



March 7, 2007

Anesthetic and Life Support Drugs Advisory Committee
Food and Drug Administration; Department of Health and Human Services

RE: Request for Formal Oral Presentation
Public Advisory Committee Meeting – March 29, 2007

Dear Sirs:

Pursuant to the notice (Federal Register Vol 7, No. 25, Pg 5723-4; February 7, 2007), I would like to request 20 min of presentation time to share data, information and views relevant to the meeting topic of neurodegenerative findings in juvenile animals exposed to anesthetic drugs and guidance for future clinical studies.

I am a board-certified anesthesiologist with an active practice at Brigham and Women's Hospital in Boston, MA. I am familiar with the issues and challenges administering anesthesia and analgesia to neonates and young children. I am also Vice President of Medical Affairs at Aspect Medical Systems. Aspect manufactures a patient monitoring system which measures the effects of anesthetic agents in the brain. This system is currently used in the care of approximately 5 million adult and pediatric patients per year. We are collaborating and funding research on anesthesia outcomes in both children and adults.

"Anesthesia" has recently been recognized as one of the top 5 medical advances in history[1], and current anesthetic agents are widely presumed to be safe. Unfortunately, emerging data suggest cause for concern regarding the consequences of both too much as well as too little anesthetic effect.

The pediatric patient may be particularly susceptible to potential toxic effects of anesthetic agents in the brain. As carefully outlined by Mellon *et al*, animal studies demonstrate that certain anesthetics can induce neurodegenerative changes in the developing brain, as well as the potential for prolonged behavioral changes.[2]

In juvenile patients receiving sevoflurane volatile anesthesia there are behavioral and neurophysiologic changes that may represent neurotoxicity. During inhalation induction of anesthesia with sevoflurane and nitrous oxide, up to 88% of young patients develop epileptiform changes in the EEG.[3] Similarly, emergence agitation and delirium are also observed frequently in this patient population following volatile anesthesia.[4] Because of seizure activity appears to be linked to activation of pathways leading to apoptosis, or programmed cell death, the subsequent consequences of volatile-induced seizure activity require additional investigation in this patient population.[5]

In addition to the investigations in young animals, there is a growing body of preclinical work in other model systems that demonstrate anesthetic neurotoxicity. In one investigation, neurotoxicity of nitrous oxide and ketamine was greater in aged

rats compared to young rats. Three independent laboratories have demonstrated dose-related associations between volatile anesthetic exposure and apoptosis in adult models.[6-8] Of particular concern is the potential for apoptosis and acceleration of biochemical pathways implicated in adult dementia.[9]

As the Advisory Committee focuses on the need for future studies to determine the clinical relevance of these findings, the aged patient population should also be considered as vulnerable to harmful effects. The relative risks associated with high - or even moderate - doses of specific anesthetic regimens need to be evaluated. In adults, a variety of clinical outcomes which could be related to neurotoxicity need to be evaluated. Recent papers have described a spectrum of effects including postoperative delirium, cognitive dysfunction[10], inflammatory response, acceleration of co-existing disease, cancer recurrence[11], and late mortality[12] as potential consequences of anesthetic exposure. Given the millions of elderly patients who undergo surgery and anesthesia each year, the public health implications are quite significant.[13-14]

Recently the FDA warned healthcare professionals regarding potential risks in children and adults associated with topical anesthetics.[15] Similar guidance to anesthesia professionals to prescribe “anesthetics in the lowest concentration consistent [with clinical goals]” may be appropriate. Recommendations to ‘limit exposure’ to anesthetics should not go too far, since the consequences of giving too little anesthesia are also significant. For example, in infants and children, inadequate sedation and analgesia may have harmful effects. In adults, inadequate anesthetic effect may cause “anesthesia awareness” which can result in long term psychological injury.[16] In children, the incidence of awareness has been reported to be considerably higher, although the psychological consequences are unknown at present.[17]

Aspect Medical Systems believes that future clinical studies investigating anesthetic exposure should include neuromonitoring of anesthetic effect in the brain. Clinical research that elucidates the linkages between anesthetic effect/exposure and neurologic outcomes in all patients – particularly the very young and the aged – will be extremely valuable. As always, we are willing to collaborate with interested investigators and pharmaceutical researchers.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'SK', with a stylized flourish at the end.

Scott D. Kelley, M.D.

References

1. Snow SJ. Anaesthesia: symbol of humanitarianism. *BMJ* 2007;334 Suppl 1:s5.
2. Mellon RD, Simone AF, Rappaport BA. Use of anesthetic agents in neonates and young children. *Anesth Analg* 2007;104:509-20.

3. Vakkuri A, Yli-Hankala A, Sarkela M, et al. Sevoflurane mask induction of anaesthesia is associated with epileptiform EEG in children. *Acta Anaesthesiol Scand* 2001;45:805-11.
4. Meyer RR, Munster P, Werner C, Brambrink AM. Isoflurane is associated with a similar incidence of emergence agitation/delirium as sevoflurane in young children--a randomized controlled study. *Paediatr Anaesth* 2007;17:56-60.
5. Meller R, Clayton C, Torrey DJ, et al. Activation of the caspase 8 pathway mediates seizure-induced cell death in cultured hippocampal neurons. *Epilepsy Res* 2006;70:3-14.
6. Jevtovic-Todorovic V, Beals J, Benshoff N, Olney JW. Prolonged exposure to inhalational anesthetic nitrous oxide kills neurons in adult rat brain. *Neuroscience* 2003;122:609-16.
7. Eckenhoff RG, Johansson JS, Wei H, et al. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology* 2004;101:703-9.
8. Xie Z, Dong Y, Maeda U, et al. The common inhalation anesthetic isoflurane induces apoptosis and increases amyloid beta protein levels. *Anesthesiology* 2006;104:988-94.
9. Xie Z, Dong Y, Maeda U, et al. The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation. *J Neurosci* 2007;27:1247-54.
10. Hudetz JA, Iqbal Z, Gandhi SD, et al. Postoperative Cognitive Dysfunction in Older Patients with a History of Alcohol Abuse. *Anesthesiology* 2007;106:423-430.
11. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology* 2006;105:660-4.
12. Monk T, Saini V, Weldon B, Sigl J. Anesthetic Management and One-Year Mortality after Noncardiac Surgery. *Anesthesia & Analgesia* 2005;100:4-10.
13. Meiler SE. Long-term outcome after anesthesia and surgery: remarks on the biology of a newly emerging principle in perioperative care. *Anesthesiol Clin* 2006;24:255-78.
14. Steffen E, Meiler, Terri G. Monk, James B. Mayfield, C. Alvin Head. (2003). "Can We Alter Long-Term Outcome?" *APSF Newsletter* Retrieved March 7, 2007, from http://www.apsf.org/resource_center/newsletter/2003/fall/01alter.htm.
15. Waknine Y. (2007). "Excessive Use of Topical Anesthetics Can Be Fatal." *Medscape Medical News* Retrieved March 7, 2007, from <http://www.medscape.com/viewarticle/551916>.
16. Lenmarken C, Bildfors K, Enlund G, Samuelsson P, Sandin R. Victims of awareness. *Acta Anaesthesiologica Scandinavica* 2002;46:229-31.
17. Davidson AJ, Huang GH, Czamecki C, et al. Awareness during anesthesia in children: a prospective cohort study. *Anesth Analg* 2005;100:653-61.

