Anesthesiology 2008; 109:377–88

We Care, Therefore We Are: Anesthesia-related Morbidity and Mortality

The 46th Rovenstine Lecture

*James Edward Cottrell, M.D.**

EMERY Andrew Rovenstine, M.D. (Professor, Department of Anesthesiology, New York University, New York; 1895–1960), was a giant in the founding of our specialty, and I feel greatly honored to have been selected to deliver this Rovenstine Memorial Lecture. The closest I came to Dr. Rovenstine was the privilege of occupying his former office at the old Bellevue Hospital in 1974. The textbooks he left behind, with underlined passages and notes written in the margins, were fascinating, and I have made them available through the Wood Library Museum of Anesthesiology.

The message I want to bring to you today is the message that I have brought to this society since way back when I became the American Society of Anesthesiologists' Vice President of Scientific Affairs: To make the future of our specialty shine, we need to grab hold of the questions about anesthesiology that our patients and recent research have brought to the forefront. Whether you are a clinician, a clinician researcher, a nonclinician researcher, or a potential patient (as we all are), we need to show how much we care by supporting efforts to answer questions that address our patients' fears. When their fears become our research focus, public advocacy will convert our poor showing in National Institutes of Health (NIH) research funding into a scientific powerhouse.[1]

Responses like "no time," "no money," "medical students with previous research experience choose other specialties," "department chairs don't have sufficient research background," or "we've solved all of our major problems" are not acceptable, and they are, in fact, not true. For example, take "we've solved all of our major problems." What about mortality? We have made substantial progress in the sense that we are anesthetizing sicker patients who undergo more complex procedures without an increase in mortality, but mortality from anesthesia has not decreased significantly since the 1960s.[2] What about "medical students who do research don't go into anesthesiology"? Our residents have done research, and like residents who match into other highly desired specialties—such as dermatology, plastic and reconstructive surgery, orthopedics, and radiology—they use their qualifications to gain admission to a specialty that receives little NIH funding.[1] What about the qualifications of anesthesia chairs? I am confident that our chairpersons compare favorably to chairs in specialties that receive the lion's share of funding.

Most of all, we need to reject the rejoinder that anesthesiology receives little research funding because it is a specialty without a disease. As my friend Jeff Balser, M.D., Ph.D. (Professor, Department of Anesthesiology, Vanderbilt University, Nashville, Tennessee), says, "Every disease in every patient who is going to be anesthetized is 'our' disease." In addition to diseases that are known to affect anesthetic management—such as coronary artery disease, chronic lung disease, and renal failure—there may be many that we are yet to discover. What about conditions that are exacerbated by anesthetics? These may include fetal apoptosis (brain cell suicide), Alzheimer disease (AD), Parkinson disease, Huntington disease, and asymptomatic cognitive dysfunction that becomes symptomatic as postoperative cognitive dysfunction (POCD). These are the diseases whose connection to anesthesia can connect us to grant proposals that—if properly formulated—NIH cannot refuse.

So today I want to talk about some of the morbidities that we need to investigate most urgently. We will review characteristics of the young brain, discuss anesthetic effects on the young brain— effects that are being delineated today—and talk about characteristics of the old brain and anesthetic effects on the older brain. In doing so, we will consider the controversy over which is worse— deep anesthesia or light anesthesia—and talk about factors that probably aggravate cognitive dysfunction. Then we will consider the apparent lack of difference between regional *versus* general anesthesia, some of the confounding factors in that discussion, and some potential alleviating procedures, such as the use of continuous peripheral nerve catheters instead of deep sedation after regional anesthesia.

We will also look at the neurodegenerative diseases. What happens when patients with AD have anesthesia and surgery? Do anesthetics hasten the progression of cognitive dysfunction? In light of that risk, I will review some of the agents and techniques that have shown protective potential in laboratories. Preconditioning is

* Professor of Anesthesiology.

Received from the Department of Anesthesiology, SUNY Downstate Medical Center, Brooklyn, New York. Submitted for publication February 22, 2008. Accepted for publication June 13, 2008. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Cottrell: Department of Anesthesiology, SUNY Downstate Medical Center, 450 Clarkson Avenue, Box 6, Brooklyn, New York 11203-2098. james.cottrell@downstate.edu.

one such technique. Could we deliver a nondamaging stressor 24–48 h before surgery—a stressor that would generate a protective cascade, protective against an ischemic cascade? And what about neurogenesis? Can we stimulate the production of new brain cells that would repair damage not prevented by preconditioning? These prospects have left the arena of science fiction, but their clinical utility remains unknown.

Last but not least, I want to add a *lagniappe*—"a little something extra" (for those of you who are not from Louisiana or Mississippi)—and tell you about work being done at my institution that involves memory, targeted prevention and erasure of memory, and the potential that research might have for treating phantom pain, preventing memory of intraoperative awareness, and treating posttraumatic distress syndrome. Then I will conclude with a vision of how we can make ourselves and our specialty more profoundly appreciated by the press, the public, our patients, and funding agencies!

The Young Brain

The developing nervous system is highly susceptible to neurotoxic insults during rapid synaptogenesis, during the brain growth spurt, before neurons have migrated to their final destination and fully differentiated.[3] In human newborns, the brain has a full complement of 40–50 billion neurons.[4] However, *in utero*, for every neuron that survives, 1–2 neurons undergo apoptosis and die.[5] The signal for initiating those cell suicides is normally a lack of synaptic feedback due to failure to form synaptic connections, such that rates of cell death average approximately 8,000 neurons per second during the last 11 weeks of gestation. This suggests that neurons have a ready capacity to trigger cell death quickly in response to a lack of stimulation, or in response to a neurotoxic insult. With that response potential in mind, let's look at some of the evidence about adverse effects of anesthetics in children and newborns.[6]

In 1953, James Eckenhoff, M.D. (Professor, Department of Anesthesiology, University of Pennsylvania, Philadelphia, Pennsylvania; 1915–1996), looked at personality changes in children after anesthesia and surgery.[7] They developed more temper tantrums, more phobias, and more bed-wetting. Those changes were most frequent (38%) in the youngest children (younger than 4 yr) and least frequent (8%) in the oldest children (older than 8 yr). Unsatisfactory anesthetic induction was a prominent risk factor. So way back in 1953, there was an indication that anesthesia might have an adverse effect on young children.

One of the first animal models to test the effect of anesthesia on fetuses was developed while I was at New York University. Jack Chalon, M.D. (Professor, Department of Anesthesiology, New York University, New York), exposed pregnant mice to halothane and found that their offspring performed significantly more slowly than those of control mice.[8] Unfortunately, early reports indicating a potential problem did not receive the attention they deserved. That changed in 2003 with the publication of Jevtovic-Todorovic *et al.*'s "Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits"—a title that says it all.[9] Several studies have augmented those findings,[10–13] including a recent investigation by Fredriksson *et al.*[14] They injected mice with propofol, ketamine, thiopental, propofol with thiopental, ketamine with thiopental, or high-dose propofol during the critical stage of mouse development (10 days old) and found increases in brain cell death and significant reductions in functional performance. Now the laboratory evidence is sufficient to heighten concern about anesthetizing pregnant women during their third trimester, about anesthesia in our neonatal and pediatric patients, and about sedation in the neonatal intensive care unit. What are the proposed mechanisms for this neurotoxicity in laboratory animals? Do anesthetics trigger the same mechanisms in human fetuses and neonates?[15,16] And if they do, can we prevent or reduce that effect?

Olney *et al.* have proposed that anesthetic drug effects on fetal and neonatal γ-aminobutyric acid and *N*-methyl-D-aspartic acid receptors cause translocation of a Bcl-2–associated protein to mitochondrial membranes, leading to an apoptotic cascade.[15] If we can interfere with the apoptotic cascade in abnormally inhibited neurons, we might be able to prevent anesthetic-induced neuronal apoptosis. Some ways to do that have been found in laboratory animals. Using the early postnatal rat model in which Jevtovic-Todorovic *et al.* found that anesthesia generates neural apoptosis and long-term learning deficits, Yon *et al.*[17] found that melatonin reduced that damage in the most vulnerable brain regions: "Melatonin-induced neuroprotection was mediated, at least in part, *via* inhibition of the mitochondria-dependent apoptotic pathway since melatonin caused an up-regulation of the antiapoptotic protein, bcl-X_L, reduction in anesthesia-induced cytochrome C release into the cytoplasm and a decrease in anesthesia-induced activation of caspase-3." An analogous effect of melatonin has been found in fetal sheep.[18] Augmentation of another endogenously generated substance with neuroprotective potential, erythropoietin,[19,20] has also shown promise against *N*-methyl-D-aspartic acid receptor antagonist neurotoxicity in rat[21] and mouse[22] neonates and in hypoxic-ischemic injured neonatal rats.[23] Perhaps the problem can even be alleviated by anesthetic choice in pregnant females. Ma *et al.*[24] have presented evidence that "xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain." What about hypothermia? A human trial looking at whole body hypothermia (72 h at 33.5°C) in neonates with hypoxic ischemia encephalop-

athy found a decrease in death or moderate to severe disability from 62% down to 44%.[25,26]

So what can we say about anesthesia and the young brain? What recommendations can we take home? We have been warned about this potential problem since 1953, and those warnings have been supported by substantial laboratory evidence published over the past 5 yr. I recommend that until and unless we establish that human fetuses and newborns do not suffer anesthetic neurotoxicity, we should minimize or avoid late third-trimester anesthesia, delay elective surgery in preterm and early postnatal infants, avoid nitrous oxide and ketamine because they seem to be the most toxic anesthetics,[6] and limit surgical procedure times whenever possible. Meanwhile, we need to continue to look for ways to reduce fetal and newborn anesthetic toxicity in the laboratory, especially in nonhuman primates. We have made progress in defining the potential problem and possible solutions, but I think this question is so serious that it presents our specialty with an enormous obligation and opportunity to find answers.

