The History of Neuroanesthesiology

The People, Pursuits, and Practices

William L. Lanier, MD

Abstract: Neuroanesthesiology has a rich history. Although advances in research and clinical practice were cornerstones for the development of this field, other equally critical factors came into play. These include the development of subspecialty societies, formal dissemination of information through textbooks and journal publications, and, most importantly, strong leadership. This article reviews important advances within the subspecialty and many individuals behind those advances. The analysis and speculative synthesis provide insights into the current status of neuroanesthesiology and possible directions for the subspecialty's future.

Key Words: neuroanesthesiology, history, cerebral ischemia, cerebral physiology, general anesthesia, cerebral protection, SNACC, Society for Neuroscience in Anesthesiology and Critical Care

(*J Neurosurg Anesthesiol* 2012;24:281–299)

Human skeletal remains from the late Paleolithic era reveal burr holes in the calvarium, with evidence of postsurgical healing.[1] These are likely the first evidence of neurological surgery, and the patients clearly survived, although the reasons for conducting the surgery are unclear.[1] With the introduction of inhalational anesthesia in the 1840s CE, and the development of neurosurgery as a subspecialty in the late 19th and early 20th centuries by the likes of William Macewen and Victor Horsley in Great Britain, Fedor Krause in Germany, and Harvey Cushing in the United States,[1] it is not surprising that both neurosurgeons and anesthesia providers would someday have clinical and academic interests in codifying best practices and developing the infrastructure (eg, textbooks, journals, organizations, and training programs) to advance a neuroanesthesiology subspecialty.

What is somewhat surprising is that, even in the United States, the birthplace of general anesthesia, approximately 40 years passed from the early development of neurosurgery as a subspecialty until the coalescing of neuroanesthesiology as a distinct anesthesiology discipline.[1,2] During this interval, the broader specialty of anesthesiology had to establish its core organization and values before subspecialization could be taken seriously. The formation and growth of the American Society of Anesthesiologists (ASA) and the American Board of Anesthesiology in the United States and similar organizations internationally, and the maturation of general anesthesiology journals worldwide, were necessary foundations for the eventual birth of neuroanesthesiology.

Despite these rate-limiting steps, in the larger neurosurgical centers, teams of anesthesiologists and neurosurgeons were forming bonds in an attempt to provide the best care possible. Although these efforts would seem primitive by today's standards, practitioners were sorting through the role of general anesthesia versus awake surgery, modes of airway protection, whether ventilation should be controlled or allowed to proceed spontaneously (eg, as a marker of cerebral well-being), the role of blood pressure measurement and management, and routine fluid management. Electrocardiography was not routine. Some debated that, if general anesthesia were used, vasodilating anesthetics should be avoided. When these issues are viewed in the context of a neurosurgical environment of that era, devoid of the greatest advances of today (eg, operating microscopes, computer-assisted stereotactic surgery guided by multiple imaging modalities), and patients who often had advanced diagnoses before coming to surgery, the anesthesiologists' intraoperative experiences—even when tempered with lower expectations for outcome than would be present today—must have been often frightening. In addition to this, neurosurgical diagnoses were commonly performed during extensive hospitalizations and—like other diagnostic experiences—moved at a glacial pace. Potential neurosurgical patients often remained at bed rest, had fluid restrictions, and were subjected to dye loads during diagnostic testing, all of which promoted dehydration and complicated intraoperative hemodynamic management.

Within this context, it is informative to review some of the highlights that preceded the naming of neuroanesthesiology, the progress to date, and the implications for the future of the subspecialty. It is not possible to name all who have meaningfully contributed, so I shall focus on those who served as examples during critical phases of the subspecialty's development, or were pioneers in the development of neuroanesthesiology's niche areas. The content of this article will be complemented by

Received for publication July 10, 2012; accepted July 12, 2012.
From the Department of Anesthesiology, College of Medicine, Mayo Clinic, Rochester, MN.
The author has no funding or conflicts of interest to disclose.
Reprints: William L. Lanier, MD, Department of Anesthesiology, College of Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (e-mail: lanier.william@mayo.edu).

2 other historical articles in this issue of *Journal of Neurosurgical Anesthesiology*[3,4] and an editorial recently published in *Anesthesia and Analgesia*.[5] Collectively, these 4 publications are intended to celebrate not only the discipline of neuroanesthesiology but also the 40th anniversary of the world's premier neuroanesthesiology organization, the Society for Neuroscience in Anesthesiology and Critical Care.

PERSONS AND PERSONALITIES

The development of any new discipline of medicine is dependent not only on an infusion of ideas but also on the energy and personalities of the innovators who attract collaborators and the next generation of students. In this regard, neuroanesthesiology has had a rich history.

Several of the early efforts to develop an intellectual and creative matrix for neuroanesthesiology's beginnings are attributed, in hindsight, to Albert Faulconer of Mayo Clinic (Fig. 1A). By 1949, he, along with neurologist, Reginald Bickford, began publishing on the electroencephalogram (EEG) responses to anesthetics[6] and, almost immediately thereafter, experimented with a controller device that would adjust the dosing of a barbiturate infusion, and in turn anesthetic depth, based on EEG pattern[7] (Fig. 1B). Elsewhere, Faulconer and coauthors were reporting on EEG use to predict outcomes after cerebral hypoxia.[8] For these innovations, some credit the studious, self-effacing Faulconer with being the father of modern neuroanesthesiology; however, in the minds of many others, that title goes to one of Faulconer's colleague, the more animated John D. "Jack" Michenfelder, who, exactly 2 decades after Faulconer's first reports on anesthetics and the EEG, would widely disseminate the subspecialty's name and core principles[9] (Fig. 2).

When comparing and contrasting these and many other talented individuals who contributed to the nascent subspecialty of neuroanesthesiology, we will soon appreciate that the differences in momentum imparted by each to the field were not necessarily a reflection of their intellect alone or the raw scientific merits of their discoveries; instead it was in their ability to promote their ideas publicly and introduce concepts (and energy) that would stimulate others to become interested in neuroanesthesiology. This is a theme that has recurred throughout the history of neuroanesthesiology.

Caring for neurologically impaired patients in the perioperative period, and conducting neuroanesthesiology research, is a complex business, and those whom we would today label neuroanesthesiologists have long had meaningful affiliations with neurosurgeons, neurologists, pathologists, and basic scientists. As much as we anesthesiologists like to think of ourselves as "the internists of the operating rooms," it is those bonds with neurosurgeons that formed much of the subspecialty's culture. In major medical centers where progressive and scholarly neurosurgeons were found, there too, one tended to find progressive, budding neuroanesthesiologists. This occurred in cities like Rochester, MN; Philadelphia, PA; Pittsburgh, PA; San Francisco, CA, and New York, NY in the United States, and internationally in Manchester, UK; Leeds, UK; Glasgow, Scotland; Montreal, QC, Canada; and London, ON, Canada. Not surprisingly, just as the "surgical personality" has been a driving force behind many of the accomplishments in surgery, likewise memorable (and sometimes theatrical) personalities were critical to the development of neuroanesthesiology. Some brief profiles are instructive.

In Pittsburgh, anesthesiologist Peter Safar, whose name would someday be linked with both cardiopulmonary resuscitation and brain resuscitation, was in the late 1950s and early 1960s inventing mouth-to-mouth resuscitation,[10,11] a cornerstone to the later development of close-chest cardiopulmonary resuscitation.[12] He discovered the success of this technique by first having himself tracheally intubated while awake, where he

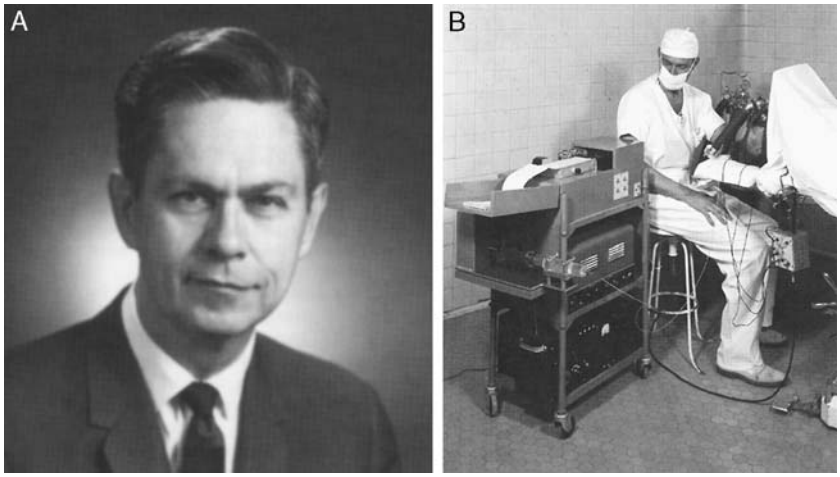

FIGURE 1. A, Albert Faulconer, MD, one of the early pioneers in using the electroencephalogram (EEG) to monitor anesthetic depth and assess perioperative cerebral well-being. B, Photo probably of Donald Soltero, MD, of Mayo Clinic demonstrating the use of an EEG-controlled device for controlling anesthesia depth (circa early 1950s).

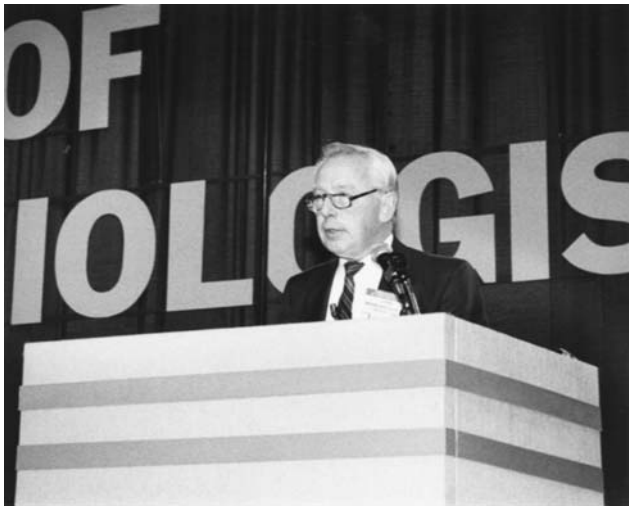

FIGURE 2. John D. "Jack" Michenfelder, MD, first president of the Society of Neurosurgical Anesthesia and Neurologic Supportive Care, and credited by many as the father of modern neuroanesthesiology. Dr. Michenfelder is seen here giving the Rovenstine Lecture at the annual meeting of the American Society of Anesthesiologists.

discovered the adequacy of expired oxygen from one person for maintaining organ function in another. Later, he would have himself pharmacologically paralyzed while awake, and then have the endotracheal tube removed to permit mouth-to-mouth ventilation, all the while remaining conscious and able to critique the effects of the intervention. From 1963 to 1965, neuroanesthesiologist Maurice Albin and co-investigating surgeon, Robert "Bob" White of Cleveland, in the pre-computer era, reported in the journals *Science* and *Nature*[13–15] their experiences with brain "isolation" and "transplantation" techniques, in which they kept the brain of one animal alive by cross-circulation from another animal and later by extracorporeal circulation using a mechanical oxygenator. Some speculated that this would form the basis of future computing techniques. The investigators were hailed for their feats in some of the most prominent lay media of their day. Given the importance of these neuroanesthesia personalities, and their proximity to the procedural end of the medical spectrum, it is not surprising that years later, elite neuroanesthesiologists John Drummond and David Warner would begin their postgraduate medical training as neurosurgery house officers.

Few were more capable of stirring up controversy and gaining attention than the sometimes charming, often abrasive and confrontational, John Michenfelder. He was appointed to the Faculty of Mayo Clinic in 1961, to join neuroanesthesiologists Howard Terry and Edward Daw and neurosurgeons Alfred Uhlein and Colin Macarty in providing anesthesia care during profound hypothermia to facilitate the clipping of cerebral aneurysms.[16,17] Michenfelder's clinical placement, and the development of the techniques at the Mayo Clinic, were partly based on the joint Mayo Clinic/University of Minnesota

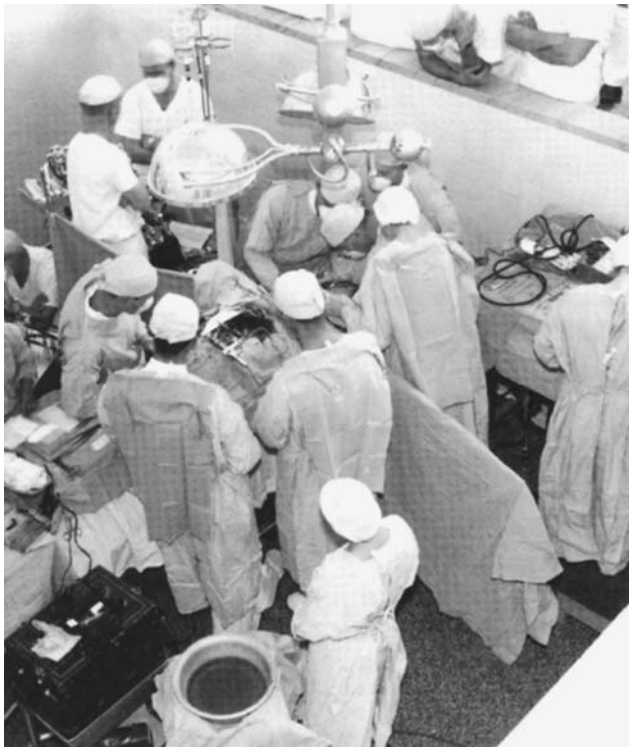

FIGURE 3. A Mayo Clinic operating room scene of multiple individuals caring for a patient having open-chest cardiopulmonary bypass and profound hypothermia to facilitate the clipping of a complex cerebral aneurysm (circa early 1960s).

development of the first successful (The patients survived!) extracorporeal blood oxygenator machines. Further, rumor has it that several of these early patients were anesthetized and cooled using the subzero ambient winter air on the loading docks of St. Mary's Hospital. Photos of these aneurysm-clipping operations would later confirm their complexity: innumerable people would cram into a single operating room to take care of the patient's anesthetic and surgical needs[14] (Fig. 3).