Anesthetic Agent Exposure

New Concerns of Adverse Impact

Scott D. Kelley, M.D.

< Conflict of Interest Statement >

Employee and Officer of Aspect Medical Systems, Inc.

Aspect manufactures BIS-brand brain monitoring system.

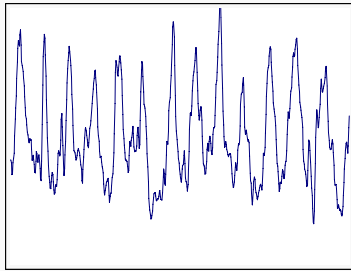
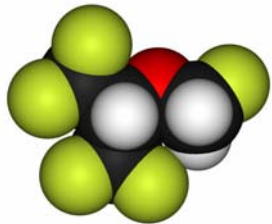
Titration of anesthesia using BIS monitoring has been demonstrated to reduce anesthetic exposure.

Anesthetic Agent Exposure

- ✓ Additional concerns in pediatric patients
- ✓ Preclinical and associative evidence of worrisome adverse consequences in adult patients
- ✓ Recommendations

Pediatric Anesthetic Exposure

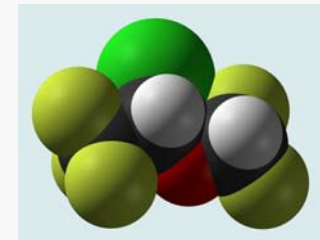
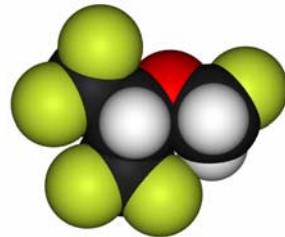
Epileptiform EEG and Emergence Syndromes



SEVOFLURANE

Epileptiform EEGs

20-88%



SEVOFLURANE	Emergence Syndrome	ISOFLURANE
30%	Agitation	34%
20%	Delirium	24%

Incidence (%) during first hour in PACU

Meyer, Pediatric Anesthesia 2007; 17:56-60

Hidden Harm?

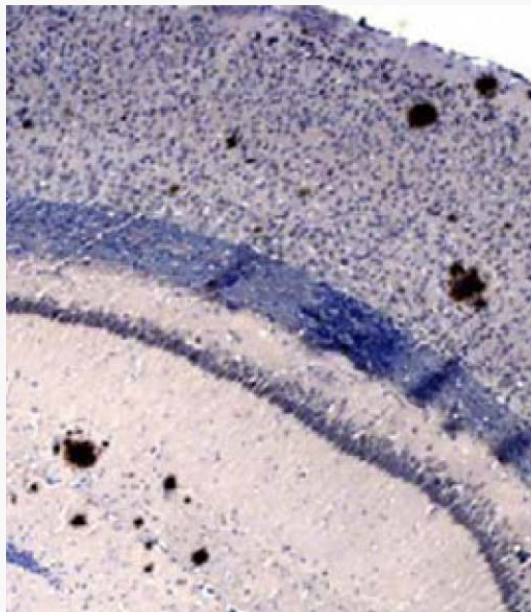
Anesthetic Exposure & Late Outcomes

- Specific Concerns & Worrisome Data
 - Alzheimer's Disease
 - Cancer
 - Morbidity & Mortality
- Important Consideration –
 - Anesthetic exposure may influence patient co-morbidities and long-term outcome

Anesthetics & Neurodegeneration

Preclinical: Not Limited to Neonatal Animals

12-month-old transgenic tg2576 and nontransgenic mice
Halothane vs Isoflurane (5 Exposures: 0.8 MAC x 120 min)



Isoflurane: Impairment of cognitive and memory measures

Halothane: Increase plaque density measures

Anesthetic Exposure & Alzheimer's Disease

No Clinical Association?

EXPOSURE	YES	NO	Odds Ratio [95% CI]
Any prior exposure of general anesthesia			
Case	208	44	1.28 [0.82-2.00]
Control	199	53	
Six or more prior events of general anesthesia			
Case	25	227	1.44 [0.77-2.71]
Control	18	234	
>Ten cumulative hours of general anesthesia			
Case	8	244	1.63 [0.53-5.04]
Control	5	247	

Adequate Size*
1,914
1,914
1,587
1,587
2,780
2,780

“It is unlikely that multiple exposures to general anesthesia increase the risk of Alzheimer's Disease”

Bohnen, J Am Geriatr Soc. 1994;42:198-201

(*80% power,
alpha = 0.05)

Anesthetic Exposure & Cancer

Preclinical Evidence & Clinical Association

- Murine Model (EL4 Lymphoma) # Liver Mets
 - Control 15.5 ± 8.7
 - Sevoflurane 19.4 ± 5.4
 - Sevoflurane + Surgery 33.7 ± 8.9
 - Sevoflurane + Surgery + Spinal 19.8 ± 9

Wada, Anesthesiology. 2007;106:499-506

- Retrospective Clinical Analysis
 - 129 consecutive breast cancer patients
 - Mastectomy + Axillary Node Dissection
 - Non-randomized:
 - 79 pts: GA only
 - 50 pts: Paravertebral + GA
 - Follow-up: 32 ± 5 months