The Older Brain

The older brain is different, but like the very young brain, it is fragile. Some people define the older brain as over 50 yr. Some define it as over 60. I define it as over 70, and in another 5 yr I hope to have gained the wisdom to define it as over 75—unless I decide to run for President, in which case it will be over 80! Okay, let's look at the not-entirely-happy reality.

The older brain has less cognitive reserve—less resilience to neuropathologic damage.[27] It also has declining anesthetic requirements—lower minimum alveolar concentration, lower minimum intraarterial concentration. There are many potential mechanisms that might underlie these age-related differences in cognitive reserve and anesthetic requirements. Oxidative phosphorylation may not work as well. We have picked up some genetic mutations—mutations that can alter outcomes. There are also genetic alleles that were silent when we were young, but manifest themselves (have phenotypic effects) as we age. And then there is free radical buildup with reduced levels of free radical scavengers such as vitamin C, melatonin, and vitamin E.

How do we look for deterioration after anesthesia and surgery? We try to measure decrement in memory or concentration, sometimes not detectable until weeks after anesthesia, with a duration of several weeks to permanent. A diagnosis of POCD is only warranted if we have evidence from a battery of before-and-after neuropsychological tests.

POCD after Noncardiac Surgery

The first major report of cognitive dysfunction after anesthesia was published in 1955 by P. D. Bedford, M.D. (Cowley Road Hospital, Oxford, United Kingdom; died 1962).[28] He reviewed 1,193 (presumably noncardiac) patients older than 50 yr who had received general anesthesia. Mental deterioration in 10% of patients seemed to be long term or permanent—a figure that concurs with recent findings. The author concluded that cognitive decline was related to anesthetic agents and hypotension. He recommended that "Operations on elderly people should be confined to unequivocally necessary cases" and that "postoperative medication should not be a routine matter." The next major study to report POCD skips ahead 43 yr to 1998—the first International Study of Postoperative Cognitive Dysfunction.[29] In noncardiac patients older than 59 yr, the incidence of cognitive dysfunction 1 week after surgery was 22% higher than in age-matched controls and 7% higher 3 months after surgery ($P < 0.004$ for both), with 10% of patients (91 of 910) evidencing POCD (identical to Bedford's finding at a longer postoperative interval). Increasing age, duration of anesthesia, lesser education, a second operation, postoperative infection, and respiratory complications were risk factors for early POCD. However, under a circumstance of significantly reduced statistical power due to a 22% loss to follow-up at 3 months, only age and benzodiazepine use before surgery remained statistically significant independent risk factors for late POCD. Hypoxemia and hypotension were not significant early or late risk factors.

Let's consider the most recent study. Twelve and seven tenths of a percent of elderly (aged >59 yr), noncardiac patients had POCD 3 months after surgery[30]—again, within the confidence interval of Bedford's 1955 report. Corroborating earlier work,[31] this study also found a substantial relation between POCD and death within 1 yr of surgery (fig. 1).

Independent risk factors for sustained POCD among the elderly included greater age, less education, POCD at hospital discharge, and a history of stroke without residual damage. Consistent with many investigations, more education may indicate greater presurgical cognitive reserve, just as previous stroke may indicate presurgical reduction of cognitive reserve.[32,33] Notably, this most recent study did not find duration of anesthesia to be a risk factor. However, sample size of elderly patients at the 3-month measurement was even smaller (308 with 39 POCD patients, 13%) than in the International Study of POCD (901 with 91 POCD patients, 10%).

POCD after Cardiac Surgery

What about POCD in coronary artery bypass patients? Most of us have heard friends or relatives say something like "since he had open-heart surgery he's not the same, he can't think as well, he's not as happy." The *New York Times* brought attention to this problem with an article titled "Saving the Heart Can Sometimes Mean Losing the

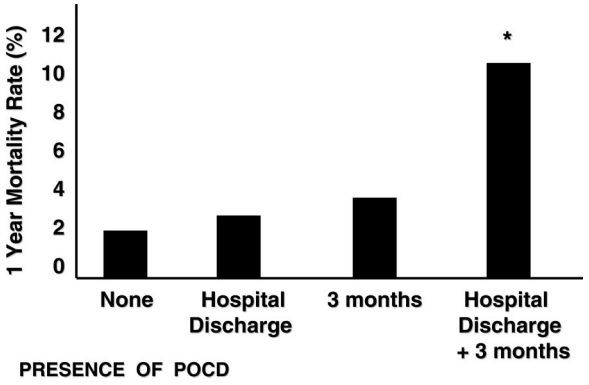

Fig. 1. Relation between the presence of postoperative cognitive dysfunction (POCD) and the percentage of patients who died in the first year after surgery. This figure includes only patients who survived to test at the 3-month (late) test time. The figure includes the following four groups: none (patients who did not experience POCD at either of the testing times), hospital discharge (patients who had POCD only at hospital discharge), 3 months (patients who had POCD only at the late [3 months postoperative] testing session), and hospital discharge + 3 months (patients who had POCD at both hospital discharge and the late testing sessions). * Hospital discharge + 3 month group was significantly different than the other three groups, P = 0.02.[30]

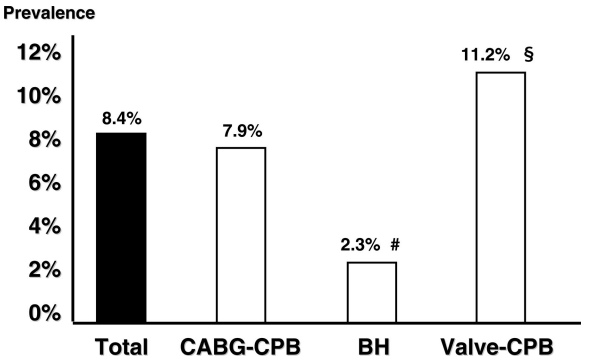

Fig. 2. Prevalence of postoperative delirium according to the type of cardiac surgical procedure. BH = beating heart surgery; CABG–CPB = coronary artery bypass grafting with cardiopulmonary bypass; CPB = cardiopulmonary bypass; Valve = valvular surgery with or without coronary artery bypass grafting with cardiopulmonary bypass. # P < 0.0001 *versus* CABG–CPB and Valve-CPB. § P < 0.0001 *versus* CABG-CPB.[38]

Memory."[34] They explained the basics of extracorporeal circulation and discussed reasons for memory loss, focusing on a patient who had gone back to work and found that he had difficulty with his job—a patient who could not perform functions that he had performed for many years. That article raised a great deal of concern, setting the stage for an article published a year later in the *New England Journal of Medicine* by Newman *et al.*[35] They found POCD in 53% of coronary artery bypass graft (CABG) patients at discharge and in 36% of patients 6 weeks later. That percentage went down to 24% at 6 months after surgery, but came back up to 42% at 5 yr after surgery—a pattern of early improvement followed by subsequent decline that was predicted by POCD at discharge.[35]

The factors that cause decline in cognitive capacity among non-CABG patients also affect CABG patients. However, some of those risk factors, such as duration of exposure to anesthetics, may be masked by damage done to CABG patients by increased liability to cerebral emboli, cerebral ischemia during reperfusion, and overwarming[36] at the end of the procedure.

Does off-pump *versus* on-pump make a difference? A small study found no difference,[37] but a large study of more than 16,000 patients found a greater incidence of delirium in patients exposed to on-pump cardiopulmonary bypass, with duration of surgery (and so anesthesia) as a significant risk factor (fig. 2).[38] Although these patients were not followed up for POCD, a relation between delirium and POCD should not be discounted,[39,40] such that off-pump patients may be at lesser risk for POCD.