Michenfelder was assigned to perform laboratory research with Richard "Dick" Theye, who had a keen interest in the oxygen-carrying capacity of the blood and in developing a technique to determine oxygen consumption of the organs and the whole body. Michenfelder, Theye, Joseph Messick, and technician James Milde altered this concept and applied it to the brain, developing the canine sagittal sinus outflow model for quantifying cerebrocortical blood flow and oxygen consumption in virtually real time.[18] The model was also expanded to allow measurements of intracranial pressure (ICP) and the EEG. Over the ensuing decades, it became a true workhorse of neuroanesthesia research at the Mayo Clinic and elsewhere. As Michenfelder (assisted by pupils Petter Steen, Alan Artru, Leslie Newberg Milde, and others) focused on cerebral electrical activity and metabolism and later cerebral protection, Safar in Pittsburgh, although interested in isolated cerebral

protection, was more interested in whole body resuscitation. Safar and Michenfelder, both identified as neuroanesthesiologists, had legendary public fights at prominent meetings. At an American Heart Association function, the brain-versus-whole-body–resuscitation debate caused a frustrated and disgusted Michenfelder ("I came here to talk about brains!") to walk off the stage during a postlecture panel discussion (P. Safar, personal oral communication, 1991). Thereafter, at the Annual Meetings of the American Society of Anesthesiologists, any event placing Safar and Michenfelder in the same arena promised to bring standing-room-only crowds to witness the academic pugilism.

This tradition for drama would be critical in attracting interested parties into neuroanesthesia, and the tradition would be carried on by the likes of Harvey Shapiro of San Diego, CA, simultaneously serving as an academic neuroanesthesiologist, mayor of a nearby city, and local television personality. Although an accomplished clinical and laboratory investigator himself, perhaps Shapiro's most enduring contribution to neuroanesthesiology was the attraction of other talented young neuroanesthesiologists to the environment he had begun. Among these were Michael Todd and John Drummond, who formed one of the most productive research collaborations in the history of neuroanesthesiology. After Todd left San Diego for the University of Iowa, he would team up with David Warner, forming another of the most productive research teams. Similar to those who preceded them, and like James Cottrell and William Young who flourished after the mentorship of New York University's Herman Turndorf, all were comfortable on the stage and helped set the tone and temperament of neuroanesthesiology, particularly in North America. Outside of North America, there were equally appealing individuals whose culture-appropriate personalities attracted bright physicians to neuroanesthesiology.

In Glasgow, Scotland, Gordon McDowall and colleagues critically evaluated anesthetic effects on ICP, cerebral blood flow (CBF), and cerebral metabolism. An avid sailor, McDowall's neuroanesthesia legacy lived on after his unexpected and premature death, in the form of the Gordon McDowell Lectureship. John Michenfelder delivered the first lecture.

Hiroshi Takeshita of Japan traveled to the inhospitable climate and racially homogenous Rochester, MN, in the early 1970s to study with Richard Theye at Mayo Clinic. There he was paired with John Michenfelder, and the 2 became great friends, with Takeshita returning to the Mayo Clinic many times. During 1971, there was much excitement when the Mayo Clinic investigators discovered and reported that ketamine, unlike other anesthetics they had evaluated, could actually stimulate cerebral metabolism while producing anesthesia.[19] Only years later did the Mayo Clinic investigators learn that this phenomenon had originally been discovered and published in the Japanese literature months before their report, by none other than the ever-humble Takeshita,[20] who remained silent about having "scooped" the Mayo Clinic investigators. Back in Japan, Takeshita achieved legendary status as an investigator and mentor to other neuroanesthesiologists, first at Yamaguchi University, where he mentored and collaborated in the careers of neuroanesthesiologists Takefumi Sakabe, Tsuyoshi Maekawa, Toshizo Ishikawa, and others, and later at Kokura Memorial Hospital, where he mentored a second crop of neuroanesthesiologists. When in Japan, I once asked a prominent neuroanesthesiologist, "What is the significance of Professor Takeshita to Japanese neuroanesthesia?" His response, promptly delivered, alluded to a deity when describing Professor Takeshita's contributions as a physician, scientist, mentor, and leader. On hearing his response, I gave a huge approving smile, not only at the assessment, but also at the charming, respectful phraseology, unlike anything I had ever heard spoken about an anesthesiologist. The person, misinterpreting my response (and quite atypical for his culture and temperament) rebuked me: "My comment was not meant to be humorous."

Equally critical to the growth of the specialty were other less-public souls who had equal expectations that subgroups of anesthesiologists could someday improve the care of neurosurgical and neurologically impaired patients based on a better understanding of pathology, physiology, pharmacologic, and health care logistics. However, early on, missing was a seed of nomenclature, textbooks, and organizations around which a subspecialty could crystallize.

INTELLECTUAL AND ORGANIZATIONAL INFRASTRUCTURE

The first neuroanesthesia textbook in English did not appear until 1964.[1] It was authored by Andrew Hunter of Manchester, England. By 1966, R.G. Gilbert, Fred Brindle, and Anibal Galindo of Canada's McGill University published the second English-language neuroanesthesia textbook.[1] Other comprehensive textbooks would follow, and later niche textbooks related to select aspects of neuroanesthesiology. Among some of the more successful comprehensive textbooks have been "*A Basis and Practice of Neuroanesthesia*" edited by Emeric Gordon of the Karolinska Institute, Stockholm (1975)[21]; "*Anesthesia and Neurosurgery*" by James Cottrell of the State University of New York, Brooklyn, and Herman Turndoff of New York University (1980)[22]; "*Clinical Neuroanesthesia*" by Roy Cucchiara and John Michenfelder of Mayo Clinic (1990),[23] and "*Textbook of Neuroanesthesia: With Neurosurgical and Neuroscience Perspectives*" by Maurice Albin of the University of Texas Health Science Center, San Antonio (1997).[24] There also have been influential practical guides to clinical neuroanesthesiology care, with perhaps none as influential and long-lived as *Handbook of Neuroanesthesia: Clinical and Physiologic Essentials*, edited by Philippa Newfield and James Cottrell. It was first published in 1983,[25] and is now in its 5th edition.[26] Today, there is no shortage of books dedicated to neuroanesthesiology, and

this advance has been critical to the intellectual development of the specialty. Further, leading neuroanesthesiologist authors have contributed meaningful chapters to the leading general anesthesiology textbooks. Indeed, students and practitioners of neuroanesthesiology have no shortage of textbook information on the salient neuroanesthesia issues of our era, written by highly authoritative authors.

Perhaps the most efficient catalyst to subspecialty growth was when its name was widely publicized in the title of a 1969 comprehensive review article in the journal *Anesthesiology*. The mammoth 35-page article, authored by John Michenfelder, Gerald Gronert, and Kai Rehder of Mayo Clinic, was entitled simply "Neuroanesthesia."[9] First authorship of this article, along with many other original research discoveries, helped win Michenfelder, in the hearts of many, the moniker "father of modern neuroanesthesia." Although some have also given Michenfelder, his co-authors, and their review article credit for naming the subspecialty (an accolade Michenfelder himself acknowledged in his Rovenstine Lecture at the 1988 Annual Meeting of the American Society of Anesthesiologists[27]), the term "neuroanesthesia" had actually first appeared in the indexed literature in Rosomoff's 1963 *Anesthesiology* article,[28] and by 1965 a professional organization, the Neuroanesthesia Traveling Club of Great Britain and Ireland, had embraced the name.[2] However, as seen below, the name "neuroanesthesia" was introduced even before that, in 1961 (ie, the Commission on Neuroanesthesia), predating the Rosomoff article by at least 2 years and the Michenfelder article by 8 years. Hence, the budding subspecialty's name appears to have been introduced by many individuals and groups and began gaining acceptance over the decade preceding the 1969 *Anesthesiology* review article.

Also on the check-off list of essential elements for subspecialty formation was the development of subspecialty organizations where like-minded individuals could gather and share ideas. This part of the neuroanesthesia story has been beautifully outlined by Maurice Albin,[2] a pioneer neuroanesthesiologist and first-rate medical historian. In 1965, Allan Brown of Edinburgh, Scotland, and Andrew Hunter of Manchester, England, co-founded the aforementioned Neuroanesthesia Traveling Club of Great Britain and Ireland. This organization's formation came between the meeting of the 1961 Commission on Neuroanesthesia, sponsored by the World Federation of Neurology, and a June 1973 organizational meeting in Philadelphia of the Neurosurgical Anesthesia Society (NAS). According to Albin, the participants in NAS formation: Thomas Langfitt, Chief of Neurosurgery at the University of Pennsylvania; James Harp, Harvey Shapiro, and Harry Wollman, anesthesiologists from the University of Pennsylvania; and other interested parties, totaling 36 anesthesiologists and 4 neurosurgeons, met in Philadelphia in conjunction with the Sixth International Cerebral Blood Flow Symposium. The rules for the NAS were established, and John Michenfelder was voted the first President. At the first annual meeting of the organization in October 1973, the NAS's name was changed to the Society of Neurosurgical Anesthesia and Neurological Supportive Care (SNANSC), a name intended to encourage participation from physicians and scientists from diverse backgrounds. From its inception through 1991, the presidency of the organization was rotated between neurosurgeons and anesthesiologists but, as interest from neurosurgeons waned, the requirement for rotation was removed from the bylaws. In 1986, the name of the organization was changed to Society of Neurosurgical Anesthesiology and Critical Care (SNACC) and the SNACC abbreviation was retained in 2009 when the membership voted to change the title to Society of Neuroscience in Anesthesiology and Critical Care. In changing the name, the society retained the SNACC acronym while hoping to emphasize the organization's value in addressing complex neurological issues related to anesthesiology and critical care, without any implied restrictions to neurosurgical patients.[29] SNACC currently has approximately 550 members.

SNACC was formally recognized by the ASA as an anesthesiology subspecialty society in 1976, as a result of the efforts of James Cottrell, who, at that time, served as Chair of the ASA Subspecialty Committee.[2] In its new role, SNACC gained delegate representation in the ASA House of Delegates. Although having a US foundation, the organization boasts an active international membership and (in recent years) international officers. SNACC has clearly become the world's foremost neuroanesthesia research and education society, and its organization and scope of activities have become a template for similar societies and meetings throughout the world, including those in the British Isles, Continental Europe, India, Japan, Korea, and Mexico.

By the late 1980s, James Cottrell and colleague John Hartung became convinced that neuroanesthesiology would benefit from having its own subspecialty journal. For reasons expressed in a later editorial,[30] after being recruited by a publisher, they invited editorial board members and authors to join their effort. The first issue of the *Journal of Neurosurgical Anesthesiology* was published in March of 1989, and by 1993, the journal was indexed by the National Library of Medicine.[31] By 2007, the journal's impact factor had reached 2.5,[32] making it one of the most successful subspecialty anesthesiology journals ever. According to a publisher's web site, "The journal publishes original material in the form of Clinical and Laboratory Investigations, Clinical Reports, Review Articles, Journal Club synopses of current literature in related journals, presentation of Points of View on controversial issues, Book Reviews, Correspondence, and selected Abstracts from affiliated neuroanesthesiology societies."[33] Among its many virtues, participation in the journal has been an important exercise in the careers of many of the world's contemporary neuroanesthesiology leaders. The journal is affiliated with SNACC and other neuroanesthesiology societies worldwide, further coalescing efforts of neuroanesthesiologists to advance the subspecialty. Cottrell has served as Editor, and

Hartung has served as Associate Editor, since the journal's inception.

RESEARCH DIRECTIONS

The evolution of neuroanesthesiology as a subspecialty has been intimately dependent upon clinical research in humans and linked to integrative physiology and pharmacology research in animal models. Historically, neuroanesthesiology research concepts, and their relevance to clinical care, were readily understood by—and communicated among—pure clinicians, clinician investigators, and laboratory-based researchers. Unfortunately, with the advent of the molecular biology and genomics era in biomedical research, a chasm has often developed between cutting edge research concepts and those clinical concepts exercised daily by the clinicians. This, in turn, has taken away some of the enthusiasm that once fueled relationships between established neuroanesthesiology research mentors and their anesthesiology trainees. Clearly, a healthy future for neuroanesthesiology research is dependent upon the research concepts—especially those involving molecular biology and genomics—appearing relevant to the interests of the next generation of anesthesiology trainees. Better education is likely the method for making this evolution succeed and prosper.

Neuroanesthesiology research has prospered most when addressing 3 broad topics: (1) the mechanisms of brain injury and cerebral protection, (2) the pharmacology and physiology of neuroanesthesia-related interventions, and (3) facilitating the clinical practices and understanding of disease pathology, as related to neurosurgeons and others who care for neurologically impaired or at-risk patients. These and related topics will be discussed.