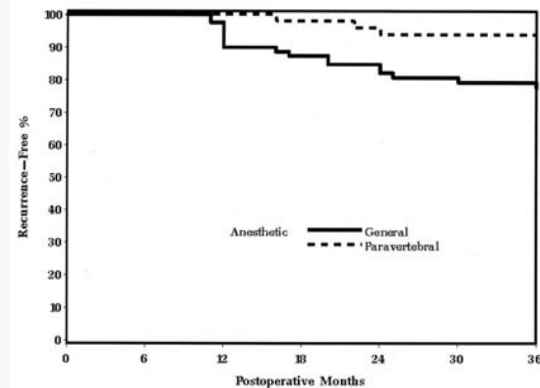


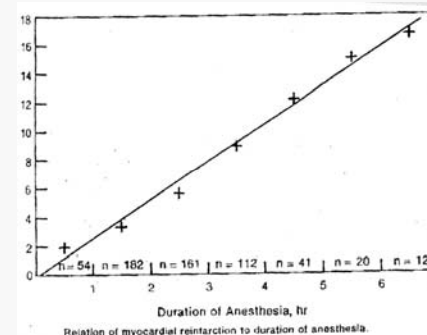
Fig. 1. Univariable association between paravertebral block and cancer recurrence, $P = 0.013$ log-rank test. The association

Exadaktylos, Anesthesiology. 2006; 105: 660-4

Anesthetic Exposure & Outcome

Association with Morbidity & Mortality

“Time under anesthesia was strikingly correlated with reinfarction rates in the entire group” Steen. JAMA 1978; 239:2566-70



14,788 pts Lower extremity bypass (GA - 9757; Spinal - 2848; Epidural - 2183)

- General Anesthesia vs Spinal Anesthesia:

- Cardiac events (OR, 1.8; 95% CI, 1.32-2.48; P < .0001).
- Postoperative pneumonia (OR: 2.2; 95%CI, 1.1-4.4; P = .034)
- Graft failure (OR, 1.43; 95%CI, 1.16-1.77; P < .001).
- Return to surgery (OR, 1.40; 95%CI, 1.20-1.64; P< .001) Singh N,J Vasc Surg. 2006 44:964-8

Independent Multivariate Predictors	Relative Risk [95% CI]	P Value
Comorbidity (Charlson Score 3+ vs 0-2)	16.116 [10.110 – 33.717]	<0.0001
Deep Hypnotic Time (Cumulative time BIS < 45 per hour)	1.244 [1.062-1.441]	0.0121

Anesthetic Exposure & Outcome

Increasing Attention

Anesthetic Management and One-Year Mortality After Noncardiac Surgery

Terri G. Monk, MD, MS*, Vikas Saini, MD, FACCT, B. Craig Weldon, MD*, and Jeffrey C. Sigl, PhD†
Monk, *Anesth Analg* 2005; 100:4-10

EDITORIAL

Anesthetic Depth Is Not (Yet) a Predictor of Mortality!

Neal H. Cohen, MD, MPH, MS



Anesthetic Agent Exposure

- Preclinical and associative evidence of adverse effects
- **Broad populations at risk**
 - Developing neonates and pediatric patients
 - Elderly patients with co-morbidity
- **RECOMMENDATIONS:**
 - ✓ Request preclinical and clinical safety studies to determine impact of anesthetic exposure on late outcomes
 - ✓ *“Although the applicability of this to humans and our practice is not clear, it has raised concerns for the pediatric anesthesiologist and brings an added dimension to the Goldilocks conundrum: how much of our drugs and techniques is “too much,” how much is “too little,” and how much is “just right”?”* Davis Anesth Analg 2005;100:650-652
 - ✓ Engage APSF to alert anesthesia professionals to new concerns and to explore clinical options for patient care



Background Material Supporting FDA Advisory Committee Presentation

FDA Anesthetic and Life Support Drugs Advisory Committee Public Hearing
March 29, 2007

Scott D. Kelley, MD
Vice President Medical Affairs
Aspect Medical Systems, Inc.

Bibliography of Literature Cited in Letter and Presentation: (Abstracts accessed from PubMed)

1. Bianchi SL, et al. (2007). "Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics." *Neurobiol Aging* (doi:10.1016/j.neurobiolaging.2007.02.009). Inhaled anesthetics have been shown to increase the aggregation of amyloid beta in vitro through the stabilization of intermediate toxic oligomers, which are thought to contribute to neurocognitive dysfunction in Alzheimer's disease. Inhaled anesthetics may escalate cognitive dysfunction through enhancement of these intermediate oligomer concentrations. We intermittently exposed 12-month-old Tg2576 transgenic mice and nontransgenic littermates to isoflurane and halothane for 5 days. Cognitive function was measured before and after anesthetic exposures using the Morris Water Maze; amyloid beta plaque burden and caspase-3 mediated apoptosis were quantified by immunohistochemistry. At 12 months of age, anesthetic exposure did not further enhance cognitive decline in the transgenic mice. Immunohistochemistry, however, revealed that the halothane-exposed Tg2576 mice had more amyloidopathy than the isoflurane treated mice or the nonexposed transgenic mice. Isoflurane exposure impaired cognitive function in the nontransgenic mice, implying an alternative pathway for neurodegeneration. These findings indicate that inhaled anesthetics influence cognition and amyloidogenesis, but that the mechanistic relationship remains unclear.
2. Bohnen NI, et al. (1994). "Alzheimer's disease and cumulative exposure to anesthesia: a case-control study." *J Am Geriatr Soc.* 42(2): 198-201.
OBJECTIVE: To evaluate prior exposure to general anesthesia as a potential risk factor for Alzheimer's disease (AD). DESIGN: A retrospective, population-based, case-control study. SETTING: The Rochester Epidemiology Resource. PATIENTS: Cases were all incident cases of AD from 1975 to 1984 who resided for 40 years or more in Olmsted County prior to the onset of their dementia (n = 252). One age- and gender-matched control for each case was selected from all registrations for care at Mayo Clinic during the year of onset in the incident case. The case and control groups each had 252 individuals. Of these, 208 cases and 199 controls had at least one exposure to general anesthesia prior to the year of onset of dementia in the matched AD patient. MEASUREMENTS: The cumulative duration of anesthesia and the total number of general anesthetic exposures prior to the age of onset of dementia and the corresponding year in each matched control were ascertained. RESULTS: There was no significant difference in mean cumulative exposure (in minutes) to general anesthesia (patients vs controls: 188.4 vs 170.5 minutes, ns). Neither exposure to six or more episodes of general anesthesia (OR = 1.44; 95% CI: 0.77-2.71) nor cumulative exposure to 600 minutes or more of general anesthesia (OR = 1.63; 95% CI: 0.53-5.04) were associated with a significantly increased risk of AD. CONCLUSION: It is unlikely that multiple exposures to general anesthesia increase the risk of AD.

