary outcome measures (*e.g.*, postoperative nausea and vomiting [PONV]). The failure to control for anesthesia-related factors that can influence the incidence of PONV (*e.g.*, volatile anesthetics, opioid analgesics, reversal drugs, amount of intravenous fluid administered during and after surgery, use of prophylactic and rescue antiemetics) may render the conclusion regarding the effects of nitrous oxide on PONV invalid. In addition, the relative risk of the patients for developing PONV (*e.g.*, history of PONV, motion sickness, nonsmoking status, postoperative opioid use) were not reported in the description of the demographic characteristics of the two study groups.

These factors are particularly important in interpreting the validity of these findings because the differences in their secondary outcome variables were the end result of multiple statistical comparisons. Furthermore, several well-controlled studies involving patients undergoing ambulatory (and short-stay) surgical procedures have not found any clinically significant differences between patients receiving or not receiving nitrous oxide during surgery.[2–5] Therefore, before condemning a valuable anesthetic adjuvant with well-characterized amnestic, anesthetic, and opioid-sparing effects,[6] more tightly controlled studies are needed. It is potentially misleading to readers to present conclusions based on poorly controlled secondary outcome variables.[1]

Paul F. White, Ph.D., M.D., F.A.N.Z.C.A.,* Ronald H. Wender, M.D. *University of Texas Southwestern Medical Center, Dallas, Texas. paul.white@utsouthwestern.edu

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Nitrous Oxide: Time to Laugh It Off? Not Quite

To the Editor:—We read with keen interest the pragmatic study by Myles *et al.*[1] and wish to congratulate the authors for their outstanding work. Despite the concerns regarding its adverse effects, nitrous oxide has actually had a central position in anesthetic practice primarily because it is inexpensive, widely available, and has a long-standing safety profile. The most obvious advantage of using nitrous oxide is that it allows a dose reduction of other anesthetic agents and opioids, which translates into less cardiovascular depression and significant cost reduction (which are particularly important in the developing countries). Nitrous oxide is not associated with nephrotoxicity or hepatotoxicity and is safe to use in patients susceptible to malignant hyperthermia. It possesses an analgesic property that all modern anesthetics lack and is short acting, with quick onset and offset of action. In fact, inhalation of nitrous oxide has also been found effective in reducing pain associated with injection of propofol,[2] which is fast replacing thiopentone as an induction agent. There has been concern regarding disadvantages of nitrous oxide, such as megaloblastic anemia, teratogenicity, neurotoxicity, increased intracranial pressure, myocardial ischemia, increased pulmonary arterial pressure, immunosuppression, postoperative nausea and vomiting, risk of hypoxia, and expansion of air-filled spaces. But the suggestions to retire nitrous oxide from its current position have gained more impetus by the advent of newer, shorter-acting agents, particularly remifentanil, and newer inhaled anesthetics, and growing interest in total intravenous anesthesia, rather than by appreciation of its own toxicity. In this context, the scenario in the developing world is still very different from the developed world, where most newer agents, including remifentanil and desflurane, are still not available. Even not-so-new agents such as sevoflurane are available in limited centers. Above all, the costs of anesthetic agents, including propofol, are significant concerns. While most of the Western world has already bid farewell to halothane, it is still widely used (in combination with nitrous oxide) in most third-world countries. In recent years, the use of nitrous oxide has decreased significantly in Western countries, and many anesthesiologists prefer not to use it at all. We believe that nitrous oxide, like any other drug used in anesthetic practice, has its own advantages and disadvantages. Although there are specific situations where it should be avoided, we believe that not only should its routine use be questioned, but also its routine avoidance! We are also concerned about the routine use of 100% oxygen because the anesthesia trainees need to develop confidence using lower oxygen concentrations, which they might have to use in certain specific situations, such as laser surgeries. We opine that nitrous oxide is a useful agent that should remain freely available for anesthesiologists to use judiciously like all other agents, and we fear that newer generations of anesthesiologists might not have enough experience with judicious use of laughing gas because of the lack of its use during their training.

Deepak Sharma, M.D., D.M., Hari H. Dash, M.D.* *All India Institute of Medical Sciences, New Delhi, India. drhh_dash@yahoo.com

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Nitrous Oxide and Supplementary Oxygen: Let's Give Moderation a Chance

To the Editor:—I read with interest the article of Myles *et al.*[1] and the accompanying editorial by Hopf.[2] Hopf celebrates the article by Myles *et al.* and suggests that it " . . . is likely to have a major impact on clinical practice in anesthesia." She even confesses to having stopped using nitrous oxide nearly a decade ago because of the importance of high tissue oxygen in preventing wound complications.