Aggravating Factors

What factors aggravate the development of POCD in the elderly? Inflammation caused by surgical trauma is an early candidate. We know about the up-regulation of interleukin 1, and this in turn can affect the anesthetic receptors.[41] The ensuing cascade of events ultimately affects the anesthetic γ-aminobutyric acid and *N*-methyl-D-aspartic acid receptors and increases production of β-amyloid, and we know that β-amyloid, even in nondemented patients, can cause cognitive problems if there is enough of it.[41]

Genetic predispositions are another aggravating factor. For example, Mathew *et al.*[42] have shown the contribution of P-selectin and C-reactive protein alleles in modulating susceptibility to cognitive decline caused by inflammation after cardiac surgery (fig. 3).

Are anesthetics aggravating factors? Culley *et al.*[43] found that spatial memory is impaired for 2 weeks after 2 h of 1.2% isoflurane and 70% nitrous oxide in aged rats. What about nitrous oxide alone? In a more recent inves-

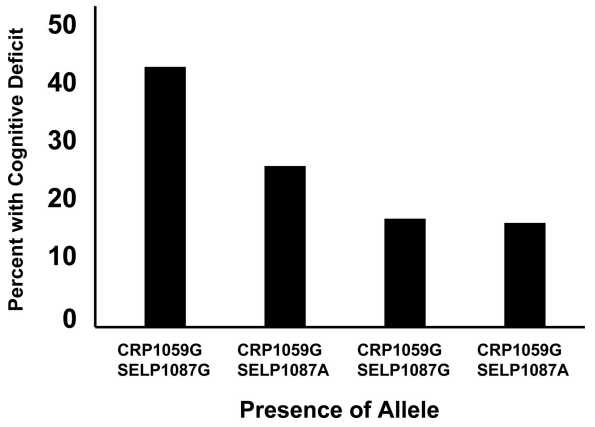

Fig. 3. Incidence of postoperative cognitive deficit by C-reactive protein (CRP) 1059G/C and P-selectin (SELP) 1087G/A genotypes. The incidence of cognitive deficit was 16.7% in carriers of minor alleles at both of these loci compared with 42.9% in patients homozygous for the major allele. n = 386.[42]

Table 1. Local Cerebral Glucose Utilization (μmol · 100 g · min^{-1} ± SD) during 1 and 2 MAC of Isoflurane and Sevoflurane Anesthesia in Subregions of Rat Mesencephalon, Diencephalon, and Telencephalon

Brain Region	Control	1 MAC Isoflurane	1 MAC Sevoflurane	2 MAC Isoflurane	2 MAC Sevoflurane
Substantia nigra (compact part)	58 ± 33	49 ± 2	58 ± 3.3	60 ± 7	60 ± 4.1
Interpeduncular nucleus	83 ± 4.1	62 ± 13.1	100 ± 7.8	74 ± 16.3	119 ± 4.5
Medial habenula	64 ± 2.5	59 ± 2.3	62 ± 3.3	97 ± 7.3	84 ± 4.1
Hippocampus CA3	50 ± 3.3	47 ± 4.3	56 ± 4.9	55 ± 4.3	68 ± 4.9
Hippocampus CA4	57 ± 2	50 ± 4.1	63 ± 5.7	73 ± 5.3	84 ± 6.5

MAC = minimum alveolar concentration.

From Lenz *et al.*[46]; adapted with permission.

tigation, Culley *et al.*[44] found that aged rats exposed to 70% nitrous oxide for 4 h took more time to complete a maze test and made fewer correct choices before making their first error compared with control rats over the following 2 weeks. In a separate group of rats, they found that the same nitrous oxide exposure profoundly, but transiently, reduced the activity of cortical methionine synthase—an enzyme whose depletion produces a myelopathy that is implicated in dementia and may be related to accumulation of homocysteine (a cytotoxic amino acid normally remethylated to methionine, an essential amino acid, by methionine synthase).

Evidence from Monk and coauthors' (2005) study indicated that cumulative deep hypnotic time is associated with more POCD,[31] but a recent study by Farag *et al.*[45] looked at lighter anesthesia (Bispectral Index 50) *versus* deeper anesthesia (Bispectral Index 39) and found that deeper levels of anesthesia were associated with better cognitive function 4–6 weeks postoperatively. How could that be? As Lenz *et al.*[46] and others have shown, equilibrated anesthetic does not mean equal anesthesia. Using glucose utilization as a measure of metabolic rate, we can see (table 1) that anesthetics affect different brain subregions to a greater or lesser extent—with most areas showing a reduction in metabolism, some areas showing no change in metabolism, and a few areas in which metabolism actually increases during anesthesia.

So if synaptic feedback is key to preventing the apoptotic cascade, neurons capable of generating action potentials (nonanesthetized) that do not receive sufficient input from connecting neurons (anesthetized) to generate summed signals that are large enough to trigger depolarization might be at greater risk than neurons that are in a state of stable quiescence (fig. 4), and the ratio of nonanesthetized to anesthetized neurons should be higher in less deeply anesthetized patients.

In this conjectured brain scenario, a nonanesthetized neuron whose dendrites are surrounded by anesthetized neurons is in solitary confinement. Eventually, it may kill itself. The nonfunctional fetal neuron and the nonanesthetized adult neuron may undergo apoptosis for the same reason—insufficient functioning connections—but in the case of the fetal neuron, that is because *it* has not made enough functional connections, whereas for the nonanesthetized neuron, too many of its anesthetized neighbors have become nonfunctional. Whether a neuron finds itself in solitary confinement because it fails to make enough connections (fetal neuron), or because it is stuck in a neighborhood from which most of its neighbors seem to have left (nonanesthetized neuron in an otherwise anesthetized brain region), the effect may be the same. Much is at stake here, and there is much to learn. As put by Farag *et al.*,[45] "Our observations highlight the

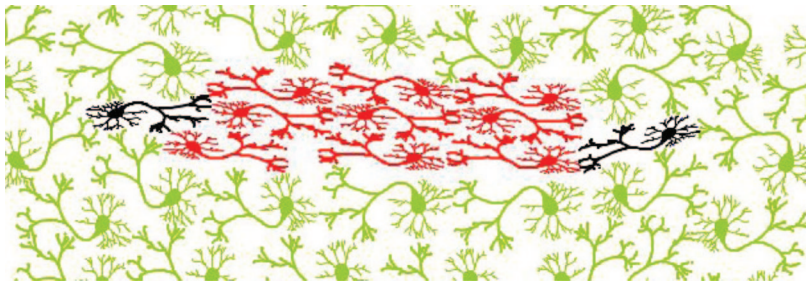

Fig. 4. Neurons in nonanesthetized cortical subregions (*red* and *black*) may be in a sort of reverse penumbra. That is, a penumbra where the cluster in the center is OK because each neuron is connected to potentially active neurons and they can maintain sufficient activity through a local-talk network to ward off apoptosis (the default program), but farther away from the core, approaching fully anesthetized subregions (*green*), there will be nonanesthetized neurons that do not receive enough talk to have anything to say in response. Neurons that do not receive sufficient input (*black*, with dendrites connecting to anesthetized neurons) would be in a state of nonanesthetized inactivity, which may be physiologically worse than being anesthetized during a period of inactivity because, unlike anesthetized neurons, they retain the capacity to transcribe and translate enzymes needed to undergo apoptosis (apoptosis is an active process, requiring substantial metabolic activity). Indeed, a state of prolonged nonanesthetized inactivity may be analogous to the state of a neuron in a developing fetus that fails to grow sufficient functional dendritic and axonal connections, and so undergoes apoptosis.[6]

need for further studies to better understand the contribution of perioperative management to POCD."

Perhaps this perspective is also relevant to the frequently observed lack of difference in POCD, or the weakness of the difference in POCD, between patients who receive general anesthesia and patients who receive regional anesthesia with sedation.[47] That is, perhaps perioperative sedation associated with regional anesthesia generates areas of nonanesthetized neurons surrounded by anesthetized neurons, setting up a proapoptotic condition that is analogous to the effect of general anesthesia. Ancelin *et al.*[48] found that "Adding sedation to peridural anesthesia led to a decline in verbal secondary memory," and Jankowski *et al.*[49] at the Mayo Clinic found that replacing postoperative sedation with continuous peripheral nerve catheters was associated with a 58% decline in the incidence of postoperative delirium. Again, there are empirical[39] and neuropathologic[40] reasons to suspect a link between delirium and POCD, and there is evidence that patients with the apolipoprotein ε_4 allele experience postoperative delirium at more than twice the rate of patients without apolipoprotein ε_4.[50]

What about the effects of anesthetics on the neurodegenerative diseases? Hydrophobic cavities keep sticky proteins from becoming irreversibly glued together. Unfortunately, molecules of inhalational anesthetics can fill those cavities and reduce the amount of energy required to maintain protein assembly (fig. 5).[51]

This anesthesia-facilitated disinhibition of protein binding helps monomers to aggregate into oligomers, and if those monomers are amyloid β, the resulting oligomerization can lead to protofibrils that are small enough to diffuse into neurons and large enough to be neurotoxic. Amyloid β oligomers seem to contribute to the neurodegeneration characterized by Alzheimer in the early 20th century. Thirteen million Americans are projected to have AD by the middle of the 21st century. Many of them will need to be anesthetized, and many of them will have been anesthetized before they became demented.