Mechanisms of Brain Injury and Cerebral Protection

Critical to cerebral protection engaging the interest of budding neuroanesthesiologists was the need not only for intriguing easily understood scientific concepts but also the contributions of entertaining academicians who knew how to take to the stage and capture audiences attention. Progress in neuroanesthesiology benefited from all of these.

Much of the early efforts to protect the brain and spinal cord focused on manipulating metabolic supply/demand relationships, and the research often involved induced hypothermia and metabolic depressant anesthetics. Recently, other mechanisms of protection have come to the forefront.

Cerebral Protection by Hypothermia

In 1938, the American neurosurgeon Temple Fay began using hypothermia for the treatment of intractable pain, traumatic brain injury, cerebritis, and brain abscesses. Fay's influence was critical to cardiac surgeons Claude Beck and Charles Bailey later promoting deep hypothermia and circulatory arrest for cardiac surgery.[34] By 1959, Fay reported that when prolonged induced hypothermia was used in humans during endogenous circulation to treat a host of neurological conditions, the patients tended to die, not from induced hypothermia, but during rewarming from a phenomenon that would later be known as rewarming shock.[35] In the animal laboratory, Petter Steen and John Michenfelder at Mayo Clinic would later use a band saw to perform thin whole-body cross-section slices on cats that were frozen solid after intravascular contrast injection. These methodologies would demonstrate that blood flow maldistribution was the origin of toxic acid (and other) metabolites that poisoned the body after prolonged modest hypothermia and endogenous circulation.[36,37] The antidote to this problem was using cardiopulmonary bypass-assisted circulation to offset some of the adverse effects of hypothermia.

The beneficial effects of profound hypothermia for providing cerebral protection during the repair of complex cardiac and cerebrovascular disorders, and typically involving circulatory arrest during the most critical operative events, were long attributed to simple suppression of supply/demand metabolism. As stated by John Michenfelder in his 1988 book, *Anesthesia and the Brain*, "Thus the proven protective effects of hypothermia can be fully explained on a metabolic basis alone—no other mechanisms need to be invoked, and none are known."[38] In this analysis, the term "metabolism" is worthy of clarification. Circa 1988, the discussions of the day, and Michenfelder's own research and his textbook analysis,[38] were focusing on the supply of brain energy substrates and the brain's demand for those substrates.

With the last of the prolonged *modest hypothermia* during endogenous circulation animal experiments published in 1980, and demonstrating failure for cerebral protection and animal survival,[37] neuroanesthesiology investigators appeared to abandon the field. This was because they believed that lesser temperature reductions would simply not reduce metabolism enough to provide cerebral protection. Interest in therapeutic *mild hypothermia* did not gain momentum until non-anesthesiology basic science researchers, Raul Busto, Myron Ginsberg, and colleagues from the University of Miami, Florida, reported in 1987 that small reductions in temperature, incapable of measurably altering supply/demand metabolism, provided protection from ischemia in a rat model of global cerebral ischemia.[39] Later Natale and D'Alecy would confirm the concept in a canine model of cardiac arrest–induced complete cerebral ischemia.[40] Other confirmatory studies would follow, including 2 by neuroanesthesiology investigators who would explore the minimum temperature reduction required to produce protection. David Warner, Michael Todd, and colleagues at the University of Iowa, and Thomas Wass and William Lanier from the Mayo Clinic, would, respectively, report that a 1.2°C difference in temperature correlated with cerebral protection in a rat model of focal ischemia,[41] and a 1°C difference in temperature resulted in cerebral protection in a canine model of complete ischemia.[42] Other investigators would demonstrate that, even when temperature manipulation was first induced

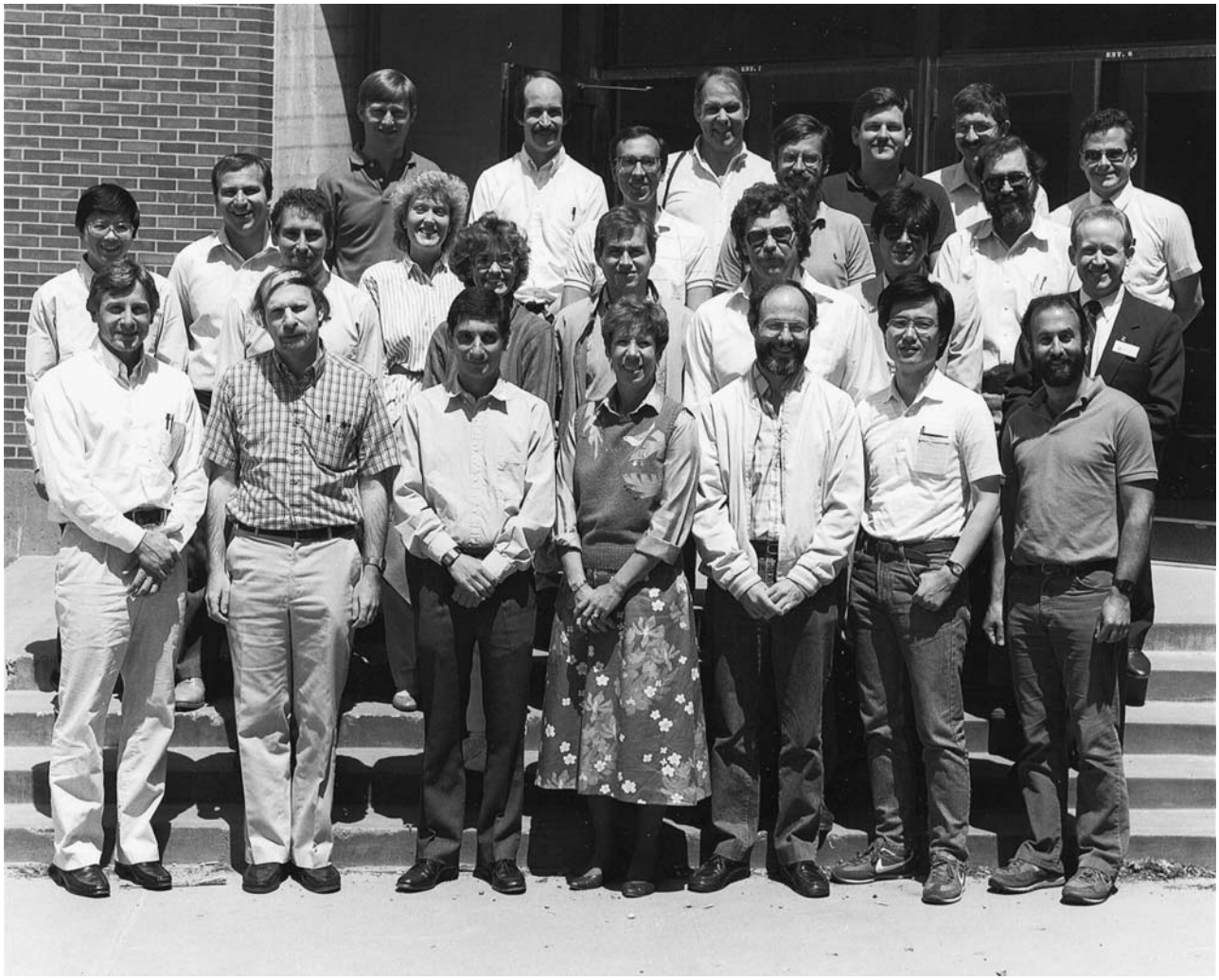

FIGURE 4. Founding members of the Unincorporated Neuroanesthesia Research Group who met in Iowa City, IA, in 1987. With international growth, the organization would become the International Neuroanesthesia Research Group, and the relationships formed were critical to the conduct of the Induced Hypothermia for Anesthesia Surgery Trial. Organizers of the 1987 meeting were Michael Todd (3rd row, extreme right, beard and dark glasses) and David Warner (4th row, 2nd from left).

after a period of transient cerebral ischemia had resolved, neurological outcomes could be altered.[43] Clearly there was something special about induced mild hypothermia that did not conform to the simplest concepts of supply/demand physiology during ischemia, and the effect occurred at small temperature reductions that should be well tolerated by humans.

In the 1980s, Michael Todd and David Warner became convinced that neuroanesthesiologists had ample opportunities to publicly display their research *successes*, but they had inadequate opportunities to frankly and unabashedly discuss with colleagues their research *challenges and failures*. Todd and Warner felt that this type of openness was required for neuroanesthesiology researchers to achieve optimal success. Thus, in 1987, Todd and Warner invited some 2-dozen neuroanesthesia researchers to Iowa City, IA, for a 3-day meeting. The group would label itself the Unincorporated Neuroanesthesia Research Group (Fig. 4) and, with international expansion, later become the International Neuroanesthesia Research Group. Membership was initially restricted to researchers under the age of 40 years, with Michael Todd representing an exception. This rule was operant until other members of the group exceeded the age ceiling, then the rule was dropped. The semiformal meetings were held around the world, on an annual basis. At one of these meetings, held in Banff, AB, Canada, in February 1993, Warner and Todd discussed with the group the possibility of performing a trial of induced mild hypothermia, during endogenous circulation, for cerebral protection during aneurysm clipping surgery. A group consisting of neuroanesthesiologists Todd, Warner, and Adrian Gelb, neurosurgeon Christopher Loftus, and neuroepidemiologist James Torner later met with the National Institutes of Health (NIH) officials in Bethesda, MD, to discuss funding for such a trial. To prove that the investigators were

motivated and capable of conducting such a study, they recruited investigators from 5 academic medical centers who designed, self-funded, and completed a 114-patient, multicenter, proof-of-concept trial. Bradley Hindman, Michael Todd, Adrian Gelb, Christopher Loftus, Rosemary Craen, Armin Schubert, Michael Mahla, and James Torner then published a report of their research findings in 1999.[44] From these preliminary data, protocols were refined, and the project's proponents went back to the NIH in search of financial support. Their proposal was funded on the first formal submission. Funding led to the 30-center, 3-continent, 1001-patient Induced Hypothermia for Aneurysms Surgery Trial (IHAST), whose principle report was published in the prestigious *New England Journal of Medicine*.[45] The trial's database was designed to permit retrospective subgroup analysis of the relationship with outcomes of anesthetic technique,[46,47] glucose concentrations,[48] and a host of other issues. Impeccable study execution and data collection during the parent IHAST research resulted in 3-month outcome data on 1000 of the 1001 patients entered into the trial: an unprecedented accomplishment for an NIH-funded trial of this complexity. With little challenge, the completion of the IHAST trial should be viewed as neuroanesthesia's finest hour.

Ironically, although the IHAST research proved negative, induced hypothermia has, in other scenarios, shown some encouraging results for improving neurological outcomes in adult survivors of out-of-hospital cardiac arrest who fail to immediately awaken,[49,50] as well as in neonates who have sustained hypoxic-ischemic encephalopathy.[51] These applications were identified by non-neuroanesthesiologists.

Cerebral Protection by Metabolic Depressant Anesthetics

The metabolic-depression-as-a-means-of-cerebral-protection themes that motivated explorations of hypothermia also helped fuel investigations into anesthetics. In 1974, Allan Smith and colleagues first reported that pentobarbital would protect the brain from acute, permanent focal cerebral ischemia in a canine model.[52] This was soon followed by explorations by other investigators, mostly showing that barbiturates provided protection in models of incomplete or focal cerebral ischemia.[53] The sagittal sinus outflow model, developed by John Michenfelder and colleagues, would later demonstrate that the metabolic depression by barbiturates correlated with brain electrical activity, however, unlike metabolic depression by hypothermia, peaked when the EEG became isoelectric.[54,55] This led to a theory, never tested for decades, that large doses of barbiturates should provide maximal cerebral protection. An extrapolation of this theory, also never properly tested for many years, was that equally metabolic depressant anesthetics should all be fairly equally cerebral protective, provided they were given in large doses sufficient to suppress the EEG. Subsequent studies of lidocaine, isoflurane, etomidate, propofol, and other drugs were conducted, often with less than optimal scientific discipline, in probing the metabolic depressant/protection relationship. Unfortunately, neuroanesthesiology researchers began exhaustively repeating previous animal studies, and using surrogate markers (eg, electrophysiological and metabolic endpoints) to investigate potentially protective effects of anesthetics. The error of this approach is perhaps best elucidated in a recent report by Erickson and Lanier, in which they identified some 28 published reports describing 57 separate protocols that evaluated barbiturate protection in animal models, many of them conducted by neuroanesthesiologists,[53] yet, it was not until 1996 that neuroanesthesiologists first explored and reported on the relationship between the extent of metabolic depression by a single anesthetic and cerebral protection by that anesthetic in a standardized animal model of focal cerebral ischemia. In that research, David Warner, now at Duke University, demonstrated that smaller doses of barbiturate, which preserved some brain electrical activity and should have only modestly depressed cerebral metabolism, actually had better evidence of cerebral protection than did larger doses of barbiturate that maximally depressed the EEG and should have maximally depressed metabolism.[56]

The failure of neuroanesthesiologists to test this concept for so many years, and their similar failure to test the concept of barbiturate cerebral protection in humans experiencing focal cerebral ischemia, defies understanding. The only 2 human outcome studies of barbiturate protection in focal cerebral ischemia were directed by cardiac anesthesiologists,[57,58] one showing protection in cardiac valvular surgery patients[57] and the other showing no protection in patients having coronary artery bypass grafting (CABG),[58] both in patients subjected to cardiopulmonary bypass-assisted circulation and in whom focal cerebral ischemia was suspected. Ironically, in the sole instance in which a neuroanesthesiologist directed a barbiturate outcome trial in humans, it was Peter Safar leading the team, and the setting was cardiac arrest,[59] a setting in which the predominant animal literature of the time correctly predicted the negative effects of the human trial.[38]

The theory of metabolic depression as a common link for cerebral protection in neuroanesthesiology scenarios began unraveling on many fronts in the 1990s and afterward. Critical events were the aforementioned studies of the Raul Busto, David Warner, and William Lanier research groups. Further, Takanobu Sano, John Drummond, Piyush Patel, and Daniel Cole at the University of California, San Diego, would demonstrate that at equivalent quantities of metabolic reduction, induced hypothermia was more protective than deep anesthesia.[60] Drummond et al[61] also reported actual exacerbation of ischemic brain injury by etomidate. Elsewhere, prolonged infusions of propofol were being reported to produce death in humans as a result of systemic acidosis.[62] In St. Louis, non-anesthesiologists Steven Rothman and John Olney, and other investigators from around the world, were reporting that excitatory amino acid antagonist drugs, some of which had anesthetic and sedative properties akin to ketamine and phencyclidine (angel dust), were cerebroprotective, even though they tended to stimulate cerebral metabolism.[63,64] These collective findings

forced neuroanesthesia investigators to realize that hypothermia, anesthetic administration, and other common perioperative interventions that affected cerebral metabolic rate did not have predictable effects on postischemic neurological outcome based on those metabolic effects.[64–66] The same held true for studies of brain trauma and spinal cord ischemia. Unfortunately, the concept of cerebral protection as a predictable consequence of metabolic depression still remains in the minds of many practitioners today.

