respiratory outcomes. Review of the data in table A3 seems to confirm this finding. Nevertheless, the model and the logistic coefficients from table 1 suggest that these factors are protective for severe respiratory outcomes. In fact, across all outcomes in which these factors were reported as significant predictors, in both table 1 and table A3, they seem to be protective. For example, take the hypothetical case used by the authors: a 60-y-old person with a smoking history and a history of high blood pressure. They report a 0.5% probability of this patient developing severe perioperative hypertension. If this patient were a nonsmoker, his risk of developing severe perioperative hypertension increases to 0.7%. Similarly, an obese male smoker has a computed risk of 0.5% of developing any severe respiratory outcome. His thin, female, nonsmoking counterpart's computed risk is 1.9%. Is this due to a typographic error? If not, can the authors explain this data?

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Adverse Outcomes and the Multicenter Study of General Anesthesia: II

To the Editor:—As a follow-up to the 1990 publication of the results of "Multicenter Study of General Anesthesia"[1,2] (a randomized, controlled clinical trial of four general anesthetics), a subset of the authors have published a secondary analysis of the original data, seeking predictors of severe perioperative adverse outcomes by a multistage method (univariate contingency table analysis followed by stepwise logistic regression analysis).[3] The general approach and statistical methods were up to date and received the approbation of a statistician editorialist, although he did specify the need for prospective validation of the predictors from this trial data set in a new data set.[4] Various demographics, disease states, operative procedures, and anesthetics were related to certain individual severe adverse outcomes and supersets of severe adverse outcomes, particularly changes in hemodynamic variables. These outcomes—hypotension, hypertension, tachycardia, and bradycardia—were defined as a 20% change from preinduction values. An adverse outcome was declared severe if a therapeutic intervention of a significant degree was required; one example was given—administration of an antiarrhythmic drug to treat ventricular arrhythmia. Observations of these hemodynamic variables continued for up to 7 days postoperatively. It is not specified what proportion of these hemodynamic events occurred during each of the perioperative and postoperative periods.

I wish to challenge some of these results, particularly those concerning anesthetic choice and adverse hemodynamic outcome. In their original report, it was explicitly stated that the low incidence of death, myocardial infarction, and stroke and the study size (46 events in 16,023 patients completing the protocol) prevented definitive comparisons between anesthetics for morbidity and mortality; there were 10 patients in each anesthetic group with one or more of these outcomes. The original report clearly showed different patterns of hemodynamic alterations among the anesthetics, more tachycardia with isoflurane, and more hypertension with fentanyl. In this new exploratory analysis, halothane, isoflurane, and fentanyl, as contrasted to enflurane, were classified as increasing the risk of "any severe cardiovascular outcome" (the superset of hemodynamic changes plus arrhythmias).

It is unreasonable at the present time to categorize hemodynamic variables as true outcome variables such as death, myocardial infarction, and stroke. Blood pressure and heart rate changes during anesthesia are a reflection of the dynamic interaction of patient disease, surgical procedure, anesthetic drugs, and clinical care. Such variables are considered process or intermediate variables. It is clearly plausible that changes in blood pressure and heart rate might be part of the process of producing real morbidity and mortality. If this correlation between process and outcome were statistically well established, then hemodynamic changes might be considered surrogate endpoints for the endpoints of interest.[5] Such might not be the case in these patients. Mangano reviewed and summarized an enormous body of literature, concluding that hypotension and tachycardia were predictors of perioperative cardiac morbidity; hypertension and arrhythmias were indeterminate as predictors.[6] Many of the studies considered important concerning hypotension and tachycardia were in patient populations with a high prior probability of ischemic heart disease. Moreover, the definitions of hypotension and tachycardia tended to be more stringent in the reports reviewed by Mangano than in the definitions by Forrest *et al.* Considering the generally healthy patients in the Multicenter Study (more than 90% ASA physical status 1 and 2), the rather modest vital sign deviations defined as hemodynamic abnormalities, the unreported specific meaning of significant therapy, and the lack of blinding as to anesthetic agent, allowing a bias in the willingness or attentiveness for treating arrhythmias and hemodynamic changes, I would argue that hemodynamic changes should be treated only as process variables in this study.

Forrest *et al.* do mention some appropriate reservations about the generalizability of their results. However, the loudest messages of their paper are that anesthetic choice alters the risk of hemodynamic changes and that hemodynamic changes are important outcome variables; thus anesthetic choice is an important determinant of outcome. Though not advocating a sloppy inattentiveness to hemodynamics during anesthesia, I believe a more conservative interpretation of their data is to be preferred for healthy patients: 1) the current level of research effort can not distinguish mortality and serious morbidity between the most common anesthetic agents, and 2) the clear differences in hemodynamic patterns among these anesthetic agents has an unknown, perhaps nonexistent, relationship with mortality and serious morbidity.

