Monitoring The Whole Brain: What Are We Thinking?

Michael Ramsay MD
Chairman Department of Anesthesia
Baylor University Medical Center
President Baylor Research Institute
Professor Texas A&M Health Science Center
Clinical Professor UT Southwestern Medical School
Speaker Disclosures

I receive research support from Masimo Corp and Consult for Pfizer
Cognition
Peri-Operative Cognitive Disorders

• **Emergence Excitation**: transient acutely agitated state

• **Postoperative Delirium**: inattention and disorganized thinking

• **Postoperative Cognitive Dysfunction**: measurable decline in cognitive function. Maybe Short-Term reversible or Long-Term cognitive decline.
  – POCD may occur after cardiac or non-cardiac anesthesia even procedures requiring regional, local anesthesia and sedation. Consistent factor is increasing age.

• **Cognitive decline** is frequent in the elderly and leads to functional decline therefore it is important that we identify triggers to manage the health of our senior citizens.
Postoperative cognitive impairment at extremes of life and with critical illness in response to depth of sedation and anesthesia


Cognitive Trajectories after Postoperative Delirium

Division of Geriatric Medicine and Meyers Primary Care Institute, University of Massachusetts Medical School, Worcester (J.S.S.); and the Aging Brain Center, Institute for Aging Research, Hebrew SeniorLife (E.R.M., S.K.I., L.Q., T.G.F., A.G., R.N.J.), the Divisions of General Medicine and Primary Care (E.R.M.) and Gerontology (E.R.M., S.K.I., A.G., R.N.J.) and the Department of Neurology (T.G.F.), Beth Israel Deaconess Medical Center, and Harvard Medical School (E.R.M., S.K.I., T.G.F., R.N.J.) — all in Boston

Abstract

BACKGROUND—Delirium is common after cardiac surgery and may be associated with long-term changes in cognitive function. We examined postoperative delirium and the cognitive trajectory during the first year after cardiac surgery.

CONCLUSIONS—Delirium is associated with a significant decline in cognitive ability during the first year after cardiac surgery, with a trajectory characterized by an initial decline and prolonged impairment. (Funded by the Harvard Older Americans Independence Center and others.)
Presence of electroencephalogram burst suppression in sedated, critically ill patients is associated with increased mortality

Paula L. Watson, MD, Ayumi K. Shintani, MPH, PhD, Richard Tyson, MD, Pratik P. Pandharipande, MD, MScI, Brenda T. Pun, RN, MSN, ACNP, and E. Wesley Ely, MD, MPH
Department of Medicine (PLW, RT, BTP, EWE), Division of Allergy, Pulmonary, and Critical Care; Center for Health Services Research (PLW, EWE); VA Tennessee Valley Geriatric Research, Education and Clinical Center (EWE); Department of Biostatistics (AKS); and the Department of Anesthesiology and Critical Care (PPP), Vanderbilt University Medical Center, Nashville, TN

Abstract
Burst Suppression on Processed Electroencephalography as a Predictor of Postcoma Delirium in Mechanically Ventilated ICU Patients

Jennifer M. Andreisen, MD1; Timothy D. Girard, MD, MSc1,2,4; Pratik P. Pandharipande, MD, MSc1,4; Mario A. Davidson, PhD1; E. Wesley Ely, MD, MPH1,2,4; Paula L. Watson, MD1

Objectives: Many patients, due to a combination of illness and sedation, spend a considerable amount of time in a comatose state that can include time in burst suppression. We sought to determine if burst suppression measured by processed electroencephalography during coma in sedative-exposed patients is a predictor of post-coma delirium during critical illness.

Design: Observational convenience sample cohort.

Setting: Medical and surgical ICUs in a tertiary care medical center.

Patients: Cohort of 124 mechanically ventilated ICU patients.

Interventions: None.