The Role of Glucose and Glucocorticoids in Modulating Outcomes

By the mid-1980s, glucose-containing solutions were a component of the default fluids for volume replacement (particularly early in an anesthetic) and *the* recommended carrier for infused medications. This clinical approach was disrupted when, in 1987, William Lanier reported in *Anesthesiology* that small, clinically relevant volumes of 5% glucose-containing solution (ie, 1.05 L per 70 kg body weight) meaningfully worsened outcome after a cerebral ischemic event in a non-human primate model.[67] Further metabolic research would determine that this adverse effect occurred even though high-energy phosphate compounds were better preserved during ischemia as a result of glucose administration.[68,69] Instead, a lactic acid mechanism was invoked.[70] Unknown to Lanier, this was not the first discovery of the phenomenon (there were already a few other outcome reports of the glucose effect) nor would it be the last.[70] William Hoffman, David Warner, and others would demonstrate the phenomenon in rat models of cerebral ischemia.[71,72] In related scenarios, John Drummond and others would confirm the neurotoxic effects of glucose in spinal cord ischemia models,[73] and Arthur Lam would report an association between hyperglycemia and outcome after closed head injury in humans.[74] The collective research and political activities of these neuroanesthesia investigators contributed to glucose-containing fluids being removed as a default fluid infusion out of concern for exacerbating ischemic neurological injury. Although no prospective human trials with proper endpoints and adequate statistical power were ever conducted by neuroanesthesiologists to evaluate the effect of rigid glucose control on neurological outcomes clinically in at-risk patients,[75] a retrospective analysis of the IHAST database, performed by Jeffrey Pasternak, identified a correlation between incremental changes in glucose concentrations and neurological outcome in aneurysm surgery patients.[48]

In other research, Wass and Lanier and others identified that corticosteroids—once indiscriminately used in neurosurgical patients—could produce adverse postischemic outcomes as a result of glucose-dependent and glucose-independent effects.[70,76] This research also had an effect on lessening corticosteroid use clinically.

Other Approaches to Cerebral Protection

By the 1980s, neuroanesthesiologists increasingly began to look for basal metabolic rate-independent mechanisms for protecting the brain at risk for insult and injury. Calcium entry blockers, which neurosurgeons would later champion as a method for improving outcomes from vasospasm after subarachnoid hemorrhage, would be evaluated by neuroanesthesiologists as a treatment for improving neurological outcomes after cardiac arrest. Petter Steen (a colleague of John Michenfelder) of Oslo, Norway, and Sven Gisvold (a colleague of Peter Safar) from Trondheim, Norway, joined forces in Rochester, MN, in 1983 to introduce a slightly improved version of Safar's primate global brain ischemia model to the Michenfelder laboratory. This model was then used to demonstrate the protective effects of the calcium entry blocker, nimodipine.[77] Follow-up studies by Akio Tateishi and colleagues in the laboratory of Harvey Shapiro in San Diego, using a cat model and 2 different durations of global ischemia,[78,79] failed to confirm the effect. Nimodipine never gained use as a neuroprotective therapy after cardiac arrest, nor did other calcium-entry blockers evaluated by neuroanesthesiologists. Other avenues of protection included the evaluation of non-glucocorticoid antioxidant steroids (eg, the so-called Lazeroid 21-aminosteroids) by William Hoffman and Verna Baughman of Michael Reese Medical Center,[80] William Perkins of Mayo Clinic,[81] and others, and manipulation of estrogen receptor activity by Patricia Hurn and Richard Traystman, originally at Johns Hopkins University[82] and later Oregon Health Sciences University.[83] To date, some of these lines of investigation have fallen by the wayside and others (eg, estrogen research) are ongoing and continue to show promise.

Cerebral Protection from Closed Head Injury

Neuroanesthesiologists have also had an interest in investigating the mechanisms underlying closed-head injury and methods to improve outcome. Their research contributions have meaningfully enhanced our understanding of ICP, CBF and its autoregulation, seizures, appropriate fluid therapy, and other issues addressed elsewhere in this article. Despite considerable efforts by individual neuroanesthesiologists and groups of neuroanesthesiologists, this area of research has never received the same attention as ischemic brain injury. This lesser focus on closed head injury perhaps relates to recent research demonstrating that much of the outcome in head injury is dictated by events that occur at the scene of injury, and subsequent care may be limited in its ability to improve outcome.[84] Despite this, neuroanesthesiology researchers such as Douglas Dewitt, Donald Prough, Yoram Shapira, Alan Artru, Monica Vavilala, and Arthur Lam have studied the basic physiological aberrations that follow head injury and manipulations of physiology aimed at improving outcomes.[85–90] This research has been conducted in both animal models[85–87] and human studies.[88–90] Documentation and analysis of many of these advances were collated in Arthur Lam's book, "*Anesthetic Management of Acute Head Injury*," published in 1995.[91] In the same year, the Brain Trauma Foundation published the first of its evidence-based guidelines for managing severe traumatic brain injury.

This book, and other complementary guidelines from the Foundation, are now available in hard copy and electronically, and are updated periodically.[92,93] These books collectively address prehospital and hospital care of adult and pediatric closed-head-injury patients, and also combat-related injuries and predictors of prognosis.

Anesthetic Technique-related Injury

One must wonder why many anesthetics have been reported to produce some form of protection from ischemic brain injury in animal models, yet proof of protection is so lacking in humans. One possibility, discussed by David Warner,[94] and based on experimental evidence from the laboratory of John Drummond, Daniel Cole, and Piyush Patel in San Diego,[95] relates to the temporal aspects of protection in animal models. Specifically, the San Diego investigators demonstrated that isoflurane inhibited short-term ischemic necrosis in an animal model of focal cerebral ischemia, but it did not benefit neuronal loss by apoptosis. With time, the short-term benefits of isoflurane disappeared. Given the fact that most reports evaluating the cerebral and spinal cord protection in animal models have examined outcomes at hours or days after the insult, it is possible that any short-term benefit would not have been sustained with time. Because post-insult outcomes in humans focus on outcomes at months and years, any beneficial effects of the anesthetic may have long disappeared.

Another possibility is that anesthetics can actually harm the brain. Verna Baughman reported that nitrous oxide reversed the protective effects of isoflurane in a rat model of cerebral ischemia.[96] These and related themes were addressed in James Cottrell's Rovenstine Lecture to the ASA,[97] where he focused on anesthetic administration to very young children and the use of nitrous oxide. The concept of anesthesia-induced brain injury relies heavily on the research of neuroscientist John Olney and colleagues,[98] and the theories are still in evolution. The concept of nitrous oxide–induced brain injury—as it relates to outcomes following cerebral ischemia in adult humans—has been examined in patients having cerebral aneurysm clipping, and the results largely discredited the possibility of enhanced injury in that setting.[46,47] However, recent epidemiologic work on repetitive anesthetic use in young children reported an association with learning disabilities and aberrations of behavior later in life.[99,100] Whether these adverse outcomes were due to the anesthetics or other factors is still unclear. Only time will tell the future directions and outcomes of this line of investigation in evaluating possible neurological injury by anesthetics.

Studies of Cerebral Physiology and Pharmacology

Neuroanesthesiologists have long had an interest in studying the central nervous system effects of existing and new anesthetic agents and supplements, neuromuscular relaxants, vasoactive drugs and hemodynamic manipulation, temperature alterations, seizures, and a host of other states. The reason for this interest began quite innocently: so very little was known about the fundamental pharmacology and physiology as related to the central nervous system that virtually any new information was welcomed. This was true of Faulconer and Bickford's research into the EEG,[6,8] Harry Wolman and Craighead Alexander of the University of Pennsylvania's human studies of CBF during anesthesia,[101] or Michenfelder's research in his widely utilized canine model.[18,19,54,55] Most of the early research was targeted to topics of long-standing interest or was hypothesis-driven; however, as the methodologies used for measurement became more widely available, "investigations of opportunity" began to proliferate. Specifically, core measurements of the EEG, CBF, cerebral metabolic rate, and the ICP were performed (and repeated) for a vast number of neuroanesthesia-related interventions, whether or not there was a compelling reason to do so. Later, derivative measurements such as CBF velocity (as a surrogate for raw CBF measurements) and processed EEG (as a surrogate for raw EEG) were added. This approach left many loose ends and confusion in the literature. For example, failing to actually measure cerebral blood volume, neuroanesthesiologists began using measurements of CBF as a surrogate in interpreting ICP responses to anesthesia-related interventions. It was not until the mid-1980s when Patrick Ravussin and David Archer in Montreal,[102,103] and a decade later when Rosemary Craen, T.Y. Lee, and Adrian Gelb in London, ON, began systematically comparing blood flow and blood volume measurements.[104,105] The results were surprising and discredited many previous assumptions about CBF/blood volume coupling.

Despite fits, starts, and periodic distractions, neuroanesthesiologists have made meaningful contributions to the understanding of human physiology and pharmacology, largely as they relate to cerebral protection, disease states commonly encountered in the clinical arena, and improving operative conditions for surgeons. The contributions have taken diverse paths. Paul Modica and Rene Tempelhoff comprehensively reviewed the proseizure and antiseizure properties of anesthesia-related drugs.[106,107] Andrew Kofke et al[108] reported a multicenter clinical series in which they evaluated the efficacy of prolonged isoflurane administration to treat status epilepticus. Their research demonstrated that high-dose isoflurane would arrest seizure activity but the seizures tended to reappear and outcome was dismal once the isoflurane was discontinued. Alan Artru extensively evaluated the physiology and pharmacology of cerebrospinal fluid formation and resorption.[109] Ronald Albrecht of Chicago demonstrated the brain's ability to accommodate to prolonged hyperventilation, and the consequences of later discontinuing hyperventilation.[110] James Cottrell and Herman Turndorf published a host of studies on the effects of sodium nitroprusside infusion (a preferred technique for lowering blood pressure during cerebrovascular surgery) on systemic and cerebral dynamics, and dealing with any cyanide toxicity from the infusion.[111]

In San Diego, Iowa City, and Galveston, Michael Todd, Mark Zornow, David Warner, Reg Kaida, Douglas

DeWitt, and Donald Prough investigated the use of various intravenous fluids on brain water content.[112–115] These studies tended to show that normal brain handles normotonic fluids quite well, and it is only with the administration of hypotonic fluids or in the presence of injured brain that fluid administration becomes more critical in determining brain water. These studies—along with studies of glucose exacerbation of central nervous system injury[67,70–74]—revolutionized fluid replacement in neurosurgical operating rooms and intensive care units.

For decades, succinylcholine was rumored to meaningfully increase ICP as a result of increases in central venous pressure during fasciculations. Despite this, it was not until the mid-1980s that the first reports of a mechanistic explanation for the cerebral effects of succinylcholine began to emerge.[116–119] William Lanier, Robert Bedford, and their colleagues demonstrated that visible fasciculations and increases in central venous pressure were not critical to the cerebral response.[117–119] Instead, Lanier demonstrated in a canine model that succinylcholine was a cerebral stimulant that activated the EEG and increased CBF (and presumably CBV) and ICP as a consequence of activation of muscle afferent receptors.[116,117] This line of research also demonstrated that increases in intrathoracic pressure are quite ineffective in altering ICP during either static changes or during coughing in tracheally intubated laboratory animals.[120] Instead, ICP changes during coughing, like those after succinylcholine administration, were greatly influenced by a muscle afferent-mediated stimulation of the brain.[120]

Currently, neuroanesthesiologists are increasingly looking to molecular biology and genomic mechanisms to explain biological processes pertinent to the care of neurosurgical or neurologically impaired patients. Leading the charge in these areas are investigators such as David Warner at Duke University, Piyush Patel at the University of California San Diego, William Young at the University of California San Francisco, Gregory Crosby and Deborah Culley at Harvard Medical School, and Patricia Hurn and Jeffrey Kirsch at Oregon Health Sciences University, along with Christian Werner, Kristin Engelhard, and Eberhard Kochs in Mainz and Munich, Germany. Although these types of investigations hold the promise for neuroanesthesiologists making historical contributions to global medical care, they also represent a broadening of the gap between the focus of competitive laboratory researchers and the daily practices and thought processes of clinical neuroanesthesiologists. The effect that this will have on recruiting the next generation of neuroanesthesiology fellows is unclear.