3. Cohen NH (2005). "Anesthetic depth is not (yet) a predictor of mortality!" *Anesth Analg.* 100(1): 1-3. Abstract Not Available
4. Davidson AJ, et al. (2005). "Awareness during anesthesia in children: a prospective cohort study." *Anesth Analg.* 100(3): 653-61, table of contents.
During routine adult anesthesia, the risk of awareness is 0.1%-0.2%. No recent studies have reported the incidence in children. Altered pharmacology and differing anesthesia techniques suggest that the incidence may differ in children. In this prospective cohort study, we determined the incidence of awareness during anesthesia in children. Eight-hundred-sixty-four children aged 5-12 yr who had undergone general anesthesia at The Royal Children's Hospital were interviewed on 3 occasions to determine the incidence of awareness. The awareness assessment was nested within a larger study of behavior change after anesthesia. Reports of suspected awareness were sent to four independent adjudicators. If they all agreed, a case was classified as true awareness. Twenty-eight reports were generated. There were 7 cases of true awareness, for an incidence of 0.8% (95% confidence interval, 0.3%-1.7%). Only one aware child received neuromuscular blockers, compared with 12% in the nonaware group. No aware child reported distress, and no substantial difference was detected in behavior disturbance between aware (20%) and nonaware (16%) children. The data provide some evidence that, like adults, children are also at risk of intraoperative awareness. Although the cause remains unclear, anesthesiologists should be alerted to the possibility of awareness in children.
5. Davis PJ (2005). "Goldilocks: the pediatric anesthesiologist's dilemma." *Anesth Analg.* 100(3): 650-2. Abstract Not Available
6. Eckenhoff RG, et al. (2004). "Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity." *Anesthesiology.* 101(3): 703-9.
BACKGROUND: The majority of surgical patients receive inhaled anesthetics, principally small haloalkanes and haloethers. Long-term cognitive problems occur in the elderly subsequent to anesthesia and surgery, and previous surgery might also be a risk factor for neurodegenerative disorders like Alzheimer and Parkinson disease. The authors hypothesize that inhaled anesthetics contribute to these effects through a durable enhancement of peptide oligomerization. METHODS: Light scattering, filtration assays, electron microscopy, fluorescence spectroscopy and size-exclusion chromatography was used to characterize the concentration-dependent effects of halothane, isoflurane, propofol, and ethanol on amyloid beta peptide oligomerization. Pheochromocytoma cells were used to characterize cytotoxicity of amyloid oligomers with and without the above anesthetics. RESULTS: Halothane and isoflurane enhanced amyloid beta oligomerization rates and pheochromocytoma cytotoxicity in vitro through a preference for binding small oligomeric species. Ethanol and propofol inhibited oligomerization at low concentration but enhanced modestly at very high concentration. Neither ethanol nor propofol enhanced amyloid beta toxicity in pheochromocytoma cells. CONCLUSIONS: Inhaled anesthetics enhance oligomerization and cytotoxicity of Alzheimer disease-associated peptides. In addition to the possibility of a general mechanism for anesthetic neurotoxicity, these results call for further evaluation of the interaction between neurodegenerative disorders, dementia, and inhalational anesthesia.
7. Exadaktylos AK, et al. (2006). "Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis?" *Anesthesiology.* 105(4): 660-4.
BACKGROUND: Regional anesthesia is known to prevent or attenuate the surgical stress response; therefore, inhibiting surgical stress by paravertebral anesthesia might attenuate perioperative factors that enhance tumor growth and spread. The authors hypothesized that breast cancer patients undergoing surgery with paravertebral anesthesia and analgesia combined with general anesthesia have a lower incidence of cancer recurrence or metastases than patients undergoing surgery with general anesthesia and patient-controlled morphine analgesia. METHODS: In this retrospective study, the authors examined the medical records of 129 consecutive patients undergoing mastectomy and axillary clearance for breast cancer between September 2001 and December 2002. RESULTS: Fifty patients had surgery with paravertebral

anesthesia and analgesia combined with general anesthesia, and 79 patients had general anesthesia combined with postoperative morphine analgesia. The follow-up time was 32 +/- 5 months (mean +/- SD). There were no significant differences in patients or surgical details, tumor presentation, or prognostic factors. Recurrence- and metastasis-free survival was 94% (95% confidence interval, 87-100%) and 82% (74-91%) at 24 months and 94% (87-100%) and 77% (68-87%) at 36 months in the paravertebral and general anesthesia patients, respectively (P = 0.012). CONCLUSIONS: This retrospective analysis suggests that paravertebral anesthesia and analgesia for breast cancer surgery reduces the risk of recurrence or metastasis during the initial years of follow-up. Prospective trials evaluating the effects of regional analgesia and morphine sparing on cancer recurrence seem warranted.