According to Hopf, there are two main reasons for avoiding nitrous oxide: (1) It produces postoperative nausea and vomiting; and (2) it prevents using 80% oxygen, which Hopf suggests also reduces nausea and vomiting, and even more importantly might reduce surgical site infection.

I recently published a letter[3] expressing my doubts about the benefits of 80% oxygen, caused by the inconsistency of the results of trials, the lack of clinical benefit, and most importantly, the inexistence of data evaluating more moderate oxygen concentrations (45–60%).

It is true that nitrous oxide produces postoperative nausea and vomiting, but it also happens for halogenated inhaled anesthetics, so

The above letter was sent to the author of the referenced editorial. The author did not feel that a response was required.—James C. Eisenach, M.D., Editor-in-Chief.

you would not get any benefit from substituting halogenated anesthetics for nitrous oxide except the possibility of applying 80% oxygen. However, it is quite mystifying to read articles from the same authors who found 80% oxygen halving nausea and vomiting in the past,[4] stating now that it is of no benefit.[5] Finally, a recent clinical trial[6] shows that 80% oxygen is useless for preventing nausea and vomiting.

I personally still use 50% nitrous oxide plus 50% oxygen plus sevoflurane widely, and it is true that I might prevent some nausea and vomiting by substituting propofol for sevoflurane and nitrous oxide. But any real clinical benefit from substituting 80% oxygen for 50% oxygen is still unclear.

The two studies that found benefit from using 80% oxygen used 30% oxygen as control group, and these authors have surprisingly concluded that we should accept a linear clinical benefit beginning at 30% oxygen and ending at 80% oxygen. At the moment, this linear benefit is unproven, so it is surprising to read Hopf's suggestion that the study of Myles *et al.* could accelerate the process to accept 80% oxygen as standard practice. Moreover, Myles *et al.* did not find an independent effect of oxygen concentration in the nitrous oxide–free group.

I must join Hopf's residents in challenging the medical community to substitute evidence-based treatments for personal options.

Gonzalo Tornero-Campello, M.D., Hospital General Universitario de Elche, Elche, Alicante, Spain. gtorcam@hotmail.com

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Explanatory *versus* Pragmatic Trials? The Methods Make the Difference

To the Editor:—The efficacy (the measurable effect) of a treatment and its effectiveness (its utility in routine clinical practice) cannot be simultaneously addressed in a single trial. In the former case, the assay aims at establishing a causal relation between the delivery of a treatment and a measurable effect. This type of trial has been called *explanatory*. In the latter, the goal is to compare the impact of distinct strategies in the context of routine clinical practice, one of the strategies including the treatment to be evaluated. This kind of trial has been called *pragmatic*.[1] The importance of the clear identification of the explanatory *versus* pragmatic nature of a trial goes far beyond a semantic debate. Indeed, the way the question has been formulated (comparison of treatments or of global healthcare strategies), the experimental approach, the statistical risks allowed, the calculation of the number of patients to be included, and the analysis of the results are all very different between the two types of trials. Interestingly, we are much more familiar with explanatory trials, while the principles and methods of pragmatic ones have been reported more than 40 yr ago.[2]