Studies of Spinal Cord Physiology and Pharmacology

Although neuroanesthesiologists are daily engaged in the care of patients having disease states affecting the vertebral column or spinal cord, they have not studied the spinal cord as exhaustively as the brain. There are perhaps several explanations for this. Spinal cord injury does not cause death or major disability as frequently as does acute injury to the brain. Further, although the care (and the study of that care) of patients having surgery on the brain is very much associated with neurosurgeons and neuroanesthesiologists, the care of patients having or at risk for spinal cord injury is shared by neurosurgeons, orthopedic surgeons, cardiac and vascular surgeons, trauma surgeons, anesthesiologists (having a variety of subspecialty interests), and others. As such, the neuroanesthesiologists contributions get diluted in the care and study of these patients. Further, there is an assumption—reflected in the title of an original research article by Rosemary Hickey et al[121]—that spinal cord physiology is a microcosm of brain physiology, and extrapolations from brain research can be applied to the spinal cord. Such extrapolations, whether accurate or not, are reinforced by studies showing that the injured spinal cord responds to glucose loads[73] and hypothermia[122,123] in a manner similar to the brain. Despite these factors, neuroanesthesiologists such as Amsterdam's Cor Kalkman (and others mentioned vis-à-vis monitoring later in this article) have had a considerable interest in monitoring the spinal cord to detect and treat new-onset compromise during surgery.[124]

There is a possibility that the neuroanesthesiologists' academic interest in the spine and spinal cord may increase in the coming years, given the immense growth in surgical procedures in this area, particularly in the elderly.[125]

Facilitating the Clinical Practices and Research Within Other Specialties

Neuroanesthesiologists have had meaningful impacts on facilitating the practices and research of other practitioners who care for neurologically impaired or at-risk patients, and this has had a meaningful effect on the practice of medicine.

In the early 1990s at Columbia Presbyterian Medical Center in New York, distinguished neurosurgeon Benjamin Stein and neuroradiologist John Pile-Spellman were making advances in the treatment of arteriovenous malformations. Neuroanesthesiologist William Young began contributing to their efforts and saw an opportunity to utilize the microcatheters used for diagnosis (and later therapy) of the AVMs to study the anatomy and physiology of the regional blood flow, and the physiology and pharmacology of both normal and malformed cerebral vasculature.[126] This led to multiple research projects, numerous seminal discoveries, and considerable extramural funding for Dr. Young. These research interests, which later included genomics research,[127] continued and expanded after his move to the University of California, San Francisco. Young's collective research, commonly involving collaborations with experts in other disciplines, has produced more than 100 indexed publications on the biology of AVMs. This probably represents the single largest collection of research articles on a single disease entity ever published by a neuroanesthesiologist, and clinical practice has been meaningfully altered by the discoveries. It is additionally remarkable that a large fraction of the critical observations were made in humans.

Although the accomplishments of neuroanesthesiologist-involved clinical and research teams—like the team at Columbia University—can affect understanding worldwide and are easily monitored through their contributions to the indexed literature, other important contributions are more local in nature. Three decades before the surgeon, neuroradiologist, and neuroanesthesiologist collaborations on AVMs at Columbia University, at the University of Western Ontario, London, ON, Canada, Charles Drake, one of the world's leading cerebral aneurysm surgeons, began collaborating with neuroradiologist John Allcock to introduce novel techniques for diagnosing and treating challenging cerebral aneurysms and associated complications such as vasospasm.[128] Critical to their advances and those of their successors was input from neuroanesthesiologist Ronald Aitken.[129] Although Allcock and Aiken seldom published their contributions, Aitken was responsible for introducing induced hypotension, induced hypothermia, and other techniques to facilitate the widely acclaimed advances in aneurysm surgery attributed to Drake. Aiken's influence paved the way for a generation of distinguished neuroanesthesiologists at the University of Western Ontario who were both accomplished innovators and authors, including Adrian Gelb, Arthur Lam, and their students.[130] In later years, anesthesiologists, neurosurgeons, and neuroradiologists from the University of Western Ontario jointly sponsored the Aitken Memorial Lectureship to pay homage to Ronald Aitken's many contributions.

In Montreal, QC, Canada, during the early 1900s, surgeon Wilder Penfield was busy developing and perfecting techniques for seizure focus resection and related surgeries in awake patients in whom electrical stimulation of the cortex was performed.[131] The homunculus, a cortical map of motor and sensory function, is an end product of his observations. It is not surprising that Canadians have long had meaningful contributions to perfecting anesthesia care for patients having awake surgery, and this contribution has perhaps reached its zenith with the introduction of modern pharmacologic tools. Indeed, Canadians Ian Herrick, Rosemary Craen, and Adrian Gelb in London, ON; David Archer and Patrick Ravussin in Montreal, QC; and Pirjo Manninen in both London and Toronto, ON, refined anesthesia support techniques during awake epilepsy surgery. Others have contributed to improve seizure focus mapping and resection in anesthetized patients.[132–134] For example, at the Mayo Clinic, Leslie Milde and colleagues evaluated the effect of synthetic opioids in activating seizure activity during general anesthesia.[135]

Clearly many of the pioneers in electrophysiological monitoring were not neuroanesthesiologists; instead, they were neurologists and neurosurgeons. However, neuroanesthesiologists have in recent decades had a great interest in this field. Betty Grundy of the University of Florida, Todd Sloan of the University of Colorado, Eric Heyer of Columbia University, Eberhard Kochs of the Technical University of Munich, Christian Werner of Johannes Gutenberg University, Marc Bloom of New York University, Andrew Kofke of the University of Pennsylvania, and Cor Kalkman of University Medical Center Utrecht have done much in this regard.[124,136–139] Their work has focused mainly on electrophysiology monitoring for cerebrovascular surgery, major spine surgery, epilepsy surgery, and brain tumor resection. Despite many advances, there is still debate as to which patients should be monitored, the optimal monitoring modality, and who should conduct the monitoring. Some argue that properly trained neuroanesthesiologists should conduct their own monitoring during the anesthetic, whereas others retort that sophisticated electrophysiological monitoring is best left to other teams of experts, perhaps overseen by a neurologist, so that the anesthesiologist is not distracted from other patient care issues. Critical to the future of monitoring during neuroanesthesiology care are risk-benefit and cost-benefit analyses, demonstrating that any added efforts to monitor the patient represent sound judgment on the part of practitioners.

The long-term interest of neuroanesthesiologists in monitoring as a means to improve outcomes has often involved quantification of pressures, flows, temperatures, and other variables, typically adapting measurement techniques introduced by others. In recent years, neuroanesthesiologists such as Basil Matta and Arthur Lam have used transcranial Doppler sonography monitoring of CBF velocity to assess cerebral vasospasm and instantaneous changes in CBF.[140,141] Elsewhere, investigators such as Martin Smith[142] have applied near-infrared spectroscopy to evaluate the physiological effects of therapeutic interventions on normal and injured brain. These same scenarios have been evaluated by William Hoffman and others who placed within human brain tissues a multimodal probe to quantify focal brain pH and the partial pressures of oxygen and carbon dioxide.[143]

In the areas of venous air monitoring during sitting craniotomy, John Michenfelder, Roy Cucchiara, and Joseph Messick of Mayo Clinic; Jane Matjasko and Colin MacKenzie of the University of Maryland; and Wayne Marshall and Robert Bedford of the University of Virginia were pioneers in introducing transthoracic Doppler ultrasound sensing, transesophageal echocardiography, analysis of blood gasses and expired gasses, and pulmonary artery pressure monitoring for air embolus detection.[144–147] John Michenfelder introduced, and Maurice Albin and Leonid Bunnegin perfected, the use of right atrial catheters for the detection and retrieval of entrained air.[148,149] Initial attempts at real-time monitoring of venous air embolus were hindered by alterations in signal quality resulting from diminished blood pressure and cardiac output. Cucchiara's introduction of transesophageal echocardiography solved this problem, allowing clinicians to preoperatively assess for the presence of patent foramen ovale, and quantify the amount and course of any entrained intracardiac air.[150] Susan Black of the Mayo Clinic and the University of Alabama would help prove the bidirectional nature of shunted intra-atrial air emboli.[151] Although many individuals and geographical groups have abandoned the sitting position for neurosurgery for fear of the consequences

of venous air embolus, and contemporary surgeons are increasingly trained to operate with patients in the non-sitting positions, Black and Cucchiara, nevertheless, documented that patient benefit (in the form of better preserved postoperative neurological function) can indeed accrue from surgery performed in the sitting position.[152]

Those who provide airway management for patients having unstable cervical spines have long had concerns about the effects and risks of the various airway management techniques. The most feared complication is that airway manipulation will introduce or exacerbate injury to the cervical spinal cord. Michael Todd and colleagues at the University of Iowa investigated these issues using cinefluoroscopic and other techniques in which they could actually observe and quantify cervical spine movement during a variety of airway management interventions.[153,154] Recently, Bradley Hindman, Michael Todd, Lorri Lee, Karen Domino, and colleagues from the University of Iowa, University of Washington, and elsewhere have examined the other extreme of the airway management-patient injury spectrum by performing an analysis of the ASA Closed Claims Database. Amazingly, airway management was not a key contributor to new-onset cervical spinal cord injury.[155] Clearly, this research will have downstream implications for future research and clinical practice.

The more active phases of cerebral protection work by neuroanesthesiologists carried with them the implication of direct benefit to patients independent of the input of other practitioners. However, today, the pendulum seems to be swinging back toward reinforcing the value of neuroanesthesiologists as facilitators of other care teams. Logistical improvements introduced by neuroanesthesiologists have critically helped to speed up diagnosis and treatment times for subarachnoid hemorrhage, embolic stroke, movement disorders, and diseases in pediatric and claustrophobic patients. Anesthesiology support for the neuroradiology suite at the Mayo Clinic is but one example. Designed in part by neuroanesthesiologist William Perkins, a team of anesthesiologists and nurse anesthetists daily oversees support for 6 magnetic resonance imaging (MRI) machines, 2 computed tomography machines, 3 angiography rooms, a myelogram room, a gamma knife, and an MRI operating room. Median census for the neuroanesthesia component of the operation is approximately 10-12 patients per day. Value is added to the overall medical equation because of this type support.

Academic neuroanesthesiologist's interest in pediatric patients has perhaps been limited by the sharing of patients between adult neuroanesthesiologists and pediatric anesthesiologists. There is some truth in the observation that adult neuroanesthesiologist's caring for these patients tends to focus first on the neurological disease and second on pediatric status, and pediatric anesthesiologists tend to focus on pediatric status first. Despite this, there have been those who meaningfully contributed to bridging the gap between the two camps. Influential individuals have been Monica Vavilala and Arthur Lam in Seattle[88,89] and Sulpicio "Sol" Soriano and Mark Rockoff in Boston.[156] With the increased use of neurological imaging to perform early diagnosis of disease in children, and the increased use of the early epilepsy surgery, the subdiscipline of pediatric neuroanesthesia will surely continue to make progress.

Sharing the care of patients with those outside of academic neuroanesthesia has also influenced neuroanesthesiologists contributions to neurointensive care. Indeed, neurologists, neurosurgeons, and general intensivists have had an expanding role in the care of these patients, resulting in a diminished clinical and academic role of core neuroanesthesiologists. There are exceptions however. In Seattle, Arthur Lam and colleagues have conducted a host of studies on cerebral physiology and pathology in intensive care patients of all ages,[88,89] and Lam, Andrew Kofke, and others have contributed to core curriculum and competency guidelines for neurological intensive care training.[157] Further, at the University of Cambridge, David Menon and colleagues have used a positron emission tomography, brain dialysis, and other techniques in patients having traumatic and other forms of brain damage to address fundamental questions related to brain pathology and the effects of physiological manipulation and the introduction of therapies.[158]

Neuroanesthesiologists have also been involved in using epidemiologic methods for evaluating the incidence and contributing factors for anesthesiology-related problems. For example, Lorri Lee and Karen Domino have participated in efforts by the larger anesthesiology community to investigate the extent of visual loss following spine surgery and its associations.[159]

Elsewhere in vision loss research, laboratory collaborations between pediatric ophthalmologist Jonathan Holmes and neuroanesthesiologist William Lanier greatly expanded the list of known triggers for retinopathy of prematurity to include acid-base disturbances, enteropathy caused by a newly discovered bacterial pathogen (*Enterococcus rattus*), and other causes.[160,161] These collective studies lend promise that remediable factors other than high-inspired oxygen can be altered in the surgical and intensive care environments in an attempt to lessen the risk of vision loss in newborns.