8. Hudetz JA, et al. (2007). "Postoperative Cognitive Dysfunction in Older Patients with a History of Alcohol Abuse." *Anesthesiology*. 106(3): 423-430.
BACKGROUND:: Postoperative cognitive dysfunction (POCD) affects a significant number of patients and may have serious consequences for quality of life. Although POCD is most frequent after cardiac surgery, the prevalence of POCD after noncardiac surgery in older patients is also significant. The risk factors for POCD after noncardiac surgery include advanced age and preexisting cognitive impairment. Self-reported alcohol abuse is a risk factor for postoperative delirium, but its significance for long-term POCD has not been investigated. The goal of this study was to determine whether neurocognitive function is impaired after noncardiac surgery during general anesthesia in older patients with a history of alcohol abuse. METHODS:: Subjects aged 55 yr and older with self-reported alcohol abuse (n = 28) and age-, sex-, education-matched nonalcoholic controls (n = 28) were tested using a neurocognitive battery before and 2 weeks after elective surgery (n = 28) or a corresponding time interval without surgery (n = 28). Verbal memory, visuospatial memory, and executive functions were assessed. A neurologic examination was performed to exclude subjects with potential cerebrovascular damage. RESULTS:: Significant three-way interactions (analysis of variance) for Visual Immediate Recall, Visual Delayed Recall, Semantic Fluency, Phonemic Fluency, and the Color-Word Stroop Test implied that cognitive performance in the alcoholic group decreased after surgery more than it did in the other three groups. CONCLUSIONS:: The results suggest that a history of alcohol abuse in older patients presents a risk for postoperative cognitive impairment in the domains of visuospatial abilities and executive functions that may have important implications for quality of life and health risks.
9. Jevtovic-Todorovic V, et al. (2003). "Prolonged exposure to inhalational anesthetic nitrous oxide kills neurons in adult rat brain." *Neuroscience*. 122(3): 609-16.
Short-term exposure of adult rats to nitrous oxide (N₂O), an inhalational anesthetic and NMDA (N-methyl-D-aspartate) antagonist, causes a reversible neurotoxic vacuole reaction in neurons of the posterior cingulate/retrosplenial cortex (PC/RSC) which resembles that caused by low doses of other NMDA antagonists. Since high doses or prolonged exposure to other NMDA antagonists can cause neurons to die, we assessed whether prolonged N₂O exposure might also cause neuronal cell death. Adult female Sprague-Dawley rats were exposed to 150-vol% N₂O (approximately EC₅₀ for N₂O anesthesia in rats) for various durations from 1 to 16 h. The time course for onset and disappearance of the reversible vacuole reaction was studied, as was the time course and dose requirement for triggering cell death. A maximum vacuole reaction was observed in PC/RSC neurons in brains examined immediately after 3 h of 150-vol% N₂O exposure and the same magnitude of vacuole reaction was observed when brains were examined immediately after a longer period of N₂O exposure. When N₂O was terminated at 3 h and the rats were killed 1 h later, the vacuole reaction was markedly diminished and if the rats were killed 3 h later the vacuole reaction had completely disappeared. Prolonged exposure to 150-vol% N₂O (for 8 h or more) caused neuronal cell death which was detectable by silver staining 32 h later. Concurrently administered GABAergic agents, diazepam (an i.v. anesthetic), or isoflurane (an inhalational anesthetic), prevented this cell death reaction. Our findings demonstrate that short-term exposure of adult rats to N₂O causes injury to PC/RSC neurons that is rapidly reversible, and prolonged N₂O exposure causes neuronal cell death. These neurotoxic effects, including the cell death reaction, can be prevented by coadministration of GABA-mimetic

anesthetic agents. Duration of NMDA receptor blockade appears to be an important determinant of whether neurons are reversibly injured or are driven to cell death by an NMDA antagonist drug.

10. Lennmarken C, et al. (2002). "Victims of awareness." *Acta Anaesthesiol Scand.* 46(3): 229-31.
BACKGROUND: Intraoperative awareness with explicit recall may be followed by long-lasting mental symptoms. However, the average risk for developing mental sequelae after awareness, and the average severity and the duration of symptoms has not previously been illustrated in a consecutive series of awareness cases. METHODS: Nine patients among 18 consecutive, prospectively identified cases of intraoperative awareness with recall could be located after approximately 2 years and agreed to an interview about possible persisting problems. RESULTS: Four of the nine interviewed patients were still severely disabled due to psychiatric/psychological sequelae. All of these patients had experienced anxiety during the period of awareness, but only one had complained about pain. Another three patients had less severe, transient mental symptoms, although they could cope with these in daily life. Two patients denied any sequelae from their awareness episode. CONCLUSIONS: Up to 3 weeks after their unsuccessful anesthetic, repeated information and discussions had been offered. Despite the fact that all patients at that time claimed to be satisfied with this management, and eventually considered no further contacts necessary, this was obviously inaccurate. Therefore, professional psychiatric assessment, treatment and long-term follow-up should constitute standard practice for all patients who have experienced intraoperative awareness.
11. Meiler SE (2006). "Long-term outcome after anesthesia and surgery: remarks on the biology of a newly emerging principle in perioperative care." *Anesthesiol Clin.* 24(2): 255-78.
There is a strong possibility that the risk from anesthesia and surgery carries over from the immediate perioperative period to more remote time points. This extended risk seems to influence the progression, severity, and complication rate of certain chronic illnesses, such as vascular heart disease and some of the malignancies, although other disease processes might be affected as well. With the recognition that the perioperative process could be responsible for later adverse events comes the need to reassess existing patient safety models, because some of the risk could be preventable. To confront these challenges, it is necessary to understand the underlying biology of this association, and immunology should be particularly helpful in this pursuit. It will be of special importance to integrate our knowledge of the host immune response to anesthesia and surgery with the recent revelations on the role of immunity in the progression of many of the chronic diseases. Additionally, we need to examine how genetic diversity or acquired defects alter the immune response to tissue injury and infection so that we can improve risk stratification and preemptive therapies. In the meantime, we must strive to improve short- and long-term outcomes by expanding our efforts to reduce disease activity preoperatively, to control the surgical stress response and infection rate, and to use tissue-preserving surgical techniques. Long-term patient safety after anesthesia and surgery is not a specialty-by-specialty endeavor; it requires a highly collaborative, institutional, and national effort to foster innovative research and health care process improvements.
12. Meiler SE, et al. (2003). "Can We Alter Long-Term Outcome?" *APSF Newsletter* Retrieved March 7, 2007,, from http://www.apsf.org/resource_center/newsletter/2003/fall/01alter.htm.
Abstract Not Available
13. Meiler SE, et al. (2003). "Can We Alter Long-Term Outcome? The Role of Inflammation and Immunity in the Perioperative Period (Part II)." *APSF Newsletter* Retrieved March 7, 2007, from http://www.apsf.org/resource_center/newsletter/2004/spring/01outcome.htm.
Abstract Not Available
14. Meller R, et al. (2006). "Activation of the caspase 8 pathway mediates seizure-induced cell death in cultured hippocampal neurons." *Epilepsy Res.* 70(1): 3-14.
In response to harmful stresses, cells induce programmed cell death (PCD) or apoptosis. Seizures can induce neural damage and activate biochemical pathways associated with PCD. Since seizures trigger intracellular calcium overload, it has been presumed that the intrinsic cell

