ANESTHESIOLOGY

A Beautiful Friendship—and a Lesson about Friends and Colleagues: A Classic Partnership Revisited

David S. Warner, M.D., Michael M. Todd, M.D.

ANESTHESIOLOGY 2022; 136:176–80

Abstract

David Warner, M.D., and Michael Todd, M.D., first met in 1985. They began working together at the University of Iowa (Iowa City, Iowa) a year later with a shared interest in both laboratory and clinical neuroscience—and in the operative care of neurosurgical patients. That collaboration has now lasted for 35 yr, resulting in more than 70 joint publications. More importantly, they have had the privilege of working together with close to 1,000 colleagues from around the world, in a dozen medical specialties. Their careers are an example of what can be accomplished by friendship, mutual commitment, persistence, and a willingness to join with others.

(ANESTHESIOLOGY 2022; 136:176–80)

I, David Warner, M.D. (fig. 1), started life as a neurosurgery resident at the University of Iowa (Iowa City, Iowa). But I shortly thereafter saw the light and changed to anesthesiology. After finishing residency, and at the urging of Dr. John Tinker, I did a research fellowship in neuroscience in Lund, Sweden, with Bo Siesjo, one of the world's experts in central nervous system metabolism and ischemia. I then returned to a faculty position at Iowa.

Fig. 1. Dr. David S. Warner is the Distinguished Professor of Anesthesiology, Professor of Neurobiology and Surgery, Director of the Multidisciplinary Neuroprotection Laboratories, and Past Vice Chair for Research in the Department of Anesthesiology at the Duke University School of Medicine. He has been a longtime Editorial Board member of ANESTHESIOLOGY.

I, Michael Todd, M.D. (fig. 2), was hooked on neurosurgical anesthesia and central nervous system physiology from the start of my residency at Massachusetts General Hospital (Boston, Massachusetts), due largely to the influence of Drs. Aaron Gissen and Phillip Morris. After finishing, I spent 2.5 yr in the laboratory of Dr. Harvey Shapiro at the University of California, San Diego (San Diego, California), followed by 5 yr on faculty there (alongside Dr. John Drummond). In 1986, a number of factors encouraged my move to the University of Iowa, where a lifelong collaborative friendship began.

Since we shared a new laboratory, and since our interests were so similar, there was never any question about sharing the work. It started from the first day. Our first joint publication appeared in ANESTHESIOLOGY in 1988 and was a perfect example of the merging of two interests. The article examined the differing distribution of cerebral blood flow during halothane and isoflurane anesthesia. This was something that Dr. Todd had worked on in California, and it used the autoradiographic techniques learned by Dr. Warner in Sweden.[1] Over the next 2 yr, another 16 joint publications would appear.

But even before that first article was published, we recognized an unmet need in the neuroanesthesia community. At that time, the field (and SNACC—then the Society for Neurosurgical Anesthesia and Critical Care, now the Society for Neuroscience in Anesthesiology and Critical Care, Richmond, Virginia) was dominated by very senior academics like Jack Michenfelder, Harvey Shapiro, Maurice Albin, Jim Cottrell, and a few others. However, there was a cadre of young scientists who shared a frustration with the

Submitted for publication November 1, 2021. Accepted for publication November 5, 2021. From the Duke University School of Medicine, Durham, North Carolina (D.S.W.); the Department of Anesthesiology, University of Minnesota School of Medicine, Minneapolis, Minnesota (M.M.T.); and the Carver College of Medicine, University of Iowa, Iowa City, Iowa (M.M.T.).

 Anesthesiology 2022; 136:176–80. DOI: 10.1097/ALN.0000000000004088

Fig. 2. Dr. Michael M. Todd is currently the Professor and Vice Chair for Research in the Department of Anesthesiology at the University of Minnesota School of Medicine and Professor Emeritus of the Department of Anesthesia at the Carver College of Medicine at the University of Iowa. He served as the Chair of the Department at Iowa from 2004 to 2015, and as the Editor-in-Chief of ANESTHESIOLOGY from 1996 to 2006.

time restrictions imposed on scientific presentations at our national meetings. We wanted to bring this group together and "talk science" openly, without the time constraints.

So, in 1987 we convened an informal meeting at the University of Iowa that was restricted only to the "new kids." Fourteen people from outside of Iowa came; everyone paid their own way (fig. 3). We met in a small conference room, and there were no time limits on anyone's presentation. People discussed their work until they were done talking, and then we moved to the next presentation. The only entertainment was beer and pizza. It was a striking success, not just as a meeting, but as the start of the so-called Unincorporated Neuroanesthesia Research Group (UNRG), which continued as an international meeting until 2004—basically until the "new kids" had grown into the "old guys." But much more importantly, it helped build a collaborative network of young neuroanesthesiologists, which paid off in later years.