The role of inhalational anesthetics in the above scenario has been verified *in vitro* by a decade of work from Eckenhoff *et al.*, now supported *in vivo* by a transgenic mouse model.[52] In addition to the amyloid β–anesthesia connection, Xie *et al.*[40,53,54] have used human neuroglioma cell cultures to add anesthesia-induced apoptosis as a factor contributing to AD, and Jevtovic-Todorovic and Carter[55] have reported that old rat brains are equally (nitrous oxide) or more sensitive (ketamine) to anesthetic neurotoxicity than young rat brains.

Do the rodent and cell culture findings apply to humans? Results from retrospective studies are unsettling. Examining records of 9,170 veterans, Lee *et al.*[56] compared the risk of developing AD within 5–6 yr of cardiac surgery (CABG) during inhalational anesthesia *versus* the risk of developing AD within 5–6 yr of percutaneous transluminal coronary angioplasty, the latter seldom requiring general anesthesia. After adjustment for age, duration of hospital stay, comorbidity, and number of procedures, the CABG patients developed AD at nearly twice the rate of percutaneous transluminal coronary angioplasty patients (hazard ratio = 1.71; $P < 0.04$). Yes, CABG patients faced more predisposing factors than percutaneous transluminal coronary angioplasty patients, including embolic ischemia, but given *in vitro* evidence supporting mechanisms for a causal link between anesthesia and AD, it would be reckless to dismiss prolonged inhalational anesthesia as an independent contributing factor to the finding of Lee *et al.*

Bohnen *et al.*[57] performed a case-controlled retrospective study of 252 AD patients. Unfortunately, 199 of the 252 controls (non-AD patients) had previous exposure to general anesthesia, which greatly dilutes their statistical power to evidence an effect of anesthesia relative to AD patients. Nevertheless, Bohnen *et al.* found non–statistically significant effects in the direction of a link between AD and general anesthesia on each of three independent variables: cumulative exposure to anesthesia, exposure to six or more episodes of general anesthesia (odds ratio = 1.44), and cumulative exposure to 600 min or more of general anesthesia (odds ratio = 1.63). Gasparini *et al.*[58] also performed a retrospective case-controlled study of AD patients. In their study, the controls were Parkinson disease patients and patients with other neurologic diseases, but a link between general anesthesia and other neurologic diseases has been hypothesized,[51] such that lack of a differ-

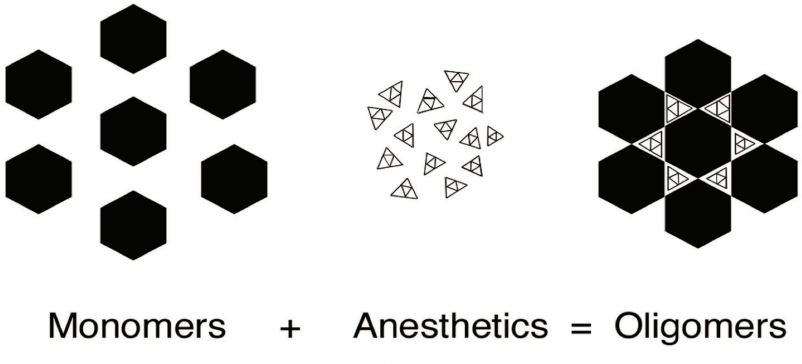

Fig. 5. Anesthesia-facilitated disinhibition of protein binding helps monomers aggregate into oligomers, and if those monomers are amyloid β, the resulting oligomerization can lead to protofibrils that are small enough to diffuse into neurons and large enough to be neurotoxic. Adapted with permission; from Carnini *et al.*[51]

ence in anesthetic exposure between AD patients and patients with Parkinson disease or other neurologic diseases does not imply a lack of a deleterious effect of anesthetic exposure.

Although a connection between anesthetics and AD has received more attention than a possible relation between anesthesia and Parkinson or Huntington disease, two investigations suggest that further research is warranted. Peretz *et al.*[59] have found evidence that supports an increased risk of Parkinson disease among anesthesiologists as compared with internists, and Wei *et al.*[60,61] have found *in vitro* laboratory evidence that isoflurane may exacerbate Huntington disease.

So there is evidence that anesthetics are a particular problem for older patients, but before we make recommendations more firm than Bedford's admonition from 1953 that "Operations on elderly people should be confined to unequivocally necessary cases,"[28] we need to know more about genetic profiles to know which older patients are most at risk. My purpose today is to stimulate our research community to ask more questions and do more research more quickly.

Potential Alleviating Factors

How might we reduce the risk of apoptosis in the very young and those with POCD, or worse, in older patients? Is there evidence that some anesthetics are more deleterious than others? Lee *et al.*[62] presented data at the 2007 American Society of Anesthesiologists Annual Meeting indicating that "In aged rats, propofol anesthesia is devoid of the persistent memory effects observed with other general anesthetic agents in this model. Thus, it appears that general anesthesia-induced memory impairment may be a function of the agent rather than the anesthetic state itself." In a rat cardiopulmonary bypass model, isoflurane with 60% xenon has been shown to prevent the decrement in neurocognitive function caused by bypass during isoflurane alone.[63] So the protective potential of xenon is being evaluated in humans, and preliminary results are encouraging.[64]

My department's laboratory has investigated the effects of lidocaine during global ischemia in rats. We found that neuron death in the hippocampus is substantially reduced in animals that have received clinically relevant doses of lidocaine. Function was also better retained after global ischemia in animals that received lidocaine.[65] Looking at CABG patients, Wang *et al.*[66] found that lidocaine (1.5-mg/kg bolus followed by a 4-mg/min infusion during operation and 4 mg/kg in the priming solution of cardiopulmonary bypass) reduced POCD measured 9 days after surgery. Looking at a larger number of CABG patients, Mitchell *et al.*[67] also found reduced POCD in patients who received lidocaine—from 75% to 40% at 10 days ($P < 0.025$), from 75% to 46% at 10 weeks ($P < 0.05$), and from 48% to 28% at 6 months (not statistically significant).

What about melatonin and statins in the elderly? A review by Cheng *et al.*[68] of the beneficial effects of melatonin in experimental models of AD is encouraging, but the jury has looked hard for evidence that statin therapy prevents or ameliorates AD, with little to show.[69,70] Nevertheless, because there are other important reasons for the elderly to take statins, we can expect to need to anesthetize many AD patients who are using statins. If the evidence from stroke patients applies, statin therapy should not be withdrawn without specific indication for withdrawal.[71]

Preconditioning

Although fetuses and the elderly are particularly sensitive to ischemia, hypoperfusion, and hypoxia, "Nietzsche's Toxicology: whatever doesn't kill you might make you stronger"[72] could lead to improved clinical management of patients with fragile brains. For example, prodromal temporary ischemic attacks protect people's brains during subsequent ischemia by inducing cerebral preconditioning.[73–75] That finding enhances the intriguing possibility that prophylactic cerebral protection could be initiated before surgery.

In 1964, Dahl and Balfour[76] published evidence of "prolonged anoxic survival due to anoxia preexposure." This phenomenon was eventually replicated in a model of cerebral ischemia,[77] and induction of endogenous proteins of repair and the genes that code for them are now well documented. Although improved understanding of preconditioning has removed much of the paradox from such findings,[78] it still seems ironic that "Mild, non-lesioning transient hypoxia in the newborn rat induces delayed brain neurogenesis associated with improved memory scores"![79]

Our laboratory recently added sevoflurane as a potential preconditioner (fig. 6),[80] and the *in vitro* finding of Wang *et al.*[81] that "preconditioning-induced neuroprotection by volatile anesthetics is not agent-specific" indicates that "mechanisms involved in inducing anesthesia [*per se*] may contribute to the induction of preconditioning." If a limited dose of anesthesia triggers the same protective mechanisms as a limited bout of hypoxia, how much anesthesia can we give before what would have been a protective effect becomes a deleterious effect?

