Negative Inferences about Rare Events Require Large Samples

To the Editor.—Todd et al. compared three partially overlapping anesthetic combinations in a series of neurosurgery patients (n < 40 per group) and concluded that “the specific choice of anesthetic agent(s) may not be the most crucial aspect of successful neuroanesthetic practice.” It would be difficult to find an anesthesiologist who would have disagreed with this tentative conclusion before considering Todd and coauthors’ results.

A more engaging conclusion is implied by the authors’ penultimate summary statement: “Our data also support the belief that, despite the presumably different effects of these three anesthetic techniques on cerebrovascular physiology, only small differences in ICP were observed, and these differences were of minimal relevance in these elective patients.” The inference here is that a statistically significant fourfold increase in the incidence of patients with intracranial pressures (ICP) greater than 24 mm Hg, accompanied by “a greater degree of swelling at time of craniotomy” and a statistically significant twofold increase in recovery time, in the isoflurane/N₂O group, is of minimal relevance.

When statistically significant findings of substantive magnitude regarding clinically relevant variables are diminished, if not dismissed, readers need to be especially wary about inferences drawn from results that were not statistically significant but would be of clinical concern if validated—especially when the events measured are known to be infrequent and sample sizes are too small to provide statistical power (probability of a false negative <0.20). For example, if Todd et al. had obtained the same proportionate results with sample sizes doubled, even their single-measurement average ICP differences would have been statistically significant (as distinct from differences in incidence of high ICP, which are of more clinical concern, and which were statistically significant). If sample sizes were tripled, their observed differences in frequency of mannitol use would have been statistically significant. And if sample sizes had been five times larger (still on the small side for making negative inferences about rare events), their observed twofold increase in “brain severely swollen, specific therapy required” patients (propofol/fentanyl and isoflurane/N₂O groups compared to the fentanyl/N₂O group) would have been statistically significant.

If only differences in incidence of “new or worsened neurologic deficit” warrant inferences about anesthetic selection for neurosurgery, any negative result derived from fewer than 200 patients per group should not be considered for publication, and a study that contains fewer than 100 patients per group should be considered not to have found statistically significant results by design. Todd et al. reported their results on neurologic deficits by stating, “Thirty-five of 121 patients (29%) had some new or worsened neurologic deficit when examined 24 h postoperatively, but there were no differences among anesthetics.” Does this mean that no statistically significant differences were found, or does it mean no differences were observed? Was it a 12–12–11 split among the three groups? If not, was it a counterintuitive result in which the opioid/N₂O group—the group that had lowest average ICP, fewest ICPs >24, and fewest severely swollen brains—had the most neurologic deficits?

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In Reply.—In 1979, Eiger noted in an editorial for the Journal that “long ago my father warned me that I could not disprove the existence of dragons.” There are many dragons in medicine, and some of these are believed to threaten the castle we know as neuroanesthesia. One concerns drug selection for elective intracranial surgery, and despite a lack of any substantive clinical evidence suggesting that one anesthetic(s) is better or worse than another, some continue to argue that we should or should not use particular agents during elective neurosurgery. Some might accuse us of violating the above caveat when we state that we could not find important intergroup differences, and Hartung and Cottrell suggest that our results fail to provide conclusive proof that differences do not exist. We cannot disagree with this premise, but believe that more important issues are involved. Their letter focuses on the fact that “power analysis” suggests that