Measurements and Main Results: Depth of sedation was monitored twice daily using the Richmond Agitation-Sedation Scale and continuously monitored by processed electroencephalography. When noncomatose, patients were assessed for delirium twice daily using Confusion Assessment Method for the ICU. Multiple logistic regression and Cox proportional hazards regression were used to assess associations between time in burst suppression and both prevalence and time to resolution of delirium, respectively, adjusting for time in deep sedation and a principal component score consisting of Acute Physiology and Chronic Health Evaluation II score and cumulative doses of sedatives while comatose. Of the 124 patients enrolled and monitored, 85 patients either never had coma or never emerged from coma, yielding 69 patients for whom we performed these analyses; 42 of these 69 (61%) had post-coma delirium. Most patients had burst suppression during coma, although often short-lived (median [interquartile range] time in burst suppression, 6.4 [1.8–68] min). After adjusting for covariates, even this short time in burst suppression independently predicted a higher prevalence of post-coma delirium (odds ratio, 4.18; 95% CI, 1.27–13.62; \(p = 0.029\)) and a lower likelihood (delayed) resolution of delirium (hazard ratio, 0.78; 95% CI, 0.53–0.98; \(p = 0.04\)).

Conclusions: Time in burst suppression during coma, as measured by processed electroencephalography, was an independent predictor of prevalence and time to resolution of postcoma/post-deep sedation delirium. These findings of this single-center investigation support lighter sedation strategies. (Crit Care Med 2014; 42:2244–2251)
Risk for Cognitive Decline Greater in Older Women Following General Anesthesia and Surgery

TORONTO—Older women appear to be at higher risk than older men for deterioration in neurologic and cognitive functioning as well as ventricular brain volumes following the administration of general anesthesia and surgery. That was the conclusion of a study that tracked cognitive aging in more than 500 elderly people over time.

Elderly women and men who received general anesthesia were both at higher risk for deleterious neurocognitive outcomes when compared with elderly people who did not receive anesthesia, but the declines were more pronounced in women than men.
Original Article

Cognitive decline in the elderly after surgery and anaesthesia: results from the Oxford Project to Investigate Memory and Ageing (OPTIMA) cohort

D. Patel, A. D. Lunn, A. D. Smith, D. J. Lehmann and K. L. Dorrington

1 Core Trainee in Anaesthetics, Northwick Park Hospital, Harrow, UK
2 Emeritus Fellow, Department of Statistics, 3 Professor Emeritus, Founding Director, 4 Research Fellow, Oxford Project to Investigate Memory and Ageing, Department of Pharmacology, University of Oxford, Oxford, UK
5 Associate Professor of Physiology, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK
6 Honorary Consultant, Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford, UK

Summary

Concerns have been raised about the effects on cognition of anaesthesia for surgery, especially in elderly people. We recorded cognitive decline in a cohort of 394 people (198 women) with median (IQR) age at recruitment of 72.6 (66.6–77.8) years, of whom 109 had moderate or major surgery during a median (IQR) follow-up of 4.1 (2.0–7.6) years. Cognitive decline was more rapid in people who on recruitment were: older, p = 0.0003; male, p = 0.027; had worse cognition, p < 0.0001; or carried the ε4 allele of apolipoprotein E (APOEε4), p = 0.008; and after an operation if cognitive impairment was already diagnosed, p = 0.0001. Cognitive decline appears to accelerate after surgery in elderly patients diagnosed with cognitive impairment, but not other elderly patients.
Anesthesia’s Cognitive Effects In Young Children Vary by Age
FDA Issues Warning on General Anesthetics, Sedative Use in Children

The FDA released a warning on Dec. 14 about the use of general anesthetics and sedatives in children under 3 years old and pregnant women during their third trimester. Repeated or continuing use may harm brain development in children, according to the agency.

The FDA will now require warnings about this risk to be added to the labels of the following general anesthetic and sedation drugs:
- desflurane (Suprane)
- etomidate (Amidate)
- halothane
- isoflurane (Forane)
- ketamine (Ketalar)
- lorazepam injection (Ativan)
- methohexital (Brevital)
- midazolam injection, syrup
- pentobarbital (Nembutal)
- propofol (Diprivan)
- sevoflurane (Ultane, Sojourn)

The FDA suggests that healthcare professionals "balance the benefits of appropriate anesthesia in young children and pregnant women against the potential risks," especially for patients under 3 years old requiring multiple procedures or for surgeries lasting more than three hours. The agency recommends that parents and pregnant women should consult their physicians to discuss potential adverse events (AEs) related to use.