Clinically acceptable means of accomplishing cerebral preconditioning are being sought. In addition to volatile anesthetics, laboratory results suggest promise for pretreatment with the antibiotic erythromycin[6]—but the most impressive human trial of a preconditioning/neurogenic agent published to date uses erythropoietin[82] (see Grasso[19] and Hasselblatt *et al.*[20] for review). Limiting their study to ischemic stroke patients whose treatment could begin within 8 h of the onset of symp-

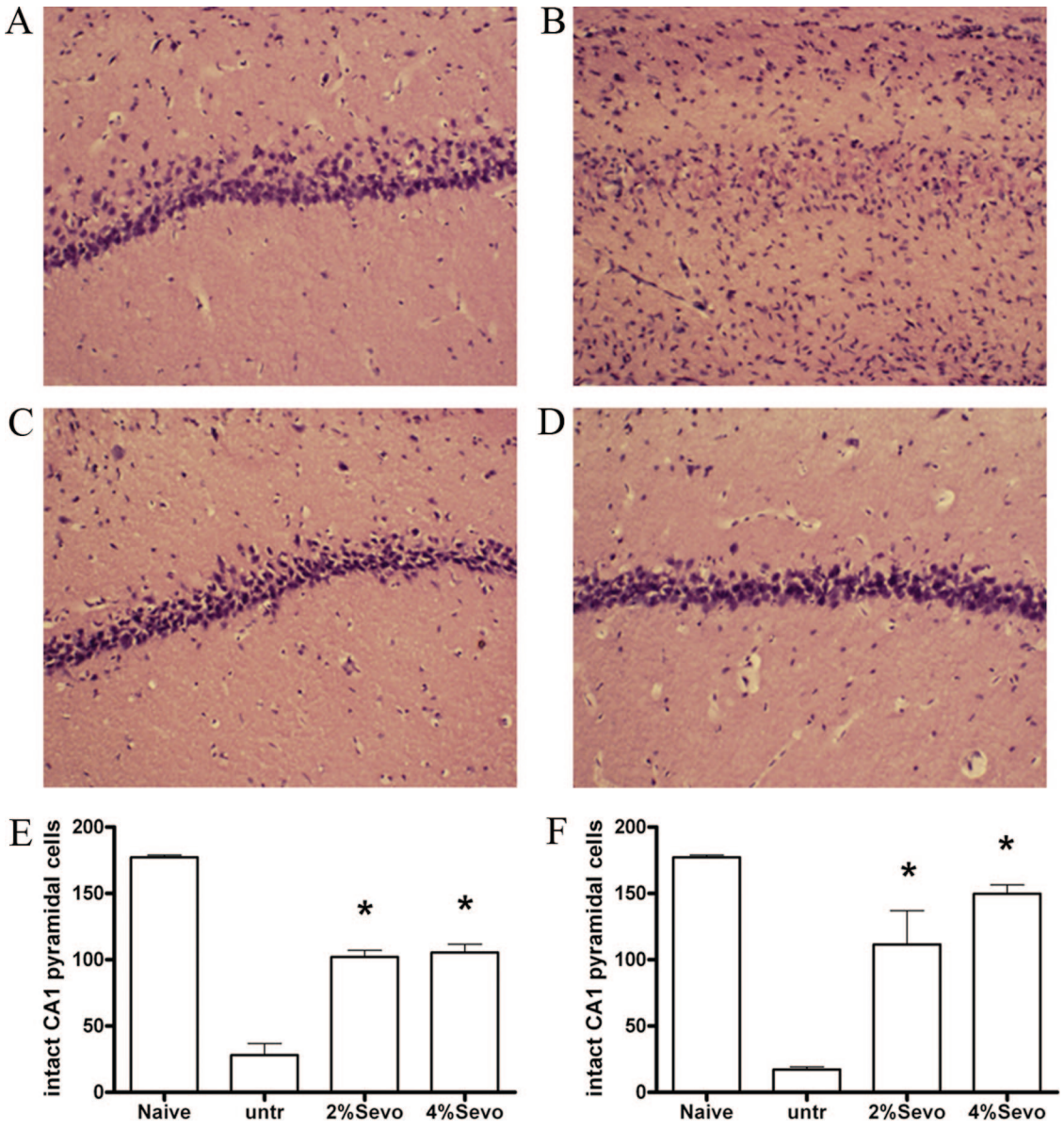

Fig. 6. CA1 pyramidal neurons after global cerebral ischemia. Representative hematoxylin and eosin–stained cryostat sections (16 μm) from the CA1 pyramidal cell layer of the experimental groups 6 weeks after the global cerebral ischemia are shown at approximately 250× magnification (*A–D*). (*A*) Tissue from naive rats not subjected to ischemia. (*B*) Tissue from rats subjected to 10 min of global ischemia without preconditioning. (*C*) Tissue from rats preconditioned with 2% sevoflurane (Sevo) for 1 h before ischemia. (*D*) Tissue from rats preconditioned with 4% sevoflurane for 1 h before ischemia. The data were quantitated by counting the number of intact CA1 neurons per 475 μm length of stratum pyramidale in each hemisphere at the same level of coronal section using light microscopy (250× magnification); the observer was blind to the experimental treatment (*E* and *F*). The numbers were averaged across both hemispheres to yield a single value for each rat and expressed as number/mm (mean ± SD). There were significantly more intact CA1 pyramidal cells with sevoflurane treatment compared with the untreated ischemic group (untr) ($P < 0.01$) at both 1 week (*E*) and 6 weeks (*F*) after ischemia.[80]

toms, Ehrenreich *et al.*[82] found that intravenous injection of recombinant erythropoietin once daily for 3 days led to 60- to 100-fold increases of erythropoietin in the central nervous system, reduced serum concentrations of the glial marker of cerebral injury S100β, reduced infarct size, and improved recovery. If these results hold up in the multicenter, randomized, controlled trial that is currently under way, there is reason to hope that erythropoietin would be even more effective as a prophylactic protectant—because we could harness erythropoietin's preconditioning effects by initiating administration 24–48 h before surgery, deliver it during surgery, and maintain administration in the intensive care unit.

Unfortunately, erythropoietin has the attribute of increasing hematocrit—a potentially deleterious effect in the context of ischemic injury and perhaps in fetuses more generally. Fortunately, nonhematopoietic analogs of erythropoietin, such as asialoerythropoietin, have been developed and are showing equivalent potency as neuroprotectants.[83,84]

Neurogenesis

The old adage that neurogenesis is only for the young was shown to be wrong in rodents in 1965[85] and also seems to be wrong for primates.[86] This raises the possibility that negative effects of surgery and anesthesia on the elderly, as well as the very young, can be compensated by therapies that strengthen the neurogenic response. Results in rats encourage the conclusion that "neural precursors resident in the brain initiate a compensatory response that results in the production of new neurons. Moreover, administration of growth factors can enhance this compensatory response . . . [and] we may eventually be able to manipulate these precursors to improve recovery of function"[87] (see also Sherstnev *et al.*[88]). In addition to ischemic preconditioning,[89] granulocyte colony-stimulating factor and erythropoietin seem to be such manipulators[90] and erythropoietin has shown protective promise against *N*-methyl-D-aspartate receptor antagonist neurotoxicity in rat[21] and mouse[22] neonates, in hypoxic-ischemic–injured neonatal rats,[23] and against amyloid-β neurotoxicity in an *in vitro* AD model.[91] Electrical deep brain stimulation has also been shown to elicit neurogenesis in rats[92] and has shown promise in a human after traumatic brain injury.[93]

Epilogue

I hope all of you have noticed that I have been talking about issues that have been in the literature since the 1950s and 1960s—effects of anesthetics on the very young, POCD in the elderly, preconditioning, and neurogenesis—and it's not just because that's when I started reading medical literature! The problems are old, but our awareness of them has enjoyed a renaissance over the past decade. Because of that newfound interest and the research it has inspired, my guess is that we will soon have anesthetic and adjuvant drugs ranked according to their deleterious effects on the very young and the very old, and that cerebral preconditioning and augmentation of endogenous processes of repair and regeneration will deliver brain protection to the young, the old, and everyone in between—before the younger among us are too far gone to benefit—and well before the 2050s and 2060s!