In a recent issue of ANESTHESIOLOGY, Myles *et al.*[3] conducted a large, clinical, multicenter trial on the impact of various intraoperative inspired gas concentrations on a wide range of postoperative complications. The question raised here definitely addresses the impact of two different strategies, *i.e.*, the use of low and high oxygen inspired concentrations combined with either nitrous oxide or nitrogen, including all related changes (*i.e.*, differences in the inspired oxygen concentrations used, differences in the inspired concentrations of volatile anesthetics, and so on). The experimental approach used is also that of a pragmatic assay, as assessed by the routine surgical context of the trial, the large inclusion criteria, the randomization, and the detailed therapeutic schemes reported in the Materials and Methods. Surprisingly however, the authors seem to have considerably minimized the consequences of the pragmatic nature of the trial. For example, this essential feature of the work is not mentioned in the title, and only the introduction section contains the word *pragmatic*. This is still more striking when looking at the statistical risks allowed for calculation of sample size. In the Materials and Methods, the authors explain in detail the choice of a statistical analysis adapted to an explanatory trial. In a pragmatic assay, reduction of the α risk (type I error) is inaccurate, because no preference is given to one of the two strategies if they turn out to be equivalent. The consequence of this is that the value for the α risk is 1, and therefore that no statistical tests are necessary! In a pragmatic assay, it is impossible not to conclude between the two strategies. The β risk (type II error) is therefore 0. Under these conditions, the risk be considered is the γ risk (type III error), which corresponds to the risk of an erroneous conclusion that one strategy is superior to the other (sign error). The probability of a sign error can also be quantified on the basis of the results, especially if the observed differences are small. For example, mentioning that the difference in the durations of hospital stay (the so-called privilege criterion) is "significantly different" between the two strategies is questionable according to a pragmatic approach. Conversely, the fact that the duration of hospital stay is superior in the 70% nitrous oxide–30% oxygen arm is enough to support the choice of the 80% oxygen–20% nitrous oxide strategy for this criterion. However, because the magnitude of the difference is small, the probability of a sign error is close to 0.25 in this case. The same reasoning held for the secondary criteria (postoperative nausea and vomiting, wound infection, respiratory complications, and so on) leads, however, to much stronger results with a minimal risk of sign errors. Finally, the impact of a pragmatic trial is theoretically limited to the context of the recruiting centers, for which cointerventions are comparable and should be explicitly and exhaustively reported. Although the great number of participating centers alleviates this limitation in the current case, the conclusions reported here may not be applicable to centers outside the recruiting hospitals. Only the convergence of additional pragmatic trials performed in contexts different from that of the current trial may provide a rationale for deciding whether intraoperative high nitrous oxide inspired concentrations are to be recommended.

Paul Merckx, M.D., Catherine Paugam-Burtz, M.D., Sandrine Boudinet, M.D., Agnes Bonnet, M.D., Jean Mantz, M.D., Ph.D.*
*Beaujon University Hospital, Assistance Publique des Hôpitaux de Paris, Paris 7 University, Clichy, France. jean.mantz@bjn.ap-hop-paris.fr

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In Reply:—We thank the correspondents for their interest in our study[1] and would like to respond to the various points of view raised.

Drs. Mirski and Gottschalk question the lack of the ability of nitrous oxide to reduce early recovery times in our trial. In the ENIGMA trial, anesthesiologists were instructed to adjust the depth of anesthesia to an appropriate level using clinical signs and/or electroencephalographic monitoring, aiming to reflect routine practice. No specific targets for depth of anesthesia were set. The fact that times to eye opening were similar in the two groups is an indication that the anesthesiologists were successful in maintaining equivalent depths of anesthesia with a variety of anesthetic combinations. Specifically, our results show that comparable depths of anesthesia and emergence times can be achieved with or without nitrous oxide. The emergence times are at least as good as in most other studies reporting recovery profiles after (median) 4-h surgeries.

Numerous studies have confirmed elevated plasma homocysteine concentration after nitrous oxide exposure. This follows inhibition of methionine synthase and occurs even at low concentrations (<20%). Currently, we do not know whether this biochemical change leads to cardiovascular morbidity, but it is a likely explanation for the increased rates of myocardial ischemia reported by others.[2] We believe a discussion of the trend toward more frequent adverse cardiac outcomes was warranted, in light of the cogent physiologic basis for concerns regarding this important outcome. Given the significant costs of cardiovascular complications to patients and the community, we believe that these findings demand further study. We have thus embarked on a follow-up study in 7,000 patients to test this hypothesis.*

The controversy over the potentially detrimental effects of nitrous oxide in neurosurgery has raged for decades, with ongoing divergence of opinion and conflicting evidence. We outlined some of the criticisms that had been levelled at nitrous oxide, in addition to highlighting its possible benefits. The only neurologic outcome we measured was stroke, and the incidence of this complication was too low for us to draw any conclusions.

Meta-analyses show that omission of nitrous oxide reduces the risk of postoperative nausea and vomiting (PONV) regardless of whether propofol or volatile anesthetics are used to maintain anesthesia.[3,4] Our study found a strong adverse effect of nitrous oxide across a range of patient and surgical types with respect to severe PONV, the definition of which was based on an extended period of symptoms or failure of therapy. This effect was evident despite the majority of patients in both arms of our study receiving a volatile anesthetic, higher concentrations of which were used in the nitrous oxide–free arm. Drs. Mirski and Gottschalk misrepresent published consensus guidelines, in that an expected PONV incidence of 10% is a low-risk setting and does not justify PONV prophylaxis. We agree that prophylactic antiemetics are efficacious in moderate- and high-risk settings, and they were administered to 35% of patients in our ENIGMA trial. In any case, the adverse effect of nitrous oxide on PONV was apparent whether or not prophylactic antiemetics were used.

