Anesthesiology
65:232, 1986

An Assessment of Statistics

To the Editor:—The February issue of ANESTHESIOLOGY contained an article by Nussmeier *et al.* on "Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate,"[1] and an accompanying Editorial,[2] which suggested that this "proven" therapeutic intervention not be denied patients. In the latter, Michenfelder comments that this study yields results demonstrating a statistically significant (at the 0.05 level) beneficial effect. This significant result was obtained from the incidence of neuropsychiatric dysfunction persisting on the 10th postoperative day. We reconstruct these data as:

Persistent Dysfunction Diagnosed	Study Group	
	Thiopental	Control
Yes	0	7
No	89	86

Using Fisher's exact test, we concur that these data give $P < 0.025$. Given the difficulties in diagnosis experienced even by fully trained neurologists and psychiatrists, the ever-present problems of observer bias, and the exclusionary criteria for a positive diagnosis, it seems possible that one of the 89 patients receiving thiopental was characterized wrongly. If the zero in the table becomes a one, then the Fisher's test no longer results in significance ($P > 0.05$). Unfortunately the authors do not provide us with information to judge chronologic changes in dysfunction, omitting all the two-part Trail-Making test material and the results of the day 5 assessments.

February also saw publication of an article that used elegant statistical methods to assess the value of thiopental loading in comatose survivors of cardiac arrest.[3] An accompanying Editorial,[4] from another Houston institution, states that the use of barbiturate coma on the pretense of preserving brain function after cardiac arrest or stroke has no clinical basis and should be abandoned. Michenfelder, too, cannot support barbiturate therapy for complete cerebral ischemia, but makes a strong recommendation for its use during cardiac surgery based on this "valid, randomized, prospective study."[2] Although the cardiopulmonary bypass study was well designed, the flaws in its execution lead us to question its validity and the need for this therapy to become an essential part of standard care of the patient undergoing open heart surgery.

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(Accepted for publication April 7, 1986.)

Anesthesiology
65:232–233, 1986

In reply:—My enthusiastic editorial endorsement of the Nussmeier *et al.* study[1] was quite deliberate but perhaps warrants some elaboration. I, of course, anticipated a healthy, skeptical response on the part of at least some of the readers. Indeed, such a response had already been elicited from one of the reviewers of the original manuscript (see editorial).[2] But let me address the concerns expressed in the preceding letters. As to the implied criticisms regarding the statistical analysis of the data, I am somewhat at a loss. Apparently Shanks *et al.*[3] agree that the proper statistical test was used and that significance was demonstrated at a P value of less than 0.025. They then manipulate the reported data in order to determine what would be required to yield a P value greater than

0.05; this makes no sense to me. Either one accepts the statistical approach to analyzing data or not. Rightly or wrongly, I believe the former, it is the commonly accepted scientific approach for linking conclusions to data.

The San Diego group, while accepting the scientific validity of the study, question its clinical application on the grounds that the management of the control group was not representative of the usual standard of practice for such patients.[4] Specifically, they fault the failure to use hypothermia, membrane oxygenators, and arterial filters during bypass as well as the use of glucose-containing solutions in the pump prime. Accordingly, they speculate that the incidence of neuropsychiatric deficits in the control group may have been artificially high, thus exaggerating the beneficial effects of thiopental therapy. Because this is far from my area of expertise, I cannot effectively respond to this criticism and will instead rely on my colleagues who specialize in cardiac anesthesia to thrash this one out.

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(Accepted for publication April 7, 1986.)

Anesthesiology
65:233, 1986

In reply:—Neither of these two thoughtful letters finds fault with our scientific methods or conclusions. Both, however, express discomfort with our clinical recommendation. Although Scheller *et al.* acknowledge our incidence of neuropsychiatric dysfunction in the control group was well within the range reported by others, they remarkably suggest that if we perfused patients properly, we would have no neurologic dysfunction in the control group and would not need barbiturate protection. For support, they cite three studies of cardiopulmonary bypass in humans, not one of which claims to show objective reduction in cerebral dysfunction by filters, membranes, or hypothermia, and three reports of temporary global cerebral ischemia in animals, a model not related to that considered here. Until someone can demonstrate an absence of neurologic dysfunction by optimal perfusion of the population we studied, thiopental seems to be indicated for patients managed with "suboptimal" perfusion.

Shanks *et al.* should know that truth is not established by a *P* value. Our recommendation was based not on this "significant" difference alone, but rather on: 1) the growing evidence that embolus is the commonest cause of cerebral dysfunction after open heart operations[1,2]; 2) the striking similarity between these temporally predictable events and animal models of focal cerebral ischemia[3,4]; 3) a wealth of data describing the benefit of barbiturates in the animal model[3–5]; and 4) the beneficial dose–response effect found in our two investigations.

Although the risk of thiopental therapy (greater hemodynamic instability after cardiopulmonary bypass and slow postoperative awakening) is not insignificant, the benefit of reducing the incidence and severity of this potentially devastating complication is compelling. We, too, anxiously await the appearance of data from other centers as the only way to establish the wisdom of our recommendation.

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(Accepted for publication April 7, 1986.)