The medical literature remains mixed on the safety and potential AEs of these drugs. According to the FDA, the agency has been studying the drugs' potential adverse effects on brain development in children since the first animal study published on this topic (1999, 283:70-74). However, recent animal and human studies have found that a single
Causes of Neurologic Failure

- Trauma/Increasing ICP
- Circulatory shock
- Hypoxemia/Hypoperfusion/Vasospasm
- Infection
- Systemic inflammation
- Metabolic and endocrine imbalances
- Pharmacologic agents; ?benzodiazepines
- Depth of drug induced brain depression?
Anesthesiology 2016; 125:1229-41 (modified)
Incidence of Cognitive Decline after Cardiac Surgery

Kok et al. Anaesthesia 2014
69:613-22

Figure 3  Incidence of postoperative cognitive decline in patients who underwent coronary artery bypass and were randomly allocated to surgery with or without cardiopulmonary bypass 4 days (blue) and 3 months (red) postoperatively. *p = 0.004.
Long-Term Cognitive Impairment after Critical Illness


- Patients in medical and surgical ICUs are at a high risk for long-term cognitive impairment. A longer duration of delirium in the hospital was associated with worse global cognition and executive function scores at 3 months (40%)(P=0.001) and 12 months (34%)(P=0.004)
- 40% equivalent to TBI
- 26% equivalent to mild Alzheimer’s
Alarming knowledge of football concussions grows

by Thomas C. Fox | Nov. 9, 2013

Several days ago I received the following article from NCR reader Jim Ewens, a graduate of Marquette High School in Milwaukee, Wisconsin from where I also graduated. He writes of the growing – and alarming – understanding we are gaining of football related brain injuries from repeated concussions. We now know these concussions can lead to long-term disabilities and even death.
“But what I see these days are sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise..... By being awake and alert...they could interact with family....feel human...sustain the zest for living which is a requirement for survival”
One Year Outcomes in Survivors of ARDS

- Functional limitations 1 year later
- Most patients have muscle wasting and weakness.
- Neurocognitive impairments. 
- Depression and memory dysfunction increased in ARDS survivors. 
  - Chest 2009;135:678
Over Sedation in ICU

- Excessive sustained alteration in consciousness
- Prolonged time on mechanical ventilation
- Increased ventilator associated pneumonia
- Increased prolonged muscular weakness
  - Annals of Intensive Care 2013, 3:24
Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

Juliana Barr, MD, FCCM1; Gilles L. Fraser, PharmD, FCCM2; Kathleen Puntillo, RN, PhD, FAAN, FCCM3; E. Wesley Ely, MD, MPH, FACP, FCCM4; Céline Gélinas, RN, PhD5; Joseph F. Dasta, MSc, FCCM, FCCP6; Judy E. Davidson, DNP, RN7; John W. Devlin, PharmD, FCCM, FCCP8; John P. Kress, MD9; Aaron M. Joffe, DO10; Douglas B. Coursin, MD11; Daniel L. Herr, MD, MS, FCCM12; Avery Tung, MD13; Bryce R. H. Robinson, MD, FACS14; Dorrie K. Fontaine, PhD, RN, FAAN15; Michael A. Ramsay, MD16; Richard R. Riker, MD, FCCM17; Curtis N. Sessler, MD, FCCP, FCCM18; Brenda Pun, MSN, RN, ACNP19; Yoanna Skrobik, MD, FRCP20; Roman Jaeschke, MD21
Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Adult Patients in the Intensive Care Unit

• Pain: treat pain assess and first

• Monitor for depth of sedation: use sedation scores and assess regularly: Use brain function monitors in the sedated paralyzed patients. Use the EEG in comatose patients

• Routinely monitor for delirium

EEG: Typical Nonconvulsivse Seizure
EEG Changes with Altered Mental Function - Delirium

- Generalized decrease in fast frequency
- Prominent delta and theta waves
- Loss of reactivity to eye opening
- Increased theta wave; reduced alpha activity
  - Plaschke et al Anesthesia 2007;62:1217-23
Alterations in the Functional Connectivity of Frontal Lobe Networks Preceding Emergence Delirium in Children


ABSTRACT

**Background:** This study aimed to characterize the electroencephalogram in children who emerged with emergence delirium (ED) compared with children without ED using methods that involved the assessment of cortical functional connectivity.