Lagniappe I

In 2002, colleagues at my institution (Downstate Medical Center, in Brooklyn), used an *in vitro* model to contribute to the realization that an evolutionarily conserved molecule, protein kinase Mζ (PKMζ; PKM in fig. 7[94]) may be both necessary and sufficient for the maintenance of long-term memory[95] (see also Pastalkova *et al.*[96]). That finding raises the prospect of pharmacologically manipulating PKMζ to selectively enhance or prevent memory formation, and even to extend or erase

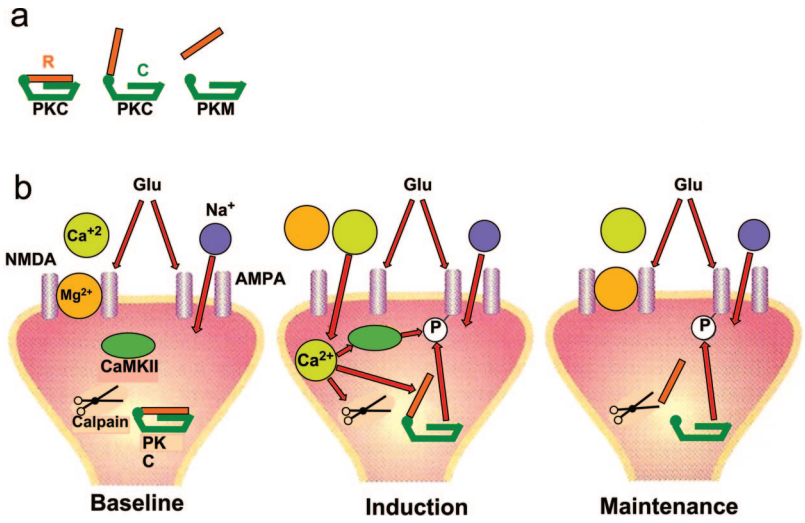

Fig. 7. Role of protein kinase M (PKM) in long-term potentiation (memory). (*A*) Schematic drawing of protein kinase C (PKC) in its resting configuration (*left*), activated state (*middle*), and persistently active form (PKM) (*right*). In its resting configuration, a pseudosubstrate sequence in the regulatory domain (R) inhibits the catalytic domain. The catalytic domain (C) is exposed *via* a conformational change upon activation by different second messengers. Proteolytic cleavage leaves the catalytic domain (PKM) constitutively active because it is not inhibited by the pseudosubstrate sequence. (*B*) Model for induction and maintenance of long-term potentiation. During baseline conditions, glutamate (Glu) released from the presynaptic bouton binds to both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and γ-aminobutyric acid and *N*-methyl-D-aspartic acid (NMDA) receptors on the postsynaptic spine. However, the excitatory postsynaptic potential is mediated exclusively *via* AMPA receptors, as γ-aminobutyric acid and NMDA receptors are blocked by Mg^{2+} ions. During induction of long-term potentiation, depolarization of the postsynaptic cell (by converging excitatory inputs or back-propagating action potentials) relieves the Mg^{2+} block of the γ-aminobutyric acid and NMDA receptor channel, allowing Ca^{2+} ions into the postsynaptic spine. The resultant Ca^{2+} increase triggers long-term potentiation by activating protein kinases such as CaMKII and PKC. These are necessary during the induction of long-term potentiation. In parallel, atypical PKC is turned into a persistently active form *via* Ca^{2+}-activated proteolytic cleavage (calpain). During maintenance, the AMPA receptors remain phosphorylated by persistent kinase activity (PKM), leading to increased conductance of AMPA receptor channels.[94]

formed memories for therapeutic purposes, such as preventing recall of intraoperative awareness and treating posttraumatic stress syndrome, phantom limb pain, and perhaps even AD. Step 1 has already been taken; this group has used a PKMς inhibitor, ZIP, to erase a long-term taste aversion memory in rats.[97] Perhaps a team of anesthesiologists will take step 2. Could NIH say no to such research?

Perhaps even closer to home, another team at my institution examined autopsy brain tissue from AD patients and found accumulations of PKMς in neurofibrillary tangles of brain areas implicated in memory loss. PKMς was not found in neurofibrillary tangles outside of the memory loss areas and was not found in any of the neurofibrillary tangles of normal age-matched controls.[98] PKMς seems to have its effect on long-term memory through persistent enhancement of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor–mediated synaptic transmission. Do we need to determine the effects of anesthetics on PKMς accumulation in neurofibrillary tangles?

Last but not least in this sampler of cutting-edge research, I hope that everybody in anesthesiology read Dr. Beverly Orser's[99] marvelous article in last June's *Scientific American*: "Lifting the Fog around Anesthesia." In addition to the best graphics ever presented in an article about anesthetics, Professor Orser advanced the hypothesis that "by finding the correct target receptors for the amnesia-inducing effects of anesthesia, it may become possible to identify patients at risk for intraoperative awareness because they lack those receptors. Alternatively, drug strategies to prevent awareness or at least its recollection could also be developed."

Lagniappe II

Okay, a little more something extra. I would like to close by telling you a story. One afternoon in 1980-something, I was waiting outside my office while medical students gathered inside for an introduction to our specialty. I overheard one of them ask, "What do anesthesiologists do?" The answer came back, "They put people to sleep."

I walked in, introduced myself, and asked them to imagine the following: You're lying face up on a cold steel table covered only by a sheet. People in disposable gowns appear at your side. One of them pulls your sheet off and cuts the skin over your sternum with a razor blade—right down to the bone. Then he saws through your chest, inserts a crank, and winds you open until he can grab your heart. After hooking you up to a pump, he cuts a valve out of your heart and sews in a valve from a pig. Then he puts you back together with needles and strings and staples.

How many of you could sleep through that?

They got the message that I have been hawking for a very long time: "Anesthesiologists are doctors who keep patients alive while surgeons do things that would otherwise kill them."[100]

We can show the public how much we care about what we do by advancing our specialty through research that addresses our patients' fears. When we show them how much we care, they too will know who we are.

References

1. Reves JG: We are what we make: Transforming research in anesthesiology. The 45th Rovenstine Lecture. Anesthesiology 2007; 106:826–35
2. Lagasse RS: Anesthesia safety: Model or myth? A review of the published literature and analysis of current original data. Anesthesiology 2002; 97:1609–17
3. Rabinowicz T, de Courten-Myers GM, Petetot JM, Xi G, de los Reyes E: Human cortex development: Estimates of neuronal numbers indicate major loss late during gestation. J Neuropathol Exp Neurol 1996; 55:320–8
4. Pakkenberg B, Gundersen HJG: Neocortical neuron number in humans: Effect of sex and age. J Comp Neurol 1997; 384:312–20
5. Davies AM: Regulation of neuronal survival and death by extracellular signals during development. EMBO J 2003; 22:2537–45
6. Cottrell JE: Fragile brain: The young and the old, 58th Annual Refresher Course Lectures and Basic Science Reviews. Park Ridge, Illinois, American Society of Anesthesiologists, 2007, pp 120–6
7. Eckenhoff JE: Relationship of anesthesia to postoperative personality changes in children. AMA Am J Dis Child 1953; 86:587–91
8. Chalon J, Tang CK, Ramanathan S, Eisner M, Katz R, Turndorf H: Exposure to halothane and enflurane affects learning function of murine progeny. Anesth Analg 1981; 60:794–7
9. Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF: Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. J Neurosci 2003; 23:876–82
10. Jevtovic-Todorovic V: General anesthetics and the developing brain: Friends or foes? J Neurosurg Anesthesiol 2005; 17:204–6
11. Stratmann G, Bell J, Alvi RS, Ku B, Saw L, Encarnacion A, Magnusson K, Bickler P, Liu JL: Cerebral protection pharmacology. J Neurosurg Anesthesiol 2006; 18:288
12. Lu LX, Yon JH, Carter LB, Jevtovic-Todorovic V: General anesthesia activates BDNF-dependent neuroapoptosis in the developing rat brain. Apoptosis 2006; 11:1603–15
13. Johnson SA, Young C, Olney JW: Isoflurane-induced neuroapoptosis in the developing brain of nonhypoglycemic mice. J Neurosurg Anesthesiol 2008; 20:21–8
14. Fredriksson A, Pontén E, Gordh T, Erikson P: Neonatal exposure to a combination of N-methyl-D-aspartate and gamma-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology 2007; 107:427–36
15. Olney JW, Young C, Wozniak DF, Ikonomidou C, Jevtovic-Todorovic V: Anesthesia-induced developmental neuroapoptosis: Does it happen in humans? Anesthesiology 2004; 101:273–5
16. Hartung J: Of mice and men and type II errors. Anesthesiology 2006; 104:206
17. Yon JH, Carter LB, Reiter RJ, Jevtovic-Todorovic V: Melatonin reduces the severity of anesthesia-induced apoptotic neurodegeneration in the developing rat brain. Neurobiol Dis 2006; 21:522–30
18. Welin AK, Svedin P, Lapatto RK, Sultan B, Hagberg H, Gressens P, Kjellmer I, Mallard C: Melatonin reduces inflammation and cell death in white matter in the mid-gestation fetal sheep following umbilical cord occlusion. Pediatr Res 2007; 61:153–8
19. Grasso G: Erythropoietin: A new paradigm for neuroprotection. J Neurosurg Anesthesiol 2006; 18:91–2
20. Hasselblatt M, Ehrenreich H, Sirén AL: The brain erythropoietin system and its potential for therapeutic exploitation in brain disease. J Neurosurg Anesthesiol 2006; 18:132–8
21. Dzietko M, Felderhoff-Mueser U, Sifringer M, Krutz B, Bittigau P, Thor F, Heumann R, Bührer C, Ikonomidou C, Hansen HH: Erythropoietin protects the developing brain against N-methyl-D-aspartate receptor antagonist neurotoxicity. Neurobiol Dis 2004; 15:177–87
22. Keller M, Yang J, Griesmaier E, Gorna A, Sarkozy G, Urbanek M, Gressens P, Simbruner G: Erythropoietin is neuroprotective against NMDA-receptor-mediated excitotoxic brain injury in newborn mice. Neurobiol Dis 2006; 24:357–66
23. McClure MM, Threlkeld SW, Fitch RH: Auditory processing and learning/memory following erythropoietin administration in neonatally hypoxic-ischemic injured rats. Brain Res 2007; 1132:203–9
24. Ma D, Williamson P, Januszewski A, Nogaro MC, Hossain M, Ong LP, Shu

