baseline blood pressure. This variability in preanesthetic blood pressures results in part from the variability in premedication practices, in part from the variability in patient anxiety levels, and in part from normal variations in blood pressure (*e.g.*, systolic blood pressure noted to range from 75 to 200 mmHg during waking hours in normotensive individuals).[2] Thus, the ability to predict those patients in whom a particular blood pressure decrease is potentially detrimental is not as clear as it first seems.

Although the cerebral autoregulatory curve is known to shift in chronic hypertensives, the magnitude of the shift and the relevance of previous studies to our patient population are unclear. Most of the previous studies were performed in patients with severe arterial hypertension and mean pressures ≥ 150 mmHg.[3] However, none of our patients had mean arterial pressures greater than 150 mmHg, and only 18 of our patients had diastolic blood pressure greater than 100 mmHg, at baseline. Thus, the significance and relevance of this factor in our patient population is unknown.

We conclude that there is no definition of hypotension that will satisfy all audiences. Relative definitions of hypotension have the advantage that they have been utilized in many previous studies. However, we believed that the limitations, described above, outweighed the benefits. After much deliberation, we chose an absolute definition based on systolic blood pressure because we thought this definition had the most clinical relevance for this study.

The authors also question the role of fluid loading in preventing hypotension. Although we did not prospectively assign patients to receive different volumes of intravenous fluids prior to initiating spinal anesthesia, we did record the amount of fluid preload administered and attempted to correlate these volumes with the incidence of hypotension. None of these correlations proved to be statistically significant. Consequently, these findings were reported only in the results section of the paper and not expanded upon in the discussion.[4]

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# Nitrous Oxide—It's Enough to Make You Vomit

*To the Editor:*—After tabulating the results of eight studies that examined the effect of $N_2O$ on vomiting,*[1–7] Watcha and White recently concluded: "The evidence at present suggests that nitrous oxide does not significantly effect [sic] the incidence of postoperative emesis in adults when halogenated inhalation agents are used (table 3)."[8] However, examination of Watcha and White's table shows that half of the studies listed found a statistically significant association between $N_2O$ and emesis,*[1,6,7] and all of the "negative" studies found a higher incidence of vomiting in their $N_2O$ groups, though not by a statistically significant amount.[2–5]

One of the "negative" studies found that twice as many $N_2O$ patients vomited, but because the sample size was small, the $P$ value was .054, so the association was discounted.[2] Another of the "negative" studies lumped vomiting, retching, and nausea together, but when vomiting alone is considered, the result is significant at $P < .006$ (chi square).[3] The one nongynecologic "negative" study excluded patients at high risk for emesis from preexisting conditions and excluded surgical procedures associated with emesis, but included patients who had experienced "nausea and/or vomiting with previous general anesthesia."[5] These exclusion criteria limit the clinical generalizability of the study's findings but do not challenge their validity. Inclusion of individuals with a history of vomiting subsequent to surgery also would be valid if both the $N_2O$ and non-$N_2O$ groups had contained approximately equal numbers of such individuals, but that was not the case. Muir and coauthors' non-$N_2O$ group was assigned significantly more patients known to vomit subsequent to surgery ($P < .03$, chi square), biasing their result from finding a high incidence of vomiting associated with $N_2O$.[5] Nevertheless, when vomiting is distinguished from nausea, Muir and coauthors found the association, but it was not statistically significant.

Instead of noting an apparent trend, Watcha and White discounted the four statistically significant findings because "none . . . was controlled for the day of the menstrual cycle"—which might be a

* Alexander GD, Skupski JN, Brown EM: The role of nitrous oxide in postoperative nausea and vomiting (abstr). Anesth Analg 63:175, 1984

valid concern for sample sizes in which women at high risk for emesis could be disproportionately assigned to an $N_2O$ group by chance; but for samples with a combined total of 683 randomly assigned individuals, this is a somewhat unrealistic concern.*[2-4,6,7] That realization aside, one wonders why not controlling for day of menstrual cycle was not perceived as invalidating the three gynecologic studies that found an association between $N_2O$ and vomiting but did not report significant results[2-4]—since women at high risk for emesis would be as likely to be disproportionately assigned to a non-$N_2O$ group.

Three studies are mentioned in Watcha and White's text, but not in their table 3. One of those found a statistically significant relationship between $N_2O$ and vomiting[9] and two did not.†[10] One of those latter two lumped nausea, vomiting, and retching such that the frequency of emesis *per se* cannot be determined.†[10] Watcha and White's table 3 also failed to include consideration of Eger and coauthors' findings regarding nitrous oxide and emesis in 270 nongynecologic patients.§[11]

Table 1 presents the results of all the above-mentioned studies except the one for which a frequency of emesis could not be determined[11] and the study that included a disproportionately high number of patients with a history of emesis subsequent to surgery in the group that did not receive $N_2O$.[5] If only nongynecologic patients are combined,†[9,11-13] $N_2O$ associates with an increase in emesis at $P < .004$. If only studies reporting a lack of statistical significance are combined,†[2-4,11,13] $P$ decreases to <.002, and if only patients undergoing gynecologic procedures are combined,*[2-4,6,7] $P$ decreases to $1.6 \times 10^{-10}$. When all ten studies are combined,*†[2-4,6,7,9,11] $N_2O$ is associated with a 90% increase in incidence of vomiting, with a 95% confidence interval of 58–132%, at $P = 2.3 \times 10^{-12}$.