We chose hospital stay as our primary endpoint because we were uncertain about which adverse events would predominate but expected that any of these could affect duration of stay. The effect was borderline ($P = 0.06$), but if true, a 9% increased rate of delayed discharge is clinically important when applied to millions of patients every year. Intensive care stay was prolonged, reflecting more serious complications in patients exposed to nitrous oxide.

The secondary analyses of postoperative complications (results given in table 3) were prespecified comparisons of randomized groups (nitrous oxide–based *vs.* nitrous oxide–free anesthesia) according to the intention-to-treat principle. In addition, these analyses were adjusted for potential confounding variables. Our conclusions were based on the results of these analyses. The subgroup analyses (results given in fig. 4) were *post hoc* and not controlled and were presented so readers could see the trend in results across a range of clinical subgroups of possible interest.

We thank Drs. Dawson and Hardman for their comments, which are relevant to the issues surrounding the conduct of large perioperative trials. Tight protocol control of all of the numerous variables surrounding modern anesthetic and surgical management is not practicable in large multicenter randomized trials,[5,6] nor is it desirable.[7,8] Construction of narrow protocols inevitably leads to criticism of the results on the basis that "we do things differently here." In contrast, flexibility in the wider aspects of patient management is more likely to provide answers that broadly reflect common practice and can be more readily generalized.[8]

Very large trials such as ours make the risks of asymmetry between groups in these variables (*e.g.*, antibiotic and antiemetic use) much lower than is the case in smaller single-center studies. Large trials balance known and unknown confounding factors. The exception to this, of course, is in variables that are directly affected by the intervention being tested. An example of this is the difference in cumulative minimum alveolar concentration scores between the two groups, as pointed out by Drs. Dawson and Hardman. Given that the study protocol stipulated a standard clinical approach to maintaining and monitoring depth of anesthesia, far from invalidating our results, it is likely to reflect one of many real differences between modern approaches to the conduct of nitrous oxide–based and nitrous oxide–free anesthesia, which may impact on outcome. With regard to the greater use of propofol where nitrous oxide was not used, we would make a similar point.

Retention of nitrogen in the inspired gas mixture is a further example of the anesthetic regimen being modified by avoidance of nitrous oxide. We agree that, on theoretical grounds, retention of some nitrogen in the inspired mixture, as stipulated by our protocol, may well have contributed to better pulmonary outcomes in the nitrous oxide–free group, by reducing atelectasis. Some anesthesiologists have a mistaken belief that nitrous oxide provides protection against absorption atelectasis, but this is not the case.[9]

Dr. White *et al.* seem to overlook two of the key design features of large randomized trials: (1) The large sample size provides balance of the numerous possible confounding factors that could affect the outcomes of interest, and (2) the inclusion of a variety of practice settings, with varying anesthetic and surgical techniques, represents "real-world" anesthesia and thus provides comfort to those concerned with whether the study results apply to them. Others have expanded on these issues extensively.[5,6,8] We provided details of risk factors for PONV and PONV risk scores in our table 1. Furthermore, the large sample size provides opportunity to test for variability of effect according to specific factors; we provided results of such analyses in figure 4.

Small single-center trials suffer from restrictive regimens that may not represent typical practice, and they are often underpowered to

* www.enigma2.org.au. Accessed November 16, 2007.

detect important differences in outcome. For example, one of the studies cited by Dr. White *et al.* reported a power calculation to detect a difference in PONV rates of 40% and 30%, and arrived at 35 patients per group,[10] whereas the true value is 450 patients per group. Underpowered studies abound in anesthetic journals. They are used by some to support a point of view, but such views conveniently ignore a larger body of relevant evidence with contrary findings—a few small trials do not replace well-conducted meta-analyses of all relevant trials.[3,4] In any case, the ambulatory care setting was not included in our study population, and we have not made any conclusions in this regard.