Y, Franks NP, Maze M: Xenon mitigates isoflurane-induced neuronal apoptosis in the developing rodent brain. ANESTHESIOLOGY 2007; 106:746–53

25. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD, Finer NN, Carlo WA, Duara S, Oh W, Cotten CM, Stevenson DK, Stoll BJ, Lemons JA, Guillet R, Jobe AH: Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005; 353:1574–84

26. Shankaran S, Laptook AR: Hypothermia as a treatment for birth asphyxia. Clin Obstet Gynecol 2007; 50:624–35

27. Wilson RS, Bennett DA, Gilley DW, Beckett LA, Barnes LL, Evans DA: Premorbid reading activity and patterns of cognitive decline in Alzheimer disease. Arch Neurol 2000; 57:1718–23

28. Bedford PD: Adverse cerebral effects of anaesthesia on old people. Lancet 1955; 269:259–63

29. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jelles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD Investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998; 351:857–61

30. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS: Predictors of cognitive dysfunction after major noncardiac surgery. ANESTHESIOLOGY 2008; 108:18–30

31. Monk TG, Saini V, Weldon BC, Sigl JC: Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100:4–10

32. Stern Y: The concept of cognitive reserve: A catalyst for research. J Clin Exp Neuropsychol 2003; 25:589–93

33. Elkins JS, Longstreth WT Jr, Manolio TA, Newman AB, Bhadelia RA, Johnston SC: Education and the cognitive decline associated with MRI-defined brain infarct. Neurology 2006; 67:435–40

34. Jauhar S: Saving the heart can sometimes mean losing the memory. New York Times September 19, 2000: Science p. 1

35. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA, Neurological Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery [published correction appears in N Engl J Med 2001; 344:1876]. N Engl J Med 2001; 344:395–402

36. Grocott HP, Mackensen GB, Grigore AM, Mathew J, Reves JG, Phillips-Bute B, Smith PK, Newman MF: Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. Stroke 2002; 33: 537–41

37. van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EW, Grobbee DE, de Jaegere PP, Kalkman CJ: Cognitive and cardiac outcomes 5 years after off-pump *versus* on-pump coronary after bypass graft surgery. JAMA 2007; 297:701–8

38. Bucerius J, Gummert JF, Borger MA, Walther T, Doll N, Falk V, Schmitt DV, Mohr FW: Predictors of delirium after cardiac surgery delirium: Effect of beating-heart (off-pump) surgery. J Thorac Cardiovasc Surg 2004; 127:57–64

39. Chonchubhair AN, O'Keefe S: Postoperative cognitive dysfunction in the elderly. Lancet 1998; 351:1888–9

40. Xie Z, Dong Y, Maeda U, Moir R, Inouye SK, Culley DJ, Crosby G, Tanzi RE: Isoflurane-induced apoptosis: A potential pathogenic link between delirium and dementia. J Gerontol A Biol Sci Med Sci 2006; 61:1300–6

41. Lucas SM, Rothwell NJ, Gibson RM: The role of inflammation in CNS injury and disease. Br J Pharmacol 2006; 147 (suppl 1):S232–40

42. Mathew JP, Podgoreanu MV, Grocott HP, White WD, Morris RW, Stafford-Smith M, Mackensen GB, Rinder CS, Blumenthal JA, Schwinn DA, Newman MF: Genetic variants in P-selectin and C-reactive protein influence susceptibility to cognitive decline after cardiac surgery. J Am Coll Cardiol 2007; 49:1934–42

43. Culley DJ, Baxter MG, Crosby CA, Yukhananov R, Crosby G: Impaired acquisition of spatial memory 2 weeks after isoflurane and isoflurane-nitrous oxide anesthesia in aged rats. Anesth Analg 2004; 99:1393–7

44. Culley DJ, Raghavan SV, Waly M, Baxter MG, Yukhananov R, Deth RC, Crosby G: Nitrous oxide decreases cortical methionine synthase transiently but produces lasting memory impairment in aged rats. Anesth Analg 2007; 105:83–8

45. Farag E, Chelune GJ, Schubert A, Mascha EJ: Is depth of anesthesia, as assessed by the Bispectral Index, related to postoperative cognitive dysfunction and recovery? Anesth Analg 2006; 103:633–40

46. Lenz C, Rebel A, van Ackern K, Kuschinsky W, Waschke KF: Local cerebral blood flow, local cerebral glucose utilization, and flow-metabolism coupling during sevoflurane *versus* isoflurane anesthesia in rats. ANESTHESIOLOGY 1998; 89:1480–8

47. Bryson GL, Wyand A: Evidence-based clinical update: General anesthesia and the risk of delirium and postoperative cognitive dysfunction. Can J Anaesth 2006; 53:669–77

48. Ancelin ML, de Roquefeuil G, Ledésert B, Bonnel F, Cheminal JC, Ritchie K: Exposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. Br J Psychiatry 2001; 178:360–6

49. Jankowski CJ, Cook DJ, Trennerry MR, Schroeder DR, Warner DO: Continuous peripheral nerve block analgesia and central neuraxial anesthesia are associated with reduced incidence of postoperative delirium in the elderly (abstract). ANESTHESIOLOGY 2005; 103:A1467

50. Leung JM, Sands LP, Wang Y, Poon A, Kwok PY, Kane JP, Pullinger CR: Apolipoprotein E e4 allele increases the risk of early postoperative delirium in older patients undergoing noncardiac surgery. ANESTHESIOLOGY 2007; 107:406–11

51. Carnini A, Eckenhoff MF, Eckenhoff RG: Interactions of volatile anesthetics with neurodegenerative-disease-associated proteins. Anesthesiol Clin 2006; 24:381–405

52. Bianchi SL, Tran T, Liu C, Lin S, Li Y, Keller JM, Eckenhoff RG, Eckenhoff MF: Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. Neurobiol Aging 2008; 29:1002–10

53. Xie Z, Tanzi RE: Alzheimer's disease and post-operative cognitive dysfunction. Exp Gerontol 2006; 41:346–59

54. Xie Z, Dong Y, Maeda U, Moir R, Inouye SK, Culley DJ, Crosby G, Tanzi RE: The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation. J Neurosci 2007; 27:1247–54

55. Jevtovic-Todorovic V, Carter LB: The anesthetics nitrous oxide and ketamine are more neurotoxic to old than to young rat brain. Neurobiol Aging 2005; 26:947–56

56. Lee TA, Wolozin B, Weiss KB, Bednar MM: Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. J Alzheimers Dis 2005; 7:319–24

57. Bohnen NI, Warner MA, Kokmen E, Beard CM, Kurland LT: Alzheimer's disease and cumulative exposure to anesthesia: A case-control study. J Am Geriatr Soc 1994; 42:198–201

58. Gasparini M, Vanacore N, Schiaffini C, Brusa L, Panella M, Talarico G, Bruno G, Meco G, Lenzi GL: A case-control study on Alzheimer's disease and exposure to anesthesia. Neurol Sci 2002; 23:11–4

59. Peretz C, Alexander BH, Nagahama SI, Domino KB, Checkoway H: Parkinson's disease mortality among male anesthesiologists and internists. Mov Disord 2005; 1614–7

60. Wei H, Wang Q, Liang G, Yang H, Wang S: Isoflurane induced neurotoxicity in a cell model of Hunting disease (abstract). ANESTHESIOLOGY 2007; 107:A477

61. Wei H, Liang G, Yang H, Wang Q, Hawkins B, Madesh M, Wang S, Eckenhoff RG: The common inhalational anesthetic isoflurane induces apoptosis *via* activation of inositol 1,4,5-trisphosphate receptors. ANESTHESIOLOGY 2008; 108:251–60