In recent years, SNACC—through its actions and name change—has emphasized a broad application of neuroscience principles in the study of anesthesia and critical care. Fortunately, as seen in the prior examples, many prominent neuroanesthesiologists were acting in this manner well before the SNACC realignment. In other examples, neuroanesthesiologists have been engaged in evaluating the origins and treatments of neurological deficits following cardiac surgery. Although gross neurological deficits have long been recognized as a complication in this scenario, the frequency and importance of new subtle deficits did not gain substantial research interest until the latter 1980s and 1990s. Neuroanesthesiologist Maurice Albin and research colleague Leonid Bunegin of the University of Texas Health Sciences Center, San Antonio, validated the methodology by which transcranial Doppler sonography could be used to detect air and particulate emboli.[162,163] These methods were then used by

them and others to address emboli number and embolic load during cardiopulmonary bypass and, in some instances, correlate the findings with neuropsychological functioning.[164] Donald Prough and David Stump of Wake Forest University, Winston Salem, NC, performed numerous studies in humans to identify the CBF responses to physiological and pharmacologic interventions during heart surgery and whether these could explain a propensity for neurological deficits.[165] In the United States, it was assumed that neurological deficits were more common after valve replacement surgery than after CABG, largely because of greater air and particulate debris washed into the cerebral vasculature during valve surgery; however, Hiroshi Takeshita and colleagues of Yamaguchi University Hospital, Japan, reported a higher incidence of deficits after CABG surgery.[166] Their observation identified a likely cause: a longer duration of cardiopulmonary bypass with CABG surgery in their country was associated with worse outcomes, when compared with valve surgery.

GLOBAL CROSS-POLLINATION

Although the field of neuroanesthesiology had many of its beginnings in Great Britain, the United States, and Canada, today academic neuroanesthesiology, complete with ongoing research and the training of a new generation of experts, is an even greater multinational enterprise. Pioneers in multinational sharing of ideas are those authors of textbooks and founders of professional societies and researchers who left their homelands to train abroad. Fine examples are Hiroshi Takeshita training at the Mayo Clinic under the tutelage of Richard Theye and John Michenfelder. Other equally dedicated physicians and scientists traveled to the University of Pittsburgh, the University of California, San Diego and San Francisco, the University of Iowa, Duke University, and elsewhere, creating a robust effect on the neuroanesthesiology community worldwide. In Europe, the basic scientist Bo Siesjo of Lund University, Sweden, served as host and mentor to later influential neuroanesthesiology researchers, including David Warner, formerly of the University of Iowa, David Smith of the University of Pennsylvania, Dale Pellegrino of Michael Reese Hospital in Chicago, and Takefume Sakabe of Yamaguchi University. In Canada, Adrian Gelb and Arthur Lam, both of whom would later move from Canada to the West Coast of the United States, shepherded many young academicians into a career of clinical neuroanesthesia and neuroanesthesia research. Yoram Shapira in Israel, and many others around the globe, also contributed to this global exchange of intellectual riches.

Clearly much of the social and scientific matrix that holds the world's neuroanesthesiology community together traces its origins to laboratory research mentors and pupils who had the courage and conviction to embrace worldwide academic fellowship.

LEADERSHIP

During much of its history, academic neuroanesthesiology has attracted some of the better minds in academic anesthesiology, partly because the clinical and research concepts are appealing and the research methodologies are difficult (ie, few meaningful variables in nervous system function are easily quantified). Many of the talented individuals in neuroanesthesiology also acquired broad-reaching leadership roles in their departments, institutions, national societies, and elsewhere. Several of these deserve mention.

James Cottrell (Fig. 5) served as a President of the ASA from 2002 to 2003. He and John Michenfelder were both ASA Rovenstine Lecturers[27,97] and winners of the ASA Distinguished Service Award.

John Michenfelder, Richard Traystman, David Warner, and William Young all won the ASA Award for Excellence in Research. Phillip Larson, John Michenfelder, and Michael Todd served as editors-in-chief of *Anesthesiology*, and Sten Lindahl served as editor-in-chief of *Acta Anesthesiologica Scandinavica*.

Moreover, healthy for the field were those neuroanesthesiologists who, after becoming department chairmen, made large incremental advances in promoting neuroanesthesiology research at their institution during their tenure. Fine examples are Harry Wollman at the University of Pennsylvania, Peter Safar at the University of Pittsburgh, Ronald Albrecht at Michael Reese Medical

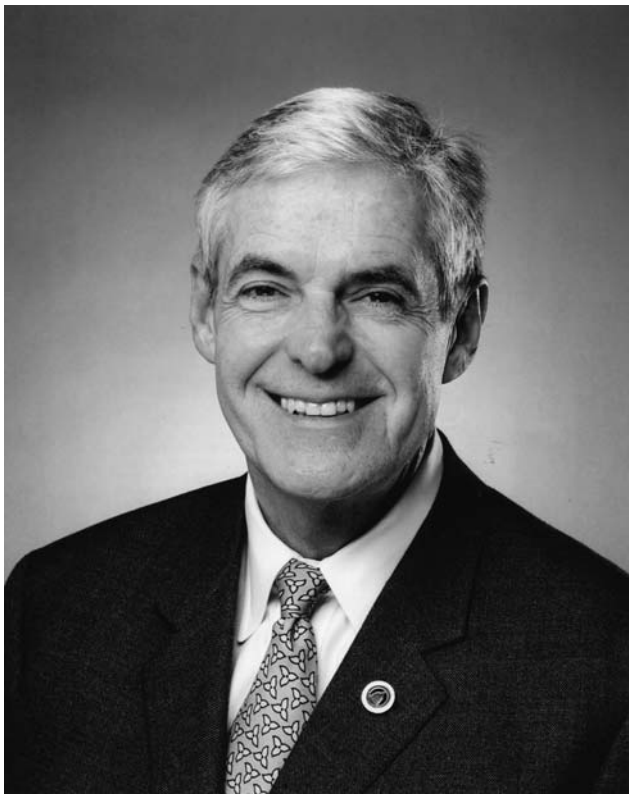

FIGURE 5. James E. Cottrell, MD, 8th president of the Society of Neurosurgical Anesthesia and Neurologic Supportive Care, and founding editor of *Journal of Neurosurgical Anesthesiology*. His political leadership paved the way for the worldwide proliferation of neuroanesthesiology.

Center, Chicago, Hiroshi Takeshita, at both Yamaguchi University and Kokura Memorial Hospital (Japan), Takefume Sakabe at Yamaguchi University (Japan), Petter Steen at the University of Oslo (Norway), Adrian Gelb at the University of Western Ontario (Canada), Donald Prough at University of Texas Medical Branch, Galveston, Jeffrey Kirsch at the University of Oregon Health Sciences Center, Hugo Van Aken at both the Catholic University of Leuven (Belgium) and University Hospital, Muenster (Germany), Eberhard Kochs at the Technical University of Munich (Germany), and Christian Werner at Johannes Gutenberg University in Mainz (Germany). Collectively, these and related leaders accounted for vast numbers of research publications, faculty careers developed, and junior researchers trained.

Few actions by neuroanesthesiologists have had greater impact on medicine in general or on a society than those of Peter Safar and Hiroshi Takeshita. As a result of Safar's laboratory and clinical research,[10–12] and leadership through the American Heart Association and other organizations, Advanced Cardiac Life Support is taught in a standardized fashion worldwide. Halfway around the globe from Safar, Hiroshi Takeshita appreciated in the late 1960s that his home country of Japan did not recognize the concept of brain death and, in later years, this would have a profound impact on the rate of organ transplantation in Japan. Through his collaboration with Occidental physicians and his leadership in the Japanese Brain Death Study Group,[167] his 2-decade interest in the subject would result in brain death being formally and legally recognized as a clinical entity in Japan, which in turn paved the way for more organ transplantation.[168]

Clearly these aforementioned individuals demonstrate that the influence of neuroanesthesiologists knows no boundaries.

ASSETS AND LIABILITIES

Although neuroanesthesiology has attracted many talented and energetic practitioners, researchers, and educators to its ranks, the subspecialty has several challenges that will affect its future. These predominantly consist of a need to infuse new ideas and a need to infuse new people. Unlike non-anesthesiology fields such as neoplastic hematology—in which transforming ideas appear multiple times per year, intervals are short between test tube concepts and bedside research, and large fractions of clinical patients are entered into human trials—neuroanesthesiologists have far too often directed their energy toward repetitive, confirmatory studies when they should have been exploring new issues or applying laboratory observations to clinical trials. These misappropriated efforts are seen in neuroanesthesiologists contribution to the 57 protocols of barbiturate protection for focal ischemia in animal models,[49] but minimal contributions to prospective trials in humans. The same pattern is seen in countless confirmatory studies of physiological or pharmacologic intervention on CBF, cerebral metabolism, and ICP. In later years, one could argue that many of these studies took a step backward as a result of substituting derivative measurements for raw measurements: CBF velocities and processed EEG are just 2 examples. Clearly if neuroanesthesiology is to survive and thrive, the subspecialty must be seen as a clearinghouse for new ideas, explored by the most creative minds. This concept requires extramural research funding which, in many cases, may take laboratory investigators, in particular, away from the day-to-day concepts cogitated by clinical practitioners, and more into the world of molecular biology and genomics. Bringing some of these concepts back to human trials would seem one way of including more neuroanesthesiologists in this research, but only time will tell if this approach will succeed.

New ideas appear to be a magnet for new trainees, but so too is some form of documentation of mastery of a training experience. Whether a subspecialty accreditation and certification is in neuroanesthesiology's best interest is open for debate; however, today's younger physicians appear to have more interest in subspecialty certification than do their predecessors. And some evidence suggests that the ability to procure posttraining certification may be a meaningful factor in anesthesiologists' choices of subspecialty training.

Absent these type attractants, resident physicians often see the practice of neuroanesthesiology as characterized by long anesthetics in patients whose outcomes are depressing or uncertain. Clearly, career-long care of neurologically impaired or at-risk patients is not consistent with the temperaments of all anesthesiology residents, nor is waiting for weeks or months (or more) to determine whether one's near-ideal anesthetic and surgical care yielded long-term benefit to the patient.

Given the enthusiasm and energy that has taken neuroanesthesiology from its nascent phase to the advances it experiences today, addressing these challenges should be well within our grasp.

REFERENCES

1. Frost EAM. History of neuroanesthesia. In: Albin MS, ed. *Textbook of Neuroanesthesia With Neurosurgical and Neuroscience Perspectives*. New York: McGraw-Hill; 1997:1–20.
2. Albin MS. Celebrating silver: the genesis of a neuroanesthesiology society: NAS→SNANSC→SNACC. *J Neurosurg Anesthesiol*. 1997;9:296–297.
3. Kofke WA. Celebrating Ruby: 40 years of NAS→SNANSC→SNACC→SNACC. *J Neurosurg Anesthesiol*. 2012;24:260–280.
4. Pasternak JJ, Lanier WL. Snapshot 1973 and 1974: critical thinkers and contemporary research ideas in neurosurgical anesthesia during the first years of SNACC. *J Neurosurg Anesthesiol*. 2012;24:300–311.
5. Mashour GA. Neuroanesthesiology: then & now. *Anesth Analg*. 2012;114:715–717.
6. Faulconer A, Pender JW, Bickford RG. The influence of partial pressure of nitrous oxide on the depth of anesthesia and the electroencephalogram in man. *Anesthesiology*. 1949;10:601–609.
7. Kiersey DK, Faulconer A Jr., Bickord RG. Automatic electroencephalographic control of thiopental anesthesia. *Anesthesiology*. 1954;15:356–364.
8. Gronqvist YK, Seldon TH, Faulconer A Jr. Cerebral anoxia during anesthesia: prognostic significance of electroencephalographic changes. *Ann Chir Gynaecol Fenn*. 1952;41:149–159.