**Methods:** Children aged 5 to 15 yr had multichannel electroencephalographic recordings during induction and emergence from anesthesia during minor surgical procedures. Of these, five children displayed ED after sevoflurane anesthesia. Measures of cortical functional connectivity previously used to evaluate anesthetic action in adults were compared between ED and age-, sex-, and anesthetic-matched non-ED children during emergence from anesthesia.

**Results:** At the termination of sevoflurane anesthesia, the electroencephalogram in both ED and control patients showed delta frequency slowing and frontally dominant alpha activity, followed by a prolonged state with low-voltage, fast frequency activity (referred to as an indeterminate state). In children with ED, arousal with delirious behavior and a variety of electroencephalogram patterns occurred during the indeterminate state, before the appearance of normal wake or sleep patterns. The electroencephalogram in children without ED progressed from the indeterminate state to classifiable sleep or drowsy states, before peaceful awakening. Statistically significant differences in frontal lobe functional connectivity were identified between children with ED and non-ED.

**Conclusions:** ED is associated with arousal from an indeterminate state before the onset of sleep-like electroencephalogram patterns. Increased frontal lobe cortical functional connectivity observed in ED, immediately after the termination of sevoflurane anesthesia, will have important implications for the development of methods to predict ED, the design of preventative strategies, and efforts to better understand its pathophysiology. *(Anesthesiology 2014; 121:740-52)*
Time series for Global Coherence functional connectivity measures for the same normal control subject (NC4) for (A) full, (B) frontal, and (C) parietal networks calculated using either common average (left column) or Laplacian rerereferencing (right column). Vertical white spaces indicate the time intervals in which data contained artifact.
Figure Legend:
Time series for estimated functional connectivity using the Global Coherence measure calculated using Laplacian rereferenced electroencephalogram data for frontal networks of patients with emergence delirium (ED) (A) ED1, (B) ED3, (C) ED4, and (D) ED5. In each subfigure: vertical solid black line = onset of ED episode, vertical dashed black line = end of ED episode (where applicable). White spaces indicate time intervals in which data contained artifact preventing the meaningful calculation of Global Coherence.
Multimodal Monitoring of the Brain

- Neurological damage
  - Clinical evaluation, serial assessment, imaging

- Systemic
  - BP, O₂ saturation, EtCO₂, temperature, glucose

- Intracranial volumes
  - ICP

- Cerebral perfusion
  - CPP, TCD ultrasonography, laser Doppler flowmetry, transcranial cerebral oximetry

- Metabolic
  - Microdialysis, jugular venous oximetry, direct brain oxygen, NIRS

- Electrophysiology
  - EEG, SSEP, BAER

Acute brain injury

Integration

Data display and analysis

Therapeutical plan
Scientific Basis for Monitoring EEG

- EEG is tightly linked to cerebral metabolism
- EEG is sensitive to common causes of cerebral injury: ischemia and hypoxia
- EEG detects neuronal dysfunction at a reversible stage
- EEG detects neuronal recovery before clinical signs
- EEG best technology for detecting epileptic activity
- Continuous EEG provides dynamic information not just a snapshot
Brain Monitoring

• The EEG has a long history of use in the ICU and OR
• A routine EEG recording lasts around 30 minutes
• Electrode failure and artifact impede the quality
• Pathological events are missed because record is short
• New resilient brain function monitors allow continual monitoring
• Enhanced signal extraction now allows diagnostic and prognostic value but also offers an understanding of how anesthetic drugs work
Fig. 4. (A) In the 10/20 convention, odd numbers refer to placements over the left hemisphere, even numbers refer to placements over the right hemisphere, and Z refers to midline locations. Upper-case letters indicate underlying brain regions: C = central; F = frontal; Fp = frontopolar; O = occipital; P = parietal; T = temporal. (B) Sample of electroencephalographic recording. Each tracing comes from 1 of the 19 electrodes in the 10/20 array, positioned according to the labels at the left side of each trace. An artifact-free segment lies in the region above the two arrowbeads on the bottom line.
Cerebral Function Monitoring

- Two channel amplified, integrated EEG recording
- Can be applied for prolonged periods
- Technique first developed in 1960s by Maynard, Prior, and Scott
  - BMJ 1969; 4: 545
Representative electroencephalogram (EEG) patterns at different stages of anesthesia