62. Lee H, Culley DJ, Xie Z, Tanzi RE, Crosby G: Propofol anesthesia does not impair spatial memory in aged rats (abstract). ANESTHESIOLOGY 2007; 107:A1842

63. Ma D, Yang H, Lynch J, Franks NP, Maze M, Grocott HP: Xenon attenuates cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction in the rat. ANESTHESIOLOGY 2003; 98:690–8

64. Lockwood GG, Franks NP, Downie NA, Taylor KM, Maze M: Feasibility and safety of delivering xenon to patients undergoing coronary artery bypass graft surgery while on cardiopulmonary bypass: Phase I study. ANESTHESIOLOGY 2006; 104:458–65

65. Popp S, Lei B, Kelemen E, Fenton A, Cottrell JE, Kass IS: Effects of low-dose lidocaine administration on transient global cerebral ischemia in rats (abstract). ANESTHESIOLOGY 2007; 107:A1130

66. Wang D, Wu X, Li J, Xiao F, Liu X, Meng M: The effect of lidocaine on early postoperative cognitive dysfunction after coronary artery bypass surgery. Anesth Analg 2002; 95:1134–41

67. Mitchell SJ, Pellett O, Gorman DF: Cerebral protection by lidocaine during cardiac operations. Ann Thorac Surg 1999; 67:1117–24

68. Cheng Y, Feng Z, Zhang QZ, Zhang JT: Beneficial effects of melatonin in experimental models of Alzheimer disease. Acta Pharmacol Sin 2006; 27:129–39

69. Zhou B, Teramukai S, Fukushima M: Prevention and treatment of dementia or Alzheimer's disease by statins: A meta-analysis. Dement Geriatr Cogn Disord 2007; 23:194–201

70. Scott HD, Laake K: Statins for the prevention of Alzheimer's disease. Cochrane Database Syst Rev 2001; (4):CD003160

71. Blanco M, Nombela F, Castellanos M, Rodriguez-Yáñez M, García-Gil M, Leira R, Lizasoain I, Serena J, Vivancos J, Moro MA, Dávalos A, Castillo J: Statin treatment withdrawal in ischemic stroke: A controlled randomized study. Neurology 2007; 69:904–10

72. Renner R: Hormesis: Nietzsche's toxicology. Sci Am 2003; 289:28–30

73. Shaigany A, Gillespie L, Mock JP, Vassarhelyi L, Danovitch SH: Aortoenteric fistula: A complication of renal artery bypass graft. Arch Intern Med 1976; 136:930–2

74. Wegener S, Gottschalk B, Jovanovic V, Knab R, Fiebach JB, Schellinger PD, Kucinski T, Jungehülsing GJ, Brunecker P, Müller B, Banasik A, Amberger N, Wernecke KD, Siebler M, Röther J, Villringer A, Weih M: Transient ischemic attacks before ischemic stroke: Preconditioning the human brain? A multicenter magnetic resonance imaging study. Stroke 2004; 35:616–21

75. Schaller B: Ischemic preconditioning as induction of ischemic tolerance after transient ischemic attacks in human brain: Its clinical relevance. Neurosci Lett 2005; 377:206–11

76. Dahl NA, Balfour WM: Prolonged anoxic survival due to anoxia pre-exposure: Brain ATP, lactate, and pyruvate. Am J Physiol 1964; 207:452–6

77. Chopp M, Chen H, Ho KL, Dereski MO, Brown E, Hetzel FW, Welch KM: Transient hyperthermia protects against subsequent forebrain ischemic cell damage in the rat. Neurology 1989; 39:1396–8

78. Gidday JM: Cerebral preconditioning and ischaemic tolerance. Nat Rev Neurosci 2006; 7:437–48

79. Pourié G, Blaise S, Trabalon M, Nédélec E, Guéant JL, Daval JL: Mild, non-lesioning transient hypoxia in the newborn rat induces delayed brain neu-

rogenesis associated with improved memory scores. Neuroscience 2006; 140: 1369–79

80. Wang J, Lei B, Popp S, Meng F, Cottrell JE, Kass IS: Sevoflurane immediate preconditioning alters hypoxic membrane potential changes in rat hippocampal slices and improves recovery of CA1 pyramidal cells after hypoxia and global cerebral ischemia. Neuroscience 2007; 145:1097–107

81. Wang C, Jin Lee J, Jung HH, Zuo Z: Pretreatment with volatile anesthetics, but not with the nonimmobilizer 1,2-dichlorohexafluorocyclobutane, reduced cell injury in rat cerebellar slices after an *in vitro* simulated ischemia. Brain Res 2007; 1152:201–8

82. Ehrenreich H, Hasselblatt M, Dembowski C, Cepek L, Lewczuk P, Stiefel M, Rustenbeck HH, Breiter N, Jacob S, Knerlich F, Bohn M, Poser W, Rüther E, Kochen M, Gefeller O, Gleiter C, Wessel TC, De Ryck M, Itri L, Prange H, Cerami A, Brines M, Sirén AL: Erythropoietin therapy for acute stroke is both safe and beneficial. Mol Med 2002; 8:495–505

83. Grasso G, Sfacteria A, Cerami A, Brines M: Erythropoietin as a tissue-protective cytokine in brain injury: What do we know and where do we go? Neuroscientist 2004; 10:93–8

84. Wang X, Zhu C, Wang X, Gerwien JG, Schrattenholz A, Sandberg M, Leist M, Blomgren K: The nonerythropoietic asialoerythropoietin protects against neonatal hypoxia-ischemia as potently as erythropoietin. J Neurochem 2004; 91:900–10

85. Altman J, Das GD: Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol 1965; 124:319–35

86. Yamashima T, Tonchev AB, Yukie M: Adult hippocampal neurogenesis in rodents and primates: Endogenous, enhanced, and engrafted. Rev Neurosci 2007; 18:67–82

87. Kempermann G, Jessberger S, Steiner B, Kronenberg G: Milestones of neuronal development in the adult hippocampus. Trends Neurosci 2004; 27: 447–52

88. Sherstnev VV, Yurasov VV, Storozheva ZI, Gruden MA, Yakovleva NE: Biochemical markers of apoptosis in different parts of the brain during learning. Neurosci Behav Physiol 2006; 36:915–9

89. Lee SH, Kim YJ, Lee KM, Ryu S, Yoon BW: Ischemic preconditioning enhances neurogenesis in the subventricular zone. Neuroscience 2007; 146: 1020–31

90. Tönges L, Schlachetzki JC, Weishaupt JH, Bähr M: Hematopoietic cytokines: On the verge of conquering neurology. Curr Mol Med 2007; 7:157–70

91. Chong ZZ, Li F, Maiese K: Erythropoietin requires NF-κB and its nuclear translocation to prevent early and late apoptotic neuronal injury during beta-amyloid toxicity. Curr Neurovasc Res 2005; 2:387–99

92. Toda H, Hamani C, Fawcett AP, Hutchison WD, Lozano AM: The regulation of adult rodent hippocampal neurogenesis by deep brain stimulation. J Neurosurg 2008; 108:132–8

93. Schiff ND, Giacino JT, Kalmar K, Victor JD, Baker K, Gerber M, Fritz B, Eisenberg B, O'Connor J, Kobylarz EJ, Farris S, Machado A, McCagg C, Plum F, Fins JJ, Rezai AR: Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature 2007; 448:600–3

94. Paulsen O, Morris RG: Flies put the buzz back into long-term-potentiation. Nat Neurosci 2002; 5:289–90

95. Ling DS, Benardo LS, Serrano PA, Blace N, Kelly MT, Crary JF, Sacktor TC: Protein kinase Mζ is necessary and sufficient for LTP maintenance. Nat Neurosci 2002; 5:295–6

96. Pastalkova E, Serrano P, Pinkhasova D, Wallace E, Fenton AA, Sacktor TC: Storage of spatial information by the maintenance mechanism of LTP. Science 2006; 313:1141–4

97. Shema R, Sacktor TC, Dudai Y: Rapid erasure of long-term memory associations in the cortex by an inhibitor of PKMζ. Science 2007; 317:951–3

98. Crary JF, Shao CY, Mirra SS, Hernandez AI, Sacktor TC: Atypical protein kinase C in neurodegenerative disease I: PKMζ aggregates with limbic neurofibrillary tangles and AMPA receptors in Alzheimer disease. J Neuropathol Exp Neurol 2006; 65:319–26

99. Orser BA: Lifting the fog around anesthesia. Sci Am 2007; 296:54–61

100. Cottrell JE: View from the head of the table: Against putting people to sleep. Surg Rounds 1989; 12:81–8