9. Michenfelder JD, Gronert GA, Rehder K. Neuroanesthesia. *Anesthesiology*. 1969;30:65–100.
10. Safar P. Mouth-to-mouth airway. *Anesthesiology*. 1957;18:904–906.
11. Safar P, McMahon M. Mouth-to-airway emergency artificial respiration. *JAMA*. 1958;166:1459–1460.
12. Safar P, Brown TC, Holtey WJ, et al. Ventilation and circulation with closed-chest cardiac massage in man. *JAMA*. 1961;176: 574–576.
13. White RJ, Albin MS, Verdura J. Isolation of the monkey brain: in vitro preparation and maintenance. *Science*. 1963;141:1060–1061.
14. White RJ, Albin MS, Verdura J. Preservation of viability in the isolated monkey brain utilizing a mechanical extracorporeal circulation. *Nature*. 1964;202:1082–1083.
15. White RK, Albin MS, Locke GE, et al. Brain transplantation: prolonged survival of brain after carotid-jugular interposition. *Science*. 1965;150:779–781.
16. Terry JR Jr., Michenfelder JD, Daw EF. Hypothermia by extracorporeal circulation for neurosurgery: an anesthetic technic. *Anesth Analg*. 1962;41:241–248.
17. Michenfelder JD. Neuroanesthesia. In: Rehder K, Southorn P, Sessler A, eds. *Art to Science: Department of Anesthesiology, Mayo Clinic*. Rochester: Mayo Clinic; 2000:51–54.
18. Michenfelder JD, Messick JM Jr., Theye RA. Simultaneous cerebral blood flow measured by direct and indirect methods. *J Surg Res*. 1968;8:475–481.
19. Dawson B, Michenfelder JD, Theye RA. Effects of ketamine on canine cerebral blood flow and metabolism: modification by prior administration of thiopental. *Anesth Analg*. 1971;50:443–447.
20. Sari A, Okuda Y, Takeshita H. Effect of ketamine on cerebral circulation and metabolism [in Japanese]. *Masui*. 1971;20:68–73.
21. Gordon E. *A Basis and Practice of Neuroanaesthesia (Monographs in Anaesthesiology)*. New York: Elsevier; 1975:354.
22. Cottrell JE, Turndorf H. *Anesthesia and Neurosurgery*. St. Louis: CV Mosby Company; 1980.
23. Cucchiara RF, Michenfelder JD. *Clinical Neuroanesthesia*. New York: Churchill Livingstone; 1990.
24. Albin MS. *Textbook of Neuroanesthesia: With Neurosurgical and Neuroscience Perspectives*. New York: McGraw Hill; 1997.
25. Newfield P. *Handbook of Neuroanesthesia: Clinical and Physiologic Essentials*. Boston: Little Brown and Company; 1973.
26. Newfield P, Cottrell JE. *Handbook of Neuroanesthesia*. 5th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2012.
27. Michenfelder JD. The 27th Rovenstein lecture: neuroanesthesia and the achievement of professional respect. *Anesthesiology*. 1989;70:695–701.
28. Rosomoff HL. Distribution of intracranial contents with controlled hyperventilation: implications for neuroanesthesia. *Anesthesiology*. 1963;24:640–645.
29. Brambrink AM. A new name behind the established acronym: Society for Neuroscience in Anesthesiology and Critical Care. *J Neurosurg Anesthesiol*. 2010;22:186.
30. Cottrell JE, Hartung J. On the need for a new journal. *J Neurosurg Anesthesiol*. 1989;1:1–2.
31. Cottrell JE, Hartung J. On rock & roll and Index Medicus. *J Neurosurg Anesthesiol*. 1993;5:69–70.
32. ISI Web of Knowledge Journal Citations Reports. Available at: http://apps.webofknowledge.com. Accessed July 6, 2012.
33. *Journal of Neurosurgical Anesthesiology*. Available at: http://journals.lww.com/jnsa/pages/aboutthejournal.aspx. Accessed July 6, 2010.
34. Wang H, Olivero W, Wang D, et al. Cold as a therapeutic agent. *Acta Neurochir (Wien)*. 2006;148:565–570.
35. Fay T. Early experiences with local and generalized refrigeration of the human brain. *J Neurosurg*. 1959;16:239–259.
36. Steen PA, Soule EH, Michenfelder JD. Detrimental effect of prolonged hypothermia in cats and monkeys with and without regional cerebral ischemia. *Stroke*. 1979;10:522–529.
37. Steen PA, Milde JH, Michenfelder JD. The detrimental effects of prolonged hypothermia and rewarming in the dog. *Anesthesiology*. 1980;52:224–230.
38. Michenfelder JD. *Anesthesia and the Brain: Clinical, Functional, Metabolic, and Vascular Correlates*. New York: Churchill Livingstone p. 28; 1988.
39. Busto R, Dietrich WD, Globus MY, et al. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab*. 1987;7:729–738.
40. Natale JA, D'Alecy LG. Protection from cerebral ischemia by brain cooling without reduced lactate accumulation in dogs. *Stroke*. 1989;20:770–777.
41. Warner DS, McFarlane C, Todd MM, et al. Sevoflurane and halothane reduce focal ischemic brain damage in the rat: possible influence on thermoregulation. *Anesthesiology*. 1993;79:985–992.
42. Wass CT, Lanier WL, Hofer RE, et al. Temperature changes of > or = 1 degree C alter functional neurologic outcome and histopathology in a canine model of complete cerebral ischemia. *Anesthesiology*. 1995;83:325–335.
43. Wass CT, Lanier WL. Hypothermia-associated protection from ischemic brain injury: implications for patient management. *Int Anesthesiol Clin*. 1996;34:95–111.
44. Hindman BJ, Todd MM, Gelb AW, et al. Mild hypothermia as a protective therapy during intracranial aneurysm surgery: a randomized prospective pilot trial. *Neurosurgery*. 1999;44:23–32.
45. Todd MM, Hindman BJ, Clarke WR, et al. Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) Investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.
46. McGregor DG, Lanier WL, Pasternak JJ, et al. Intraoperative Hypothermia for Aneurysm Surgery Trial Investigators. Effect of nitrous oxide on neurologic and neuropsychological function after intracranial aneurysm surgery. *Anesthesiology*. 2008;108:568–579.
47. Pasternak JJ, McGregor DG, Lanier WL, et al. IHAST Investigators. Effect of nitrous oxide use on long-term neurologic and neuropsychological outcome in patients who received temporary proximal artery occlusion during cerebral aneurysm clipping surgery. *Anesthesiology*. 2009;110:563–573.
48. Pasternak JJ, McGregor DG, Schroeder DR, et al. IHAST Investigators. Hyperglycemia in patients undergoing cerebral aneurysm surgery: its association with long-term gross neurologic and neuropsychological function. *Mayo Clin Proc*. 2008;83:406–417.
49. Nolan JP, Morley PT, Vanden Hoek TL, et al. International Liaison Committee on Resuscitation. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation*. 2003;108:118–121.
50. Walters JH, Morley PT, Nolan JP. The role of hypothermia in post-cardiac arrest patients with return of spontaneous circulation. *Resuscitation*. 2011;82:508–516.
51. Shankaran S, Laptook AR, Ehrenkranz RA, et al. National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005;353: 1574–1584.
52. Smith AL, Hoff JT, Nielsen SL, et al. Barbiturate protection in acute focal cerebral ischemia. *Stroke*. 1974;5:1–7.
53. Erickson KM, Pasternak JJ, Weglinski MR, et al. Temperature management in studies of barbiturate protection from focal cerebral ischemia: systematic review and speculative synthesis. *J Neurosurg Anesthesiol*. 2009;21:307–317.
54. Michenfelder JD. The interdependency of cerebral function and metabolic effects following massive doses of thiopental in the dog. *Anesthesiology*. 1974;41:231–236.
55. Steen PA, Newberg L, Milde JH, et al. Hypothermia and barbiturates: individual and combined effects on canine cerebral oxygen consumption. *Anesthesiology*. 1983;58:527–532.
56. Warner DS, Takaoka S, Wu B, et al. Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia. *Anesthesiology*. 1996;84:1475–1484.
57. Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. *Anesthesiology*. 1986;64:165–170.

58. Zaidan JR, Klochany A, Martin WM, et al. Effect of thiopental on neurologic outcome following coronary artery bypass grafting. *Anesthesiology*. 1991;74:406–411.
59. Brain Resuscitation Clinical Trial I Study Group. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. *N Engl J Med*. 1986;314:397–403.
60. Sano T, Drummond JC, Patel PM, et al. A comparison of the cerebral protective effects of isoflurane and mild hypothermia in a model of incomplete forebrain ischemia in the rat. *Anesthesiology*. 1992;76:221–228.
61. Drummond JC, Cole DJ, Patel PM, et al. Focal cerebral ischemia during anesthesia with etomidate, isoflurane, or thiopental: a comparison of the extent of cerebral injury. *Neurosurgery*. 1995;37:742–748.
62. Fong JJ, Sylvia L, Ruthazer R, et al. Predictors of mortality in patients with suspected propofol infusion syndrome. *Crit Care Med*. 2008;36:2281–2287.
63. Rothman SM, Olney JW. Excitotoxicity and the NMDA receptor—still lethal after eight years. *Trends Neurosci*. 1995;18:57–58.
64. Polis TZ, Lanier WL. An evaluation of cerebral protection by anesthetics, with special reference to metabolic depression. *Anesthesiol Clin N Am*. 1997;15:691–717.
65. Todd MM, Warner DS. A comfortable hypothesis reevaluated: cerebral metabolic depression and brain protection during ischemia. *Anesthesiology*. 1992;76:161–164.
66. Lanier WL. Cerebral metabolic rate and hypothermia: their relationship to ischemic neurologic injury. *J Neurosurg Anesthesiol*. 1995;7:216–221.
67. Lanier WL, Stangland KJ, Scheithauer BW, et al. The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: examination of a model. *Anesthesiology*. 1987;66:39–48.
68. Wagner SR 4th, Lanier WL. Metabolism of glucose, glycogen, and high-energy phosphates during complete cerebral ischemia: a comparison of normoglycemic, chronically hyperglycemic diabetic, and acutely hyperglycemic nondiabetic rats. *Anesthesiology*. 1994;81:1516–1526.
69. Lanier WL, Hofer RE, Gallagher WJ. Metabolism of glucose, glycogen, and high-energy phosphates during transient forebrain ischemia in diabetic rats: effect of insulin treatment. *Anesthesiology*. 1996;84:917–925.
70. Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc*. 1996;71:801–812.
71. Hoffman WE, Braucher E, Pelligrino DA, et al. Brain lactate and neurologic outcome following incomplete ischemia in fasted, nonfasted, and glucose-loaded rats. *Anesthesiology*. 1990;72:1045–1050.
72. Warner DS, Todd MM, Dexter F, et al. Temporal thresholds for hyperglycemia-augmented ischemic brain damage in rats. *Stroke*. 1995;26:655–660.
73. Drummond JC, Moore SS. The influence of dextrose administration on neurologic outcome after temporary spinal cord ischemia in the rabbit. *Anesthesiology*. 1989;70:64–70.
74. Lam AM, Winn HR, Cullen BF, et al. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg*. 1991;75:545–551.
75. Lanier WL, Pasternak JJ. Refining perioperative glucose management in patients experiencing, or at risk for, ischemic brain injury. *Anesthesiology*. 2009;110:456–458.
76. Wass CT, Scheithauer BW, Bronk JT, et al. Insulin treatment of corticosteroid-associated hyperglycemia and its effect on outcome after forebrain ischemia in rats. *Anesthesiology*. 1996;84:644–651.
77. Steen PA, Gisvold SE, Milde JH, et al. Nimodipine improves outcome when given after complete cerebral ischemia in primates. *Anesthesiology*. 1985;62:406–414.
78. Tateishi A, Fleischer JE, Drummond JC, et al. Nimodipine does not improve neurologic outcome after 14 minutes of cardiac arrest in cats. *Stroke*. 1989;20:1044–1050.
79. Tateishi A, Scheller MS, Drummond JC, et al. Failure of nimodipine to improve neurologic outcome after eighteen minutes of cardiac arrest in the cat. *Resuscitation*. 1991;21:191–206.
80. Hoffman WE, Baughman VL, Polek W, et al. The 21-aminosteroid U74006F does not markedly improve outcome from incomplete ischemia in the rat. *J Neurosurg Anesthesiol*. 1991;3:96–102.
81. Perkins WJ, Milde LN, Milde JH, et al. Pretreatment with U74006F improves neurologic outcome following complete cerebral ischemia in dogs. *Stroke*. 1991;22:902–909.
82. Toung TJ, Traystman RJ, Hurn PD. Estrogen-mediated neuroprotection after experimental stroke in male rats. *Stroke*. 1998;29:1666–1670.
83. Noppens RR, Kofler J, Grafe MR, et al. Estradiol after cardiac arrest and cardiopulmonary resuscitation is neuroprotective and mediated through estrogen receptor-beta. *J Cereb Blood Flow Metab*. 2009;29:277–286.
84. Atkinson JL. The neglected prehospital phase of head injury: apnea and catecholamine surge. *Mayo Clin Proc*. 2000;75:37–47.
85. Talmor D, Roytblat L, Artru AA, et al. Phenylephrine-induced hypertension does not improve outcome after closed head trauma in rats. *Anesth Analg*. 1998;87:574–578.
86. Shapira Y, Artru AA, Lam AM. Ketamine decreases cerebral infarct volume and improves neurological outcome following experimental head trauma in rats. *J Neurosurg Anesthesiol*. 1992;4:231–240.
87. Sell SL, Avila MA, Yu G, et al. Hypertonic resuscitation improves neuronal and behavioral outcomes after traumatic brain injury plus hemorrhage. *Anesthesiology*. 2008;108:873–881.
88. Vavilala MS, Lam AM. Perioperative considerations in pediatric traumatic brain injury. *Int Anesthesiol Clin*. 2002;40:69–87.
89. Vavilala MS, Muangman S, Waitayawinyu P, et al. Neurointensive care; impaired cerebral autoregulation in infants and young children early after inflicted traumatic brain injury: a preliminary report. *J Neurotrauma*. 2007;24:87–96.
90. Coates BM, Vavilala MS, Mack CD, et al. Influence of definition and location of hypotension on outcome following severe pediatric traumatic brain injury. *Crit Care Med*. 2005;33:2645–2650.
91. Lam A. *Anesthetic Management of Acute Head Injury*. Burr Ridge, IL: McGraw-Hill; 1995.
92. History of the brain trauma foundation. Available at: https://www.braintrauma.org/about/history-of-btf/. Accessed July 6, 2012.
93. Brain Trauma Foundation Guidelines. Available at: https://www.braintrauma.org/coma-guidelines/btf-guidelines/. Accessed July 6, 2012.
94. Warner DS. Perioperative neuroprotection: are we asking the right questions? *Anesth Analg*. 2004;98:563–565.
95. Kawaguchi M, Drummond JC, Cole DJ, et al. Effect of isoflurane on neuronal apoptosis in rats subjected to focal cerebral ischemia. *Anesth Analg*. 2004;98:798–805.
96. Baughman VL, Hoffman WE, Thomas C, et al. The interaction of nitrous oxide and isoflurane with incomplete cerebral ischemia in the rat. *Anesthesiology*. 1989;70:767–774.
97. Cottrell JE. We care, therefore we are: anesthesia-related morbidity and mortality: The 46th Rovenstine Lecture. *Anesthesiology*. 2008;109:377–388.
98. Olney JW, Young C, Wozniak DF, et al. Anesthesia-induced developmental neuroapoptosis: does it happen in humans? *Anesthesiology*. 2004;101:273–275.
99. Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology*. 2009;110:796–804.
100. Sprung J, Flick RP, Katusic SK, et al. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. *Mayo Clin Proc*. 2012;87:120–129.
101. Wollman H, Alexander C, Cohen PJ, et al. Cerebral circulation during general anesthesia and hyperventilation in man: thiopental induction to nitrous oxide and D-tubocurarine. *Anesthesiology*. 1965;26:329–334.
102. Ravussin P, Archer DP, Meyer E, et al. The effects of rapid infusions of saline and mannitol on cerebral blood volume and intracranial pressure in dogs. *Can Anaesth Soc J*. 1985;32:506–515.
103. Archer DP, Labrecque P, Tyler JL, et al. Cerebral blood volume is increased in dogs during administration of nitrous oxide or isoflurane. *Anesthesiology*. 1987;67:642–648.