- **Awake**
- **Sedated**
- **Surgical anesthesia**
- **Burst suppression**
- **Isoelectricity**

**BIS:**
- 100
- 80
- 60
- 40
- 20
- 0

Depth of Anesthesia

Light Anesthesia

Anesthesia
Deeper Anesthesia

Deep
Burst Suppression
Isoelectric
Anesthetic Drug EEG Signatures

• Each anesthetic drug has its own EEG signature that reflects its site of action:

  – Propofol acts at the GABA receptor and has this signature:

  ![Propofol EEG Signature]

  – Ketamine acts at the NMDA receptor:

  ![Ketamine EEG Signature]

  – Dexmedetomidine acts at the locus coeruleus: Spindles

  ![Dexmedetomidine EEG Signature]
The Spectrogram

Alpha 10 hz

Theta 1 hz
Advancement in DSA

This pattern shows both delta and alpha frequencies.

19 year-old female
200 mg propofol bolus
Maintenance w/ 100 mcg/kg/min propofol

Brown E. ASA Symposium. 2013
Anesthetic Signatures

www.anesthesiaEEG.com  Emory N Brown and Patrick Purdon
Clinical EEG of Propofol

Case Example:
52-year old female
Propofol bolus of 100, 50, and 50 mg

Burst Suppression
Ketamine

www.anesthesiaEEG.com  Emory N Brown and Patrick Purdon
Dexmedetomidine
Trends in the spectrum and coherence from 18 to 90 yr old during propofol anaesthesia.

The Old Brain

Effect of same dose of propofol

YOUNG BRAIN

OLD BRAIN
Intraoperative Asymmetry

Intraoperative asymmetry post documented CVA as displayed on DSA

Reference on file Masimo
PSA4000 with PSAArray2
Subject 13, M3010055_041112_1253

PSI

SR, EMG, ARTIFACT (%)

Mt n-Lower Mt n-Upper Emerg-Upper PSI PSI Artifact Event Markers SR EMG Artifact

CLOCK TIME (24 HOUR CLOCK)
Physiological Context

- Brain receives 15-20% cardiac output
- Brain consumes 20% of total body oxygen
- Interruption of $O_2$ delivery for 10s can cause unconsciousness
- In 3-8 min, ATP depletion can result in irreversible damage
- Frontal cerebral cortex very susceptible to hypoxia
Cerebral oximetry: the standard monitor of the future?

Anneliese Moerman and Stefan De Hert

Curr Opin Anesthesiol 2015, 28:703–709

Purpose of review
There is an increasing interest in the application of near-infrared spectroscopy (NIRS) as a monitoring tool in noncardiac surgery. This review summarizes the latest developments and current evidence for the use of NIRS in the noncardiac intraoperative setting.

Recent findings
Unanticipated intraoperative physiological disturbances and a substantial interpatient variability in the limits of cerebral autoregulation, pose our patients at risk for adverse cerebral outcome, if the brain is not monitored specifically. In addition to a means to monitor the brain, NIRS has been shown to allow an estimate of overall organ oxygenation. Preliminary data suggest a relationship between cerebral desaturation and both neurologic and major organ morbidity.

Summary
NIRS offers noninvasive monitoring of cerebral and overall organ oxygenation in a wide range of clinical scenarios. There is an increasing evidence that the optimized cerebral oxygenation is associated with improved outcomes in both neurologic and major organ morbidity in a variety of surgical settings.

Keywords
brain, cerebral oximetry, monitoring, near-infrared spectroscopy, noninvasive
The NIRS technology was first described by Franz Jobsis in 1977.

Light in the NIR spectrum (700-950 nm) can traverse biological tissue and several biological molecules – chromophores – have distinct absorption spectra in the NIR: oxyhemoglobin, deoxyhemoglobin and cytochrome C oxidase CCO.

Emitting and detecting optodes allow monitoring of multiple tissue regions.

Cerebral oximetry provides real-time information on the balance between cerebral oxygen supply and demand.