Our laboratory in Iowa was focused on a mixture of basic cerebrovascular physiology and cerebral ischemia, with a variety of other subjects that caught our attention. It was an incredibly productive time that resulted in 47 basic science publications. But we were both active clinicians working in the neurosurgical operating rooms. Not too long after we started working together (we don't remember if this was before or after the UNRG), we began to think more seriously about how we could translate our laboratory interests into our clinical lives.

Our first step was prompted by a faculty meeting at which a pharmacy representative argued that we should remove *one* of the newest opioids, sufentanil or alfentanil, from the formulary. Both drugs were expensive. An intense argument among the faculty ensued, with everyone chiming in about differing pharmacokinetics and their anecdotal preferences. Immediately after the meeting, the two of us turned to each other and said, "Why don't we really find out if it matters which drug we use?" At that time, the standard "neurosurgical anesthetic" at Iowa was a nitrous oxide–opioid anesthetic, with or without an additional volatile agent. The opioid was usually morphine or fentanyl, but sufentanil or alfentanil was also used. The pharmacokinetic differences between these drugs in controlled settings had been established, but no one knew whether these differences would translate into anything clinically meaningful in the heterogenous population of neurosurgical patients.

So, along with our colleagues Dr. Robert From and Dr. Martin Sokoll, we started work in 1988 on the first-ever formal clinical trial for all of us. With the help of published pharmacokinetic data and the advice of Dr. Donald Stanski at Stanford University (Stanford, California), we developed a method to deliver equipotent doses of alfentanil, fentanyl, or sufentanil—first as loading doses, then as continuous infusions. In the era before operating room pharmacies, Dr. From had to prepare the blinded syringes himself, labeling them simply as "loading" or "infusion." The drugs were given in standardized milliliter/kilogram or milliliter/kilogram/minute doses, combined with nitrous oxide. Supplementary isoflurane was added only if indicated by hypertension. Patients undergoing craniotomy for tumor resection were randomized to one of the three opioids. None of the surgeons or anesthesia providers knew what they were giving—it was a true double-blind study.

To our surprise, there were almost no differences between the groups, except for a lower respiratory rate in the postanesthesia care unit in the sufentanil patients, and a bit more intraoperative ephedrine administration in the alfentanil group.[2] Wake-up times were nearly identical. Even more surprising, when the anesthesiologists were asked which drug they thought they were giving, they simply could not tell (the guesses did not differ from a chance pick).

