FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND LIFE SUPPORT

DRUGS ADVISORY COMMITTEE (ALSDAC)

Thursday, March 10, 2011

8:00 a.m. to 3:00 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE MEMBERS (VOTING)

Randall Flick, MD, MPH
Assistant Professor of Anesthesiology
Mayo Clinic
Rochester, Minnesota

Jayant K. Deshpande, MD, MPH
Senior Vice President, Chief of Quality/Associate Medical Director
Arkansas Children's Hospital
Little Rock, Arkansas

Jeffrey R. Kirsch, MD *(Chair)*
Professor and Chair
Department of Anesthesiology and Perioperative Medicine
Associate Dean for Clinical and Veterans Affairs
Oregon Health & Science University
Portland, Oregon

John Markman, MD

Director, Neuromedicine

Pain Management Center

Director, Translational Pain Research

Associate Professor

University of Rochester Medical Center

Rochester, New York

INDUSTRY REPRESENTATIVE (NON-VOTING)

Bartholomew J. Tortella, MTS, MD, MBA, FACS, FCCM

Senior Director, Medical Affairs Hemophilia

Pfizer, Inc.

Collegeville, Pennsylvania

TEMPORARY VOTING MEMBERS

Jane Adams, PhD

Chair, Department of Psychology

University of Massachusetts

Boston, Massachusetts

TEMPORARY VOTING MEMBERS (CONTINUED)

Barbara Clancy, PhD (Speaker and Discussant)
Associate Professor
University of Central Arkansas,
Little Rock, Arkansas

Douglas Diekema, MD, MPH
Director, Treuman Katz Center for Pediatric
Bioethics
University of Washington
Seattle, Washington

Chris Ikonomidou, MD, PhD
Professor, Child Neurology
Waisman Center University of Wisconsin
Madison, Wisconsin

Terrie Inder, MD
Professor of Pediatrics
Washington University School of Medicine
St Louis, Missouri

1 **TEMPORARY VOTING MEMBERS (CONTINUED)**

2 **Alexander A. Kon, MD, FAAP, FCCM**

3 Chief, Pediatric Critical Care