All commercial devices assume a fixed ratio of either 70:30 or 75:25 for venous to arterial blood volume and all ignore capillary volume.
Cerebral Oximetry

- 3 main components:
  - Light source: emits NIR light of known wavelength and intensity
  - Light detector: two (2) photodetectors allow selective sampling of tissue beyond a specified depth
  - Computer converts intensity of light exiting as $O_2$ saturation

- Near field subtracted from far field gives cerebral cortex tissue oxygenation

- Obtain a baseline reading on room air: a 20% or greater trend reduction from this base is clinically relevant
NIRS measures Regional Hb Oxygen Saturation

- NIRS represents a mixture of arterial, capillary and venous oxygen saturation.
- $S_{jv}O_2$ reflects global brain oxygenation.
- NIRS has a potential as a noninvasive brain monitor across a spectrum of disorders, from routine surgery under GA and as an application in brain injury but the data is only now being collected.
Baseline rSO$_2$ Marker

Area Under the Curve

Delta (Difference) from Baseline rSO$_2$

rSO$_2$ Trend

rSO$_2$

Difference between rSO$_2$ and Peripheral SpO$_2$ (when used with the Radical-7 in Root)
Changes in Regional Oxygen Saturation

- Regional oxygen saturation decreases when:
  - Arterial oxygen saturation in tissue decreases.
  - Venous oxygen saturation in the tissue decreases.

- Arterial oxygen saturation in tissue decreases when:
  - Oxygen saturation in the circulating arterial blood is reduced.

- Venous oxygen saturation in tissue decreases when:
  - Arterial oxygen saturation (SaO₂) in the circulating blood is reduced.
  - Tissue oxygen consumption (VO₂) increases.
  - Regional blood flow is reduced (lower cardiac output or local blood flow restriction).
Fig 2 Proposed algorithm in the use of brain oximetry. CT, computed tomography; ICHT, intra-cranial hypertension; MAP, mean arterial pressure; MRI, magnetic resonance imaging. Reprinted from Denault and colleagues, 10 with permission from SAGE Publications Inc.
Interpretation

Take into account the clinical situation:

• CO
• BP
• PaCO\textsubscript{2}
• pH
• FiO\textsubscript{2}
• Temperature
• Hb
• change in position
• Local blood flow
• Pre-existing disease
• ScO\textsubscript{2} – highly sensitive but relatively non-specific
Perioperative goal-directed haemodynamic therapy based on flow parameters: a concept in evolution

L. Meng and P. M. Heerdt*

Department of Anesthesiology, Yale University School of Medicine, 330 Cedar St., PO Box 208051, New Haven, CT 06520, USA

*Corresponding author. E-mail: paul.heerdt@yale.edu

Abstract

Haemodynamic management incorporating direct or surrogate stroke volume monitoring has experienced a rapid evolution, because of emergence of the "goal-directed therapy" concept and technological developments aimed at providing a parameter leading to the goal. Nonetheless, consensus on both definitions of the ideal "goal" and strategies for achieving it remain elusive. For this review, we first consider basic physiological and patient monitoring factors relevant to the concept of "fluid responsiveness," and then focus upon randomized controlled trials and meta-analyses involving goal-directed haemodynamic therapy based on various flow parameters. Finally, we discuss the current status of noninvasive methods for monitoring fluid responsiveness.

Key words: blood pressure; fluid therapy; haemodynamics; monitoring; stroke volume
Value in Cardiac + Abdominal Surgeries

- **(Cardiac)** Baseline ScO₂ independent risk factor for 30 day and 1 year mortality.
  - *Heringlake W et al. Anesthesiology 2011; 114:58-69*

- **(Cardiac)** Actively limiting decreases in ScO₂ reduces morbidity and mortality.

- **(Cardiac)** Decrease in stroke rate.

- **(Abdominal)** Reduction in postoperative neurocognitive dysfunction in elderly patients

*Casati A et al. Anesth Analg 2005; 101:740-7*
Clinical Evidence

A review of previously cited clinical trials reveal the following benefits of regional oximetry:

- Serves as first alert for cerebral desaturation events
- Reduced PACU length of stay
- Reduced incidence of stroke
- Reduced ICU length of stay
- Reduced post-operative mechanical ventilation time
- Reduced reoperation for hemorrhage
- Reduced composite outcome of death, stroke, myocardial infarction, post-operative ventilation >48 hours and reoperation for hemorrhage
THANK YOU!