A meta-analysis of the above studies, reveals a dramatically increased risk of emesis associated with $N_2O$. Accordingly, the weight of the evidence supports an association between $N_2O$ and vomiting, both on its face and by analysis. Until evidence to the contrary is conclusive, we should take that evidence at face value. In particular, studies showing an association between $N_2O$ and emesis that are not statistically significant and that utilize sample sizes too small to have power > 0.80 (probability of a type II error, or false-negative, >0.20) should not be considered.[12] Put less formally, we should remember that absence of evidence is not evidence of absence.[13]

Unlike people, drugs should not be presumed innocent until proven guilty beyond the shadow of a doubt. In the case of $N_2O$, an association with emesis *has been* shown beyond the shadow of a doubt, which raises a question about the frequency with which a drug is used and its users' objectivity when assessing its merits.

**Table 1. Association between Postoperative Emesis and Use of Nitrous Oxide during Surgery**

| Study | $N_2O$/ Emesis | $N_2O$/ No Emesis | No $N_2O$/ Emesis | No $N_2O$/ No Emesis |
|---|---|---|---|---|
| Alexander *et al.** | 23 | 14 | 11 | 29 |
| Lonie *et al.*[1] | 20 | 21 | 8 | 38 |
| Sengupta *et al.*[2] | 11 | 22 | 4 | 27 |
| Hovorka *et al.*[a,3] | 23 | 27 | 10 | 40 |
| Korttila *et al.*[4] | 9 | 46 | 7 | 48 |
| Felts *et al.*[6] | 26 | 63 | 9 | 87 |
| Melnick *et al.*[7] | 8 | 24 | 1 | 27 |
| Watcha *et al.*[9] | 46 | 44 | 7 | 23 |
| Gibbons *et al.*§ | 11 | 10 | 10 | 9 |
| Eger *et al.*[11] | 58 | 68 | 46 | 88 |
| Total[b] | 235 | 339 | 113 | 416 |

[a] Emesis patietns only.

[b] $N_2O$ increases vomiting by >90%, $P = 2.3 \times 10^{-12}$ (chi square), 95% CI = 58–132%.

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† Gibbons P, Davidson P, Adler E: Nitrous oxide does not affect postoperative vomiting in pediatric eye surgery (abstr). ANESTHESIOLOGY 67(suppl):A540, 1987.

‡ Dr. Pandit informed me by telephone that the data may not have been coded in a manner that will allow *post hoc* separation of nausea and vomiting.

§ Patients receiving isoflurane with or without $N_2O$ for hip arthroplasty, carotid endarterectomy, or transsphenoidal hypophysectomy were monitored prospectively to test "the hypothesis that nitrous oxide causes . . . [among other untoward effects] . . . vomiting." Eger *et al.* found that 46% of patients receiving $N_2O$ vomited *versus* 34% of patients who did not receive $N_2O$.[11] According to their methodology, nominal data were to be analyzed by "Fisher's exact test (two-tailed)," which gives a $P$ value of .059 for the observed relationship. This analysis is peculiar because two-tailed tests are appropriate for two-way hypotheses (*e.g.*, "$N_2O$ *either* increases *or* decreases vomiting"). Two-tailed tests are also proper when false-positives are of particular concern and the direction of an hypothesis is not stated *a priori*. However, Eger *et al.* specifically stated a one-way hypothesis, *i.e.*, $N_2O$ increases vomiting. In the interest of avoiding false-negatives, which are the greater liability when untoward effects of anesthetics are at issue, two-tailed tests should not be used. On a one-tailed Fisher's exact test, the data of Eger *et al.* are statistically significant at $P = .036$.

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*In Reply:*—We thank the editor for the opportunity to respond to the letter by Hartung, who has commented on the association between postoperative nausea and vomiting. For many years, Hartung has been eloquently arguing for power analysis *prior* to the start of a study, so that adequate number of patients are enrolled and negative results are not due to a type II error.[1,2] It is therefore surprising that his analysis excluded the most powerful study of the effects of nitrous oxide on postoperative nausea and vomiting. The study by Muir *et al.* involved a total of 780 patients and had a power of 90% in detecting a *two-sided difference* in the incidence of postoperative nausea and vomiting of 0.16 at an $\alpha$-level of 0.05.[3] Yet, Muir *et al.* failed to demonstrate a significant difference in the incidence of emesis between patients who received or did not receive nitrous oxide. Hartung rejected this study as more patients with a history of previous postoperative emesis were assigned to the non-nitrous oxide group. However, he has included other studies in his analysis where confounding factors associated with postoperative nausea and vomiting were not evenly distributed between the study groups.*[,4,5] For example, in the study by Alexander *et al.*, the group receiving nitrous oxide also received opioids in contrast to one of the groups receiving isoflurane without nitrous oxide.* In the study by Watcha *et al.*, prophylactic droperidol was administered to some of the patients but not to others.[4] In the study by Eger *et al.*, some patients underwent spinal anesthesia, whereas others did not.[5]

We believe it is an oversimplification to perform a meta-analysis by simply pooling all cases who received or did not receive nitrous oxide (regardless of other drugs used). The selection process of trials to be included in a meta-analysis should be rigorous and uniformly applied to all trials.† In addition, the statistical tests used should be chosen on a consistent basis. For example, Hartung has used a one-tailed Fisher's exact test rather than a two-tailed test to achieve a $P$ value of $<.05$ for the data by Eger *et al.*[5] This approach is valid only if one assumes that nitrous oxide increases emesis. We submit that several well controlled studies in the anesthesia literature*[,3,5,6,7] do not support Hartung's suggestion that the association of nitrous oxide with emesis has been shown "beyond the shadow of a doubt."

We would encourage Hartung to perform a study of the effects of nitrous oxide on postoperative emesis in an "at-risk" patient population undergoing the same operative procedure where other confounding factors have been carefully controlled during the postoperative period and the number of patients enrolled in the two study groups is adequate to avoid a type II error. These data will be more convincing than an argument based on the selective use of statistical tests and clinical studies designed to answer other questions.

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