104. Howard-Lech VL, Lee TY, Craen RA, et al. Cerebral blood volume measurements using dynamic contrast-enhanced x-ray computed tomography: application to isoflurane anaesthetic studies. *Physiol Meas*. 1999;20:75–86.
105. Cenic A, Craen RA, Howard-Lech VL, et al. Cerebral blood volume and blood flow at varying arterial carbon dioxide tension levels in rabbits during propofol anesthesia. *Anesth Analg*. 2000;90:1376–1383.
106. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (Part I). *Anesth Analg*. 1990;70:303–315.
107. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (Part II). *Anesth Analg*. 1990;70:433–444.
108. Kofke WA, Young RS, Davis P, et al. Isoflurane for refractory status epilepticus: a clinical series. *Anesthesiology*. 1989;71:653–659.
109. Artru AA. Rate of cerebrospinal fluid formation, resistance to reabsorption of cerebrospinal fluid, brain tissue water content, and electroencephalogram during desflurane anesthesia in dogs. *J Neurosurg Anesthesiol*. 1993;5:178–186.
110. Albrecht RF, Miletich DJ, Ruttle M. Cerebral effects of extended hyperventilation in unanesthetized goats. *Stroke*. 1987;18:649–655.
111. Cottrell JE, Casthely P, Brodie JD, et al. Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. *N Engl J Med*. 1978;298:809–811.
112. Zornow MH, Todd MM, Moore SS. The acute cerebral effects of changes in plasma osmolality and oncotic pressure. *Anesthesiology*. 1987;67:936–941.
113. Zornow MH, Prough DS. Fluid management in patients with traumatic brain injury. *New Horiz*. 1995;3:488–498.
114. DeWitt DS, Prough DS, Deal DD, et al. Hypertonic saline does not improve cerebral oxygen delivery after head injury and mild hemorrhage in cats. *Crit Care Med*. 1996;24:109–117.
115. Kaieda R, Todd MM, Warner DS. Prolonged reduction in colloid oncotic pressure does not increase brain edema following cryogenic injury in rabbits. *Anesthesiology*. 1989;71:554–560.
116. Lanier WL, Milde JH, Michenfelder JD. Cerebral stimulation following succinylcholine in dogs. *Anesthesiology*. 1986;64:551–559.
117. Lanier WL, Iaizzo PA, Milde JH. Cerebral function and muscle afferent activity following intravenous succinylcholine in dogs anesthetized with halothane: the effects of pretreatment with a defasciculating dose of pancuronium. *Anesthesiology*. 1989;71:87–95.
118. Minton MD, Grosslight K, Stirt JA, et al. Increases in intracranial pressure from succinylcholine: prevention by prior nondepolarizing blockade. *Anesthesiology*. 1986;65:165–169.
119. Stirt JA, Grosslight KR, Bedford RF, et al. "Defasciculation" with metocurine prevents succinylcholine-induced increases in intracranial pressure. *Anesthesiology*. 1987;67:50–53.
120. Lanier WL, Albrecht RF II, Iaizzo PA. Divergence of intracranial and central venous pressures in lightly anesthetized, tracheally intubated dogs that move in response to a noxious stimulus. *Anesthesiology*. 1996;84:605–613.
121. Hickey R, Albin MS, Bunegin L, et al. Autoregulation of spinal cord blood flow: is the cord a microcosm of the brain? *Stroke*. 1986;17:1183–1189.
122. deHaan P, Kalkman CJ, Vanicky I, et al. Effect of mild hypothermia and the 21-aminosteroid U-74389G on neurologic and histopathologic outcome after transient spinal cord ischemia in the rabbit. *J Neurosurg Anesthesiol*. 1998;10:86–93.
123. Matsumoto M, Ilda Y, Sakabe T, et al. Mild and moderate hypothermia provide better protection than a burst-suppression dose of thiopental against ischemic spinal cord injury in rabbits. *Anesthesiology*. 1997;86:1120–1127.
124. Kalkman CJ, Been HD, Ongerboer de Visser BW. Intraoperative monitoring of spinal cord function. A review. *Acta Orthop Scand*. 1993;64:114–123.
125. Wang MC, Kreuter W, Wolfla CE, et al. Trends and variations in cervical spine surgery in the United States: Medicare beneficiaries, 1992–2005. *Spine*. 2009;34:955–961; discussion 962–963.
126. Young WL, Pile-Spellman J, Prohovnik I, et al. Evidence for adaptive autoregulatory displacement in hypotensive cortical territories adjacent to arteriovenous malformations. Columbia University AVM Study Project. *Neurosurgery*. 1994;34:601–610.
127. Achrol AS, Pawlikowska L, McCulloch CE, et al. UCSF BAVM Study Project. Tumor necrosis factor-alpha-238G > A promoter polymorphisms is associated with increased risk of new hemorrhage in the natural course of patients with brain arteriovenous malformations. *Stroke*. 2006;37:231–234.
128. Fox AJ. Charles George Drake, neurosurgeon. *Am J Neuroradiol*. 1999;20:358–359.
129. Aitken RR, Drake CG. A technique of anesthesia with induced hypotension for surgical correction of intracranial aneurysms. *Clin Neurosurg*. 1974;21:107–114.
130. Lam AM, Gelb AW. Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. *Anesth Analg*. 1983;62:742–748.
131. Schott GD. Penfield's homunculus: a note on cerebral cartography. *J Neurol Neurosurg Psychiatry*. 1993;56:329–333.
132. Herrick IA, Craen RA, Gelb AW, et al. Propofol sedation during awake craniotomy for seizures: electrocorticographic and epileptogenic effects. *Anesth Analg*. 1997;84:1280–1284.
133. Gignac E, Manninen PH, Gelb AW. Comparison of fentanyl, sufentanil and alfentanil during awake craniotomy for epilepsy. *Can J Anaesth*. 1993;40(pt 1):421–424.
134. Archer DP, McKenna JM, Morin L, et al. Conscious-sedation analgesia during craniotomy for intractable epilepsy: a review of 354 consecutive cases. *Can J Anaesth*. 1988;35:338–344.
135. Cascino GD, So EL, Sharbrough FW, et al. Alfentanil-induced epileptiform activity in patients with partial epilepsy. *J Clin Neurophysiol*. 1993;10:520–525.
136. Grundy BL, Sanderson AC, Webster WW, et al. Hemiparesis following carotid endarterectomy: comparison of monitoring methods. *Anesthesiology*. 1981;55:462–466.
137. Sloan TB, Heyer EJ. Anesthesia for intraoperative neurophysiologic monitoring of the spinal cord. *J Clin Neurophysiol*. 2002;19:430–443.
138. Bloom MJ, Kofke WA, Nemoto E, et al. Monitoring for cerebrovascular surgery. *Int Anesthesiol Clin*. 1996;34:137–147.
139. Werner C, Kochs E. Monitoring of the central nervous system. *Curr Opin Anaesthesiol*. 1998;11:459–465.
140. Sviri GE, Ghodke B, Britz GW, et al. Transcranial Doppler grading criteria for basilar artery vasospasm. *Neurosurgery*. 2006;59:360–366.
141. Matta BF, Lam AM, Strebel S, et al. Cerebral pressure autoregulation and carbon dioxide reactivity during propofol-induced EEG suppression. *Br J Anaesth*. 1995;74:159–163.
142. Smith M. Shedding light on the adult brain: a review of the clinical application of near-infrared spectroscopy. *Philos Transact A Math Phys Eng Sci*. 2011;369:4452–4469.
143. Hoffman WE, Charbel FT, Edelman G, et al. Comparison of the effect of etomidate and desflurane on brain tissue gasses and pH during prolonged middle cerebral artery occlusion. *Anesthesiology*. 1988;88:1188–1194.
144. Michenfelder JD, Miller RH, Gronert GA. Evaluation of an ultrasonic device (Doppler) for the diagnosis of venous air embolism. *Anesthesiology*. 1972;36:164–167.
145. Cucchiara RF, Nugent M, Seward JB, et al. Air embolism in upright neurosurgical patients: detection and localization by two-dimensional transesophageal echocardiography. *Anesthesiology*. 1984;60:353–355.
146. Matjasko MJ, Hellman J, Mackenzie CF. Venous air embolism, hypotension, and end-tidal nitrogen. *Neurosurgery*. 1987;21:378–382.
147. Marshall WK, Bedford RF. Use of a pulmonary-artery catheter for detection and treatment of venous air embolism: a prospective study in man. *Anesthesiology*. 1980;52:131–134.
148. Michenfelder JD, Martin JT, Altenburg BM, et al. Air embolism during neurosurgery: an evaluation of right-atrial catheters for diagnosis and treatment. *JAMA*. 1969;208:1353–1358.
149. Bunegin L, Albin MS, Helsel PE, et al. Positioning the right atrial catheter: a model for reappraisal. *Anesthesiology*. 1981;55:343–348.
150. Cucchiara RF, Seward JB, Nishimura RA, et al. Identification of patent foramen ovale during sitting position craniotomy by transesophageal echocardiography with positive airway pressure. *Anesthesiology*. 1985;63:107–109.

151. Black S, Cucchiara RF, Nishimura RA, et al. Parameters affecting occurrence of paradoxical air embolism. *Anesthesiology*. 1989;71:235–241.
152. Black S, Ockert DB, Oliver WC Jr., et al. Outcome following posterior fossa craniectomy in patients in the sitting or horizontal positions. *Anesthesiology*. 1988;69:49–56.
153. Sawin PD, Todd MM, Traynelis VC, et al. Cervical spine motion with direct laryngoscopy and orotracheal intubation: an in vivo cinefluoroscopic study of subjects without cervical abnormality. *Anesthesiology*. 1996;85:26–36.
154. Lennarson PJ, Smith DW, Sawin PD, et al. Cervical spinal motion during intubation: efficacy of stabilization maneuvers in the setting of complete segmental instability. *J Neurosurg*. 2001;94(suppl):265–270.
155. Hindman BJ, Palecek JP, Posner KL, et al. Cervical spinal cord, root, and bony spine injuries. A Closed Claims analysis. *Anesthesiology*. 2011;114:782–795.
156. Soriano SG, Eldredge EA, Rockoff MA. Pediatric neuroanesthesia. *Anesthesiol Clin N Am*. 2002;20:389–404.
157. Mayer SA, Coplin WM, Chang C, et al. Neurocritical Care Society; American Academy of Neurology Section on Critical Care and Emergency Neurology; Society of Neurosurgical Anesthesia and Critical care. Core curriculum and competencies for advanced training in neurological intensive care: United Council for Neurologic Subspecialties guidelines. *Neurocrit Care*. 2006;5:159–165.
158. Hutchinson PJ, Gupta AK, Fryer TF, et al. Correlations between cerebral blood flow, substrate delivery, and metabolism in head injury: a combined microdialysis and triple oxygen positron emission tomography study. *J Cereb Blood Flow Metab*. 2002;22:735–745.
159. Lee LA, Roth S, Posner KL, et al. The American Society of Anesthesiologists Postoperative Visual Loss Registry: analysis of 93 spine surgery cases with postoperative visual loss. *Anesthesiology*. 2006;105:652–659.
160. Holmes JM, Shang S, Leske DA, et al. Metabolic acidosis-induced retinopathy in the neonatal rat. *Invest Ophthalmol Vis Sci*. 1999;40:804–809.
161. Zhang S, Leske DA, Uhl JR, et al. Retinopathy associated with enterococcus enteropathy in the neonatal rat. *Invest Ophthalmol Vis Sci*. 1999;40:1305–1309.
162. Bunegin L, Wahl D, Albin MS. Detection and volume estimation of embolic air in the middle cerebral artery using transcranial Doppler sonography. *Stroke*. 1994;25:593–600.
163. Albin MS, Bunegin L, Garcia C, et al. The transcranial Doppler can image microaggregates of intracranial air and particulate matter. *J Neurosurg Anesthesiol*. 1989;1:134–135.
164. Pugsley W, Klinger L, Paschalis C, et al. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke*. 1994;25:1393–1399.
165. Prough DS, Rogers AT, Stump DA, et al. Cerebral blood flow decreases with time whereas cerebral oxygen consumption remains stable during hypothermic cardiopulmonary bypass in humans. *Anesth Analg*. 1991;72:161–168.
166. Kuroda Y, Uchimot R, Kaieda R, et al. Central nervous system complications after cardiac surgery: a comparison between coronary artery bypass grafting and valve surgery. *Anesth Analg*. 1993;76:222–227.
167. Takeuchi K, Takeshita H, Takakura K, et al. Brain Death Study Group. New Japanese criteria of brain death. *Neurosurg Rev*. 1989;12(suppl 1):265–275.
168. Takeshita H. Brain death and organ transplantation. *Masui*. 1997;46(suppl):S1–S9.