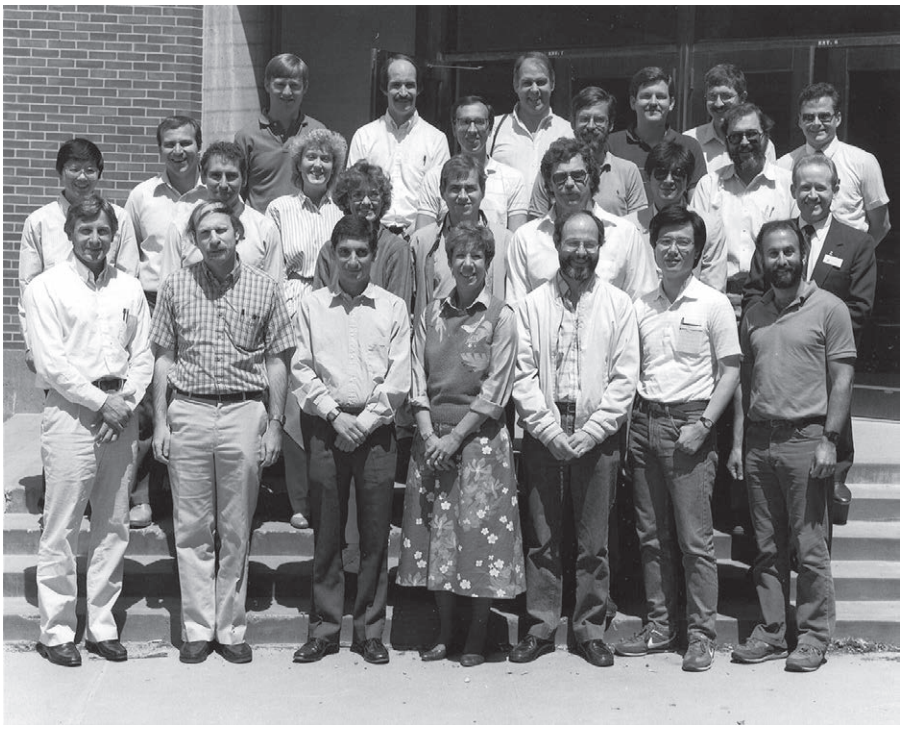

Fig. 3. First meeting of the Unincorporated Neuroanesthesia Research Group, Iowa City, Iowa, 1987. An almost complete list of attendees: David Archer, Verna Baughman, Dan Cole, Lisa Cook, Greg Crosby, Jerry Fleisher, Adrian Gelb, William Hoffman, Reiji Kaida, Ira Kass, Jeremy Katz, William Lanier, Bob McPherson, Leslie Milde, Mark Scheller, Armin Schubert, Mike Todd, David Warner, Jei-Gang Zhou, and Mark Zornow.

In retrospect, based on what we now know about clinical trials, there were a lot of flaws in that work—but it was still a huge eye-opener for us. We saw the power of a real blinded study to challenge our preconceived notions. And we learned a lot about the logistics of such a study. It started us on the path to bigger and better trials.

Neuroanesthesiologists had always been interested in "which anesthetic is better"—although there was little agreement on what constituted "better." There were endless discussions at meetings that focused primarily on physiological measures such as cerebral blood flow, cerebral metabolism, intracranial pressure (ICP), *etc.*, based largely on animal work. At the same time (in 1991 or 1992), AstraZeneca (Cambridge, United Kingdom) approached us to examine propofol. The package insert warned against use in neurosurgery due to "reduced perfusion pressure." We saw this as an opportunity to do a broader comparative study, so we designed a randomized trial (not double-blinded this time) to look at a pure volatile anesthetic (isoflurane/nitrous oxide), a pure intravenous anesthetic (propofol/fentanyl), and a "default" fentanyl/nitrous oxide/low-dose volatile anesthetic, as in our previous project.[3] This time, in addition to the standard clinical assessments, we were able to measure ICP at the time of first burr hole creation. We also introduced the now commonly used "brain swelling scale" to allow the surgeons to grade the condition of the exposed brain.

We were again surprised by our findings. Wake-up times were faster in the fentanyl/nitrous oxide group, but only by 5 min. In spite of what we *thought* we knew about volatile agents and their ability to increase ICP, we found no meaningful differences in ICP or brain conditions. More importantly, when we examined the relationship between measured ICP (which ranged from 5 to 55 mmHg) and emergence, we found no connection to patient wake-up. The patient with the highest ICP followed commands within 10 min, while a few patients with ICPs of 10 mmHg took as long as 60 min to emerge fully. This began our recognition that drug-related ICP might *not* be as important a "neuroanesthetic measure" as was widely believed.

Laboratory work continued, but we began to ponder a much bigger question. Both of us had devoted a great deal of effort to the study of cerebral ischemia and to the protection of the brain from ischemic injury, jointly publishing about 20 articles on the subject. But we realized that our laboratory studies (in rats) were not necessarily clinically applicable—certainly not without proof in humans. Hence, we started asking, "How could we study brain protection in patients? Which patients? Which protective intervention?" Since we were neuroanesthesiologists, we wanted to focus

on the operating room. We also thought that a proper study of cerebral protection should start with patients who were reasonably neurologically intact at baseline and for whom a protective intervention could be provided *before* an ischemic insult.

Fortunately, just down the hall from our laboratory was the office of James Torner, Ph.D., in the College of Public Health—someone Dave knew from his time in neurosurgery, and who was (and is) one of the foremost experts in the epidemiology of subarachnoid hemorrhage. Jim pointed out that as many as 25% of subarachnoid hemorrhage patients undergoing open aneurysm clipping awoke with new or worsened deficits. This was promising since this incidence of deficits might allow for a clinical trial—until Jim said that we would need to do a study of at least 1,000 patients to detect any meaningful difference for a treatment! We quickly realized that we were facing a challenge far greater than what we had previously encountered. And we still didn't have an intervention.

Our growing cadre of friends in the UNRG came to the rescue. At a UNRG meeting hosted by Dr. David Archer in Banff, Canada, in 1993, we organized an informal session to discuss how we should proceed. We both remember a lively and long conversation. In the end, the consensus was that in spite of some enthusiasm for barbiturates or etomidate (very popular "protective drugs" at the time), the most promising intervention would be mild hypothermia. This stemmed from the recent demonstration (in rats) that temperatures of only 33 or 34°C seemed to be strikingly protective against focal ischemia—and these temperatures were easily achieved and reversed in the operating room. We agreed that patients with reasonably good grade subarachnoid hemorrhage would be the best target group.