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In Reply:—Burke points out that certain risk factors in a univariate chi-square analysis increase the probability of outcome occurrence while there is an apparent decrease in the probability for the same risk factors in a logistic regression. "Any severe respiratory outcome" (ASRO) refers to patients with at least one of the sixteen types of severe respiratory outcomes that were studied.[1] The relative risk (cf. Table A3)[2] of ASRO in 5,965 smokers in the study population of 17,201 patients was 1.77 times the risk in 11,236 nonsmokers ($P = 3.2^{-4}$). Also the risk of ASRO in 523 patients with chronic obstructive pulmonary disease (COPD) was 3.00 times the risk in 16,678 patients without COPD ($P = 1.2^{-4}$), and the risk of ASRO in 6,014 male patients was 1.75 times the risk in 11,187 female patients ($P = 4.4^{-4}$). Since a relative risk greater than 1 is an increased risk (and less than 1 is a reduced risk), we conclude that patients who smoke, or who have COPD, or who are male, have an increased risk of perioperative ASRO. This is in accord with what we would have expected from clinical experience.

We next tested the importance of these risk factors and all others with a significant chi-square statistic, as independent predictors of severe adverse outcomes, using a series of different stepwise logistic regressions (SLR). We reported the findings for the final model (table 1)[2]; the findings were similar in each of the sequential models tested. Burke's question prompted us to request another audit of the coding used by the Data Management Center for these SLRs. An error was found in the coding. In table 1, male should be female, obesity should be nonobese, and smoking should be nonsmoking. To calculate the probability of an outcome for male, obesity, and smoking the logistic coefficients for these predictors should have a negative sign. We are grateful to Burke for pointing this out to us. There were six significant predictors for ASRO, each with a negative logistic coefficient. These were, with percent probability (Pr) in parentheses: history of cardiac failure (Pr = 6.6%), history of COPD (Pr = 4.1%), obesity (Pr = 3.6%), male (Pr = 3.3%), abdominal surgical procedures (Pr = 3.2%), and smoking (Pr = 2.8%). To the extent that there were only certain risk factors entered in the final SLR, these findings represent the important factors contributing to the risk of ASRO. We conclude from this that a history of COPD is a more important predictor of ASRO than smoking status in this SLR model.

A positive logistic coefficient for a risk factor should not be interpreted as protective for an outcome, as Burke suggests. Rather, the relative importance of each factor can be assessed in terms of its contribution to the overall probability for that outcome within the algorithm that now defines the model. For example, the probability of severe hypertension in patients with a history of hypertension is 0.3% (b = −0.75); in patients having cardiovascular surgical procedures the probability is 1.0% (b = −1.18); and in patients having gynecologic surgical procedures the probability is <0.1% (b = 1.08). Thus, cardiovascular surgery is a more important predictor of severe hypertension than either a history of hypertension or gynecologic surgery. Obviously there are likely to be influential relationships between certain risk factors (*e.g.*, COPD and smoking, coronary artery disease and age, hypertension and diabetes). We did not specifically test for such interactions in detail, but it would be of interest to do so.

We have already discussed the possible limitations and potential bias in our study. It should be noted also that not all patients in the study were included in the SLR models. Thus, although there were 5,965 smokers, 6,223 obese patients, and 6,014 males in the study, there were only 4,761 smokers (79.8%), 5,530 obese patients (88.9%), and 4,537 males (75.4%) entered in the final SLR model. In large studies such as ours it is inevitable that in some patients, some data are missing. This leads to their rejection from entry in the SLR. We cannot be sure that this did not exclude patients in a nonuniform way. Because the result was very similar in each of the SLR models, we believe that this possibility is remote.

One further difficulty in interpreting our findings is that some of the severe perioperative adverse outcomes as we defined them[1] may be in themselves risk factors, as we[1] and Pace have stated. This seems most likely with severe hemodynamic disturbances, which he argues should be classified as "process variables" rather than outcomes, citing our example of severe tachycardia in patients with cardiac disease as a risk factor for perioperative myocardial ischemia. For the purpose of our study, we defined an "outcome" simply as a result or consequence of the care provided to our patients. This definition includes mortality, serious morbidity, and dysfunction (mild, moderate, or severe). Although there is no consensus on the preferred terminology, our definition of outcome agrees with others.[3,4] In large multiinstitutional studies, it is essential that every effort is made to ensure consistency and completeness in the reporting of outcomes. We agree that our criteria for changes in blood pressure and heart rate reported as outcomes were quite modest, but we considered this to be mandated by the objective of the study in testing our hypothesis—that there are differences among the four anesthetics for adverse outcomes such as arrhythmia, hypotension and vomiting.[1] The process we used to verify our data was extensive, and when we discuss severe outcomes we have already excluded all patients with minor or moderate hemodynamic disturbance. For example, there were 5,275 patients with hypotension (30.7%)[5] and 6,969 patients with tachycardia (40.5%), but of these there were only 191 patients with severe hypotension (3.6% of the patients with hypotension) and only 153 patients with severe tachycardia (2.2% of the patients with tachycardia). In addition to rating outcomes for severity, each outcome was given an "occurred with" and "treated with" subcode and these were reviewed in detail to ensure the inclusion of only those patients with clinically important severe adverse outcomes.

In previous papers[5] we reported significant differences among the study anesthetic groups for severe outcomes (tachycardia, hypertension, ventricular arrhythmia, and bronchospasm) and found essentially the