death pathway mediated by mitochondrial dysfunction would modulate cell death following seizures. However, previous work suggests that the extrinsic cell death pathway may initiate the damage program. Here we investigate intrinsic versus extrinsic cell death pathway activation using caspase cleavage as a marker for activation of these pathways in a rat in vitro model of seizures. Hippocampal cells, chronically treated with kynurenic acid, had kynurenic acid withdrawn to induce seizure-like activity for 40 min. Subjecting rat hippocampal cultures to seizures increased cell death and apoptosis-like DNA fragmentation using TUNEL staining. Seizure-induced cell death was blocked by both MK801 (10 microM) and CNQX (40 microM), which suggests multiple glutamate receptors regulate seizure-induced cell death. Cleavage of the initiator caspases, caspase 8 and 12 were increased 4h following seizure, and cleavage of the quintessential executioner caspase, caspase 3 was increased 4h following seizure. In contrast, caspase 9 cleavage only increased 24h following seizure. Using an affinity labeling approach to trap activated caspases in situ, we show that caspase 8 is the apical caspase activated following seizures. Finally, we show that the caspase 8 inhibitor Ac-IETD-CHO was more effective at blocking seizure-induced cell death than the caspase 9 inhibitor Ac-LEHD-CHO. Taken together, our data suggests the extrinsic cell death pathway-associated caspase 8 is activated following seizures in vitro.

15. Mellon RD, et al. (2007). "Use of anesthetic agents in neonates and young children." *Anesth Analg.* 104(3): 509-20.

BACKGROUND: Some drugs used for sedation and anesthesia produce histopathologic central nervous system changes in juvenile animal models. These observations have raised concerns regarding the use of these drugs in pediatric patients. We summarized the findings in developing animals and describe the steps that the Food and Drug Administration (FDA) and others are taking to assess potential risks in pediatric patients. The FDA views this communication as opening a dialog with the anesthesia community to address this issue. **METHODS:** We reviewed the available animal studies literature examining the potential neurotoxic effects of commonly used anesthetic drugs on the developing brain. The search strategy involved crossing the keywords neurotoxic and neuroapoptosis with the following general and specific terms: anesthetic, N-methyl-d-aspartate (NMDA), ketamine, midazolam, lorazepam, fentanyl, methadone, morphine, meperidine, isoflurane, nitrous oxide, sevoflurane, halothane, enflurane, desflurane, propofol, etomidate, barbiturate, methoxyflurane, and chloral hydrate. We summarized several studies sponsored by the FDA in rats and monkeys, initially examining the potential for ketamine, as a prototypical agent, to induce neurodegeneration in the developing brain. **RESULTS:** Numerous animal studies in rodents indicate that NMDA receptor antagonists, including ketamine, induce neurodegeneration in the developing brain. The effects of ketamine are dose dependent. The data suggest that limiting exposure limits the potential for neurodegeneration. There is also evidence that other general anesthetics, such as isoflurane, can induce neurodegeneration in rodent models, which may be exacerbated by concurrent administration of midazolam or nitrous oxide. There are very few studies that have examined the potential functional consequences of the neurodegeneration noted in the animal models. However, the studies that have been reported suggest subtle, but prolonged, behavioral changes in rodents. Although the doses and durations of ketamine exposure that resulted in neurodegeneration were slightly larger than those used in the clinical setting, those associated with isoflurane were not. There are insufficient human data to either support or refute the clinical applicability of these findings. **CONCLUSIONS:** Animal studies suggest that neurodegeneration, with possible cognitive sequelae, is a potential long-term risk of anesthetics in neonatal and young pediatric patients. The existing nonclinical data implicate not only NMDA-receptor antagonists, but also drugs that potentiate gamma-aminobutyric acid signal transduction, as potentially neurotoxic to the developing brain. The potential for the combination of drugs that have activity at both receptor systems or that can induce more or less neurotoxicity is not clear; however, recent nonclinical data suggest that some combinations may be more neurotoxic than the individual components. The lack of information to date precludes the ability to designate any one anesthetic agent or regimen as safer than any other. Ongoing studies in juvenile animals should provide additional information regarding the risks. The FDA anticipates working with the anesthesia community and pharmaceutical industry to develop strategies for further assessing

the safety of anesthetics in neonates and young children, and for providing data to guide clinicians in making the most informed decisions possible when choosing anesthetic regimens for their pediatric patients.