David left Iowa in 1994 to set up his own incredibly productive and well-funded laboratory at Duke University (Durham, North Carolina), and almost immediately initiated our first *multicenter* (Duke and Iowa) trial involving remifentanil.[4] But he still remained deeply involved in the design and planning of a five-center pilot trial of hypothermia during aneurysm surgery that grew directly out of the Banff meeting. The pilot was published in 1999,[5] but by then we were well on our way toward using that pilot experience to develop the protocols and build an international group (with many of our UNRG friends) of almost 600 anesthesiologists, neurosurgeons, neuropsychologists, and research assistants at 30 centers from Melbourne, Australia, to Vienna, Austria. This was made possible by Dr. Torner as well as some extremely experienced clinical trialists at Iowa, including Skip Woolsen and Bill Clarke in the College of Public Health, and Harold Adams in Neurology, as well as by Brad Hindman, who had long been a member of the Iowa neuroanesthesia team and research group.

That took us to the National Institutes of Health (Bethesda, Maryland) and led to the Intraoperative Hypothermia for Aneurysms Surgery Trial (IHAST), which at that time was the largest National Institutes of Health–sponsored clinical trial in our profession.[6] Mike was the overall principal investigator, while Brad handled much of the day-to-day operations. Although Duke chose not to be a participating center, David took on the task of reviewing *every* anesthesia record for every enrolled patient—all 1,001 of them!—in nearly real time. He was the *only* person involved with central data management who was *not* blinded to temperatures assigned or achieved—meaning that communication between the two of us was a bit constrained (since Mike was fully blinded). This critical role was intended to ensure uniform protocol compliance patient by patient, center by center. The effort paid off. Some centers were "disciplined," and a few were dropped, but we were told by the National Institutes of Health that this was one of their best conducted trials. Our study, which found no association between intraoperative cooling and postoperative neurologic outcomes in aneurysmal subarachnoid hemorrhage, was published in the *New England Journal of Medicine* in 2005.[6]

Our collaborations have continued. We are both proud of being awarded the American Society of Anesthesiologists (Schaumburg, Illinois) Excellence in Research Award (David in 2005, Mike in 2016). When we looked a few months ago, we discovered that we had coauthored 70 publications together (an underestimate, since David's name does not show up on PubMed for some of the IHAST papers). And the number of additional coauthors on these and other publications of ours, including those that we didn't do together, is too many for us to count (we think nearly 1,000). We both consider all of these individuals from around the world as friends and colleagues, never as competitors.

Good science is not an ivory tower activity. Good laboratory science is rarely done by one person, and good clinical research is *never* a solo undertaking. Our friendship—and our association with so many others—has now lasted for 35 yr and has resulted in what we hope are lasting contributions to our specialty. We think that our experiences are a pretty good lesson for everyone.

Correspondence

Address correspondence to Dr. Todd: Department of Anesthesiology, University of Minnesota School of Medicine, 420 Delaware Street SE, B527 Mayo Memorial Building, MMC 294, Minneapolis, Minnesota 55455. mmtodd@umn.edu

References

1. Hansen TD, Warner DS, Todd MM, Vust LJ, Trawick DC: Distribution of cerebral blood flow during halothane *versus* isoflurane anesthesia in rats. Anesthesiology 1988; 69:332–7

2. From RP, Warner DS, Todd MM, Sokoll MD: Anesthesia for craniotomy: A double-blind comparison of alfentanil, fentanyl, and sufentanil. Anesthesiology 1990; 73:896–904
3. Todd MM, Warner DS, Sokoll MD, Maktabi MA, Hindman BJ, Scamman FL, Kirschner J: A prospective, comparative trial of three anesthetics for elective supratentorial craniotomy. Propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide. Anesthesiology 1993; 78:1005–20
4. Warner DS, Hindman BJ, Todd MM, Sawin PD, Kirchner J, Roland CL, Jamerson BD: Intracranial pressure and hemodynamic effects of remifentanil *versus* alfentanil in patients undergoing supratentorial craniotomy. Anesth Analg 1996; 83:348–53
5. Hindman BJ, Todd MM, Gelb AW, Loftus CM, Craen RA, Schubert A, Mahla ME, Torner JC: Mild hypothermia as a protective therapy during intracranial aneurysm surgery: A randomized prospective pilot trial. Neurosurgery 1999; 44:23–32; discussion 32–3
6. Todd MM, Hindman BJ, Clarke W, Torner J: Mild intraoperative hypothermia during intracranial aneurysm surgery. N Engl J Med 2005; 352:135–45