Drs. Sharma and Dash suggested that nitrous oxide is a useful adjunct to anesthesia because it is "inexpensive, widely available, and safe." Certainly, ongoing widespread use around the world mandates outcomes research on the effectiveness and safety of nitrous oxide. However, this view does not consider the capital costs of installing pipelines for nitrous oxide delivery and the ongoing manpower requirement to maintain the nitrous oxide manifold system. Furthermore, as highlighted in a very recent report,[11] technical errors can result in inadvertent hypoxemia that may be fatal or permanently disabling. Also, the ENIGMA trial identified nitrous oxide as a risk factor for serious wound infection and respiratory complication in patients undergoing major noncardiac surgery. These adverse events pose a significant economic burden to any healthcare system.

Dr. Tornero-Campello expresses a number of opinions in response to the editorial by Dr. Hopf that accompanied our article, but we wish to concentrate on his comments related to our study. We strongly disagree with his comment in reference to volatile anesthetics and PONV, *viz.* "so you would not get any benefit substituting halogenated anesthetics for nitrous oxide." Inhaled volatile anesthetics are more emetogenic than propofol, but omission of nitrous oxide independently reduces the risk of PONV.[3,4] Our study supports a strong effect across a range of patient and surgical types with respect to severe PONV, the definition of which was based on an extended period of symptoms or failure of therapy. This effect was evident despite the majority of patients in both arms of our study receiving volatile anesthetic and, in the nitrous oxide–free arm, at higher concentration (as might be anticipated). In addition, Dr. Tornero-Campello should not be mystified that other investigators found that the results of a subsequent meta-analysis on the effect of inspired oxygen concentration on PONV contradicted the previous results of a trial they had conducted. There is no paradox in this at all, and the investigators are to be congratulated that they retained their scientific curiosity and the motivation to question the validity of their previous findings based on one small trial.

We agree that the effects of different inspired oxygen concentrations on perioperative outcome have not been adequately investigated. We made it clear in the Discussion that no independent effect of oxygen concentration on outcomes was found in an exploratory analysis, but that it is not possible from our trial to determine with confidence whether the benefits of nitrous oxide–free anesthesia derived from omission of nitrous oxide, increased inspired oxygen concentrations, or both.

Dr. Merckx *et al.* comment on the difference between explanatory and pragmatic trials and agree with us that the ENIGMA trial was a pragmatic trial given that the two treatment arms were designed to reflect routine clinical practice: nitrous oxide–based and nitrous oxide–free anesthesia. However, they suggest that we strayed from the true objectives of a pragmatic trial in our classic approach to sample size estimation and statistical analysis of the data. According to Merckx *et al.*, the sole objective in every pragmatic trial is to make a decision about which is the better of the two treatment arms being tested. A further consequence of the decision-making focus is that no statistical tests or presentations of statistical uncertainty (*i.e.*, confidence intervals, *P* values) are required.

We do not agree with Drs. Merckx *et al.* that decision making is the defining objective of a pragmatic trial; this approach assumes that results will be definitive and uncertainty is irrelevant. Less extreme conceptions of pragmatic trials that are consistent with our approach are given by others,[7,12] and our format for reporting of trial results is consistent with current recommendations for presentation, such as the CONSORT statement.[13]

Finally, we would like to conclude by emphasizing that, currently, we believe nitrous oxide still has a role in contemporary anesthetic practice, but such use should be selective and take into account the risk profile of the patient and the surgical procedure. Patients with risk factors for PONV and with comorbidities, who undergo major surgery, are more likely to suffer harm from nitrous oxide exposure. Certainly, further large trials are warranted to explore some of the above unresolved issues.

Paul S. Myles, M.B., B.S., M.P.H., M.D., F.C.A.R.C.S.I., F.A.N.Z.C.A., F.R.C.A.,† Kate Leslie, M.B., B.S., M.D., M.Epi., F.A.N.Z.C.A., Matthew T. V. Chan, M.B., B.S., F.A.N.Z.C.A., Andrew Forbes, M.Sc., Ph.D., Michael J. Paech, M.B., B.S., D.M., D.R.C.O.G., F.R.C.A., F.A.N.Z.C.A., F.F.P.M.A.N.Z.C.A., F.R.A.N.Z.C.O.G.(Hon), Philip Peyton, M.B., B.S., M.D., F.A.N.Z.C.A., Brendan S. Silbert, M.B., B.S., F.A.N.Z.C.A., Elaine Pascoe, B.Sc. †Alfred Hospital and Monash University, Melbourne, Victoria, Australia. p.myles@alfred.org.au

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