16. Meyer RR, et al. (2007). "Isoflurane is associated with a similar incidence of emergence agitation/delirium as sevoflurane in young children--a randomized controlled study." *Paediatr Anaesth.* 17(1): 56-60.
BACKGROUND: Children may be agitated or even delirious especially when recovering from general anesthesia using volatile anesthetics. Many trials have focused on the newer agents sevoflurane and desflurane but for the widely used isoflurane little is known about its potential to generate agitation. We investigated the emergence characteristics of small children after sevoflurane or isoflurane with caudal anesthesia for postoperative pain control. METHODS: After institutional approval and parental consent, anesthesia was randomly performed with sevoflurane (n = 30) or isoflurane (n = 29) in children at the age of 3.8 +/- 1.8 years during surgical interventions on the lower part of the body. After induction, all children received caudal anesthesia with bupivacaine (0.25%, 0.8 ml x kg(-1)). Postoperatively, the incidences of emergence agitation (EA) and emergence delirium (ED) were measured by a blinded observer using a ten point scale (TPS; EA = TPS > 5 ED = TPS > 7) as well as vigilance, nausea/vomiting and shivering. RESULTS: The two groups were comparable with respect to demographic data, duration of surgery and duration of anesthesia. There were also no differences in the period of time from the end of surgery until extubation, duration of stay in the PACU, postoperative vigilance and vegetative parameters. Incidence of EA was 30% (9/30) for sevoflurane and 34% (10/29) for isoflurane during the first 60 min in the PACU (P = 0.785). Likewise, the incidence of ED was not different between the groups (20% and 24%, respectively). CONCLUSIONS: In our randomized controlled study, we found no difference in the incidence of EA or ED between sevoflurane and isoflurane. Therefore, the decision to use one or the other should not be based upon the incidence of EA or ED.
17. Monk TG, et al. (2005). "Anesthetic management and one-year mortality after noncardiac surgery." *Anesth Analg.* 100(1): 4-10.
Little is known about the effect of anesthetic management on long-term outcomes. We designed a prospective observational study of adult patients undergoing major noncardiac surgery with general anesthesia to determine if mortality in the first year after surgery is associated with demographic, preoperative clinical, surgical, or intraoperative variables. One-year mortality was 5.5% in all patients (n = 1064) and 10.3% in patients > or =65 yr old (n=243). Multivariate Cox Proportional Hazards modeling identified three variables as significant independent predictors of mortality: patient comorbidity (relative risk, 16.116; P <0.0001), cumulative deep hypnotic time (Bispectral Index <45) (relative risk=1.244/h; P=0.0121) and intraoperative systolic hypotension (relative risk=1.036/min; P=0.0125). Death during the first year after surgery is primarily associated with the natural history of preexisting conditions. However, cumulative deep hypnotic time and intraoperative hypotension were also significant, independent predictors of increased mortality. These associations suggest that intraoperative anesthetic management may affect outcomes over longer time periods than previously appreciated.
18. Singh N, et al. (2006). "The effects of the type of anesthesia on outcomes of lower extremity infrainguinal bypass." *J Vasc Surg.* 44(5): 964-8.
OBJECTIVE: Three main types of anesthesia are used for infrainguinal bypass: general endotracheal anesthesia (GETA), spinal anesthesia (SA), and epidural anesthesia (EA). We analyzed a large clinical database to determine whether the type of anesthesia had any effect on clinical outcomes in lower extremity bypass. METHODS: This study is an analysis of a prospectively collected database by the National Surgical Quality Improvement Program (NSQIP) of the Veterans Affairs Medical Centers. All patients from 1995 to 2003 in the NSQIP database who underwent infrainguinal arterial bypass were identified via Current Procedural Terminology codes. The 30-day morbidity and mortality outcomes for various types of anesthesia were compared by using univariate analysis and multivariate logistic regression to control for confounders. RESULTS: The NSQIP database identified 14,788 patients (GETA, 9757 patients;

SA, 2848 patients; EA, 2183 patients) who underwent a lower extremity infrainguinal arterial bypass during the study period. Almost all patients (99%) were men, and the mean age was 65.8 years. The type of anesthesia significantly affected graft failure at 30 days. Compared with SA, the odds of graft failure were higher for GETA (odds ratio, 1.43; 95% confidence interval [CI], 1.16-1.77; $P = .001$). There was no statistically significant difference in 30-day graft failure between EA and SA. Regarding cardiac events, defined as postoperative myocardial infarction or cardiac arrest, patients with normal functional status (activities of daily living independence) and no history of congestive heart failure or stroke did worse with GETA than with SA (odds ratio, 1.8; 95% CI, 1.32-2.48; $P < .0001$). There was no statistically significant difference between EA and SA in the incidence of cardiac events. GETA, when compared with SA and EA, was associated with more cases of postoperative pneumonia (odds ratio: 2.2 [95% CI, 1.1-4.4; $P = .034$]. There was no significant difference between EA and SA with regard to postoperative pneumonia. Compared with SA, GETA was associated with an increased odds of returning to the operating room (odds ratio, 1.40; 95% CI, 1.20-1.64; $P < .001$), as was EA (odds ratio, 1.17; 95% CI, 1.05-1.31; $P = .005$). GETA was associated with a longer surgical length of stay on univariate analysis, but not after controlling for confounders. There was no significant difference in 30-day mortality among the three groups with univariate or multivariate analyses. CONCLUSIONS: Although GETA is the most common type of anesthesia used in infrainguinal bypasses, our results suggest that it is not the best strategy, because it is associated with significantly worse morbidity than regional techniques.

19. Snow SJ (2007). "Anaesthesia: symbol of humanitarianism." *Bmj*. 334 Suppl 1: s5.
Abstract Not Available
20. Steen PA, et al. (1978). "Myocardial reinfarction after anesthesia and surgery." *Jama*. 239(24): 2566-70.
During the years 1974 and 1975 at our institution, 587 patients who had suffered previous myocardial infarctions underwent anesthesia and surgery. Thirty-six (6.1%) had a reinfarction and 25 (69%) died. Patients operated on within three months of the previous infarction had a 27% reinfarction rate. This decreased to 11% if the infarct had occurred three to six months previously and stabilized at 4% to 5% if the interval was more than six months. Risk factors associated with significantly increased reinfarction rates included preoperative hypertension, intraoperative hypotensive episodes, and noncardiac thoracic or upper abdominal operations of more than three hours' duration. Time under anesthesia was strikingly correlated with reinfarction rates in the entire group. Postoperative intensive care unit admission did not significantly affect the reinfarction rate, nor did diabetes, angina, patient age or sex, or site of the previous myocardial infarction.
21. Vakkuri A, et al. (2001). "Sevoflurane mask induction of anaesthesia is associated with epileptiform EEG in children." *Acta Anaesthesiol Scand*. 45(7): 805-11.
BACKGROUND: Sevoflurane inhalation induction of anaesthesia is widely used in paediatric anaesthesia. We have found that this method is frequently associated with epileptiform electroencephalogram (EEG) in adults, especially if controlled hyperventilation is used.
METHODS: We assessed EEG during sevoflurane inhalation induction in 31 children, aged 2-12 yr. Anaesthesia was induced with 8% sevoflurane in O₂ in N₂O 1:2. The patients were randomized to undergo controlled ventilation (CV group), or to breathe spontaneously (SB group) for 5 min. EEG was recorded as were noninvasive blood pressure and heart rate (HR). EEG recordings were classified by a clinical neurophysiologist. RESULTS: Three different types of interictal epileptiform discharge were detected. Suppression with spikes (SSP) was found in 25% and 0% in the CV and SB groups, rhythmic polyspikes (PSR) in 44% and 20%, and periodic epileptiform discharges (PED) in 44% and 0% ($P < 0.01$), respectively. The incidence of all different types of interictal epileptiform discharge (SSP+PSR+PED) was 88% and 20% ($P < 0.001$), respectively. Epileptiform EEG was associated with increased heart rate and blood pressure during anaesthetic induction. CONCLUSION: Both ventilation modes produced epileptiform EEG. With controlled ventilation, epileptiform discharges were seen in 88% of children. This warrants further studies of the suitability of this induction type in general, and

especially in children with epilepsy.

22. Wada H, et al. (2007). "Combined Spinal and General Anesthesia Attenuates Liver Metastasis by Preserving Th1/Th2 Cytokine Balance." *Anesthesiology*. 106(3): 499-506.
BACKGROUND:: Many studies have shown that regional anesthesia improves postoperative outcome and particularly lessens infection by attenuating perioperative immunosuppression related to the stress response to surgery and general anesthesia. However, it remains to be determined whether regional anesthesia improves oncologic outcome after surgery. METHODS:: C57BL/6 mice were subjected to laparotomy during sevoflurane general anesthesia alone or combined with spinal block achieved with bupivacaine (5 mug) and morphine (1.25 mug). Control groups were anesthetized only or were untreated. Liver was removed 5 h after surgery to assess antitumor killer cell activity and production of interferon gamma and interleukin 4 by liver mononuclear cells, or mice were inoculated intravenously with liver-metastatic EL4 cells and hepatic metastases were counted 12 days later. RESULTS:: Laparotomy during sevoflurane anesthesia significantly increased the number (+/- SD) of liver metastases from 15.5 +/- 8.7 (control) and 19.4 +/- 5.4 (sevoflurane alone) to 33.7 +/- 8.9. Sevoflurane anesthesia plus spinal block significantly reduced this increase to 19.8 +/- 9. The in vitro killer activity of liver mononuclear cells against EL4 cells decreased from 32.7% (control) and 29.4% (sevoflurane alone) to 18.5% after sevoflurane plus laparotomy, and the addition of spinal block increased activity to 26.6%. The interferon-gamma/interleukin-4 ratio decreased from 89.3 (control) and 95.7 (anesthesia alone) to 15.7 after sevoflurane plus laparotomy, and the addition of spinal block increased the ratio to 46.5. CONCLUSIONS:: The addition of spinal block to sevoflurane general anesthesia accompanying surgery attenuates the suppression of tumoricidal function of liver mononuclear cells, presumably by preserving the T helper 1/T helper 2 (Th1/Th2) balance, and thereby reduces the promotion of tumor metastasis.
23. Waknine Y. (2007). "Excessive Use of Topical Anesthetics Can Be Fatal." [Medscape Medical News](http://www.medscape.com/viewarticle/551916) Retrieved March 7, 2007, from <http://www.medscape.com/viewarticle/551916>.
Abstract Not Available
24. Xie Z, et al. (2006). "The common inhalation anesthetic isoflurane induces apoptosis and increases amyloid beta protein levels." *Anesthesiology*. 104(5): 988-94.
BACKGROUND: The common inhalation anesthetic isoflurane has previously been reported to enhance the aggregation and cytotoxicity of the Alzheimer disease-associated amyloid beta protein (Abeta), the principal peptide component of cerebral beta-amyloid deposits. METHODS: H4 human neuroglioma cells stably transfected to express human full-length wild-type amyloid precursor protein (APP) were exposed to 2% isoflurane for 6 h. The cells and conditioned media were harvested at the end of the treatment. Caspase-3 activation, processing of APP, cell viability, and Abeta levels were measured with quantitative Western blotting, cell viability kit, and enzyme-linked immunosorbent assay sandwich. The control condition consisted of 5% CO2 plus 21% O2 and balanced nitrogen, which did not affect caspase-3 activation, cell viability, APP processing, or Abeta generation. RESULTS: Two percent isoflurane caused apoptosis, altered processing of APP, and increased production of Abeta in H4 human neuroglioma cell lines. Isoflurane-induced apoptosis was independent of changes in Abeta and APP holoprotein levels. However, isoflurane-induced apoptosis was potentiated by increased levels of APP C-terminal fragments. CONCLUSION: A clinically relevant concentration of isoflurane induces apoptosis, alters APP processing, and increases Abeta production in a human neuroglioma cell line. Because altered processing of APP leading to accumulation of Abeta is a key event in the pathogenesis of Alzheimer disease, these findings may have implications for use of this anesthetic agent in individuals with excessive levels of cerebral Abeta and elderly patients at increased risk for postoperative cognitive dysfunction.
25. Xie Z, et al. (2007). "The inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid beta-protein accumulation." *J Neurosci*. 27(6): 1247-54.
The anesthetic isoflurane has been reported to induce apoptosis and increase Abeta generation and aggregation. However, the molecular mechanism underlying these effects remains unknown.

We therefore set out to assess whether the effects of isoflurane on apoptosis are linked to amyloid beta-protein (Abeta) generation and aggregation. For this purpose, we assessed the effects of isoflurane on beta-site amyloid beta precursor protein (APP)-cleaving enzyme (BACE) and gamma-secretase, the proteases responsible for Abeta generation. We also tested the effects of inhibitors of Abeta aggregation (iAbeta5, a beta-sheet breaker peptide; clioquinol, a copper-zinc chelator) on the ability of isoflurane to induce apoptosis. All of these studies were performed on naive human H4 neuroglioma cells as well as those overexpressing APP (H4-APP cells). Isoflurane increased the levels of BACE and gamma-secretase and secreted Abeta in the H4-APP cells. Isoflurane-induced Abeta generation could be blocked by the broad-based caspase inhibitor Z-VAD. The Abeta aggregation inhibitors, iAbeta5 and clioquinol, selectively attenuated caspase-3 activation induced by isoflurane. However, isoflurane was able to induce caspase-3 activation in the absence of any detectable alterations of Abeta generation in naive H4 cells. Finally, Abeta potentiated the isoflurane-induced caspase-3 activation in naive H4 cells. Collectively, these findings suggest that isoflurane can induce apoptosis, which, in turn, increases BACE and gamma-secretase levels and Abeta secretion. Isoflurane also promotes Abeta aggregation. Accumulation of aggregated Abeta in the media can then promote apoptosis. The result is a vicious cycle of isoflurane-induced apoptosis, Abeta generation and aggregation, and additional rounds of apoptosis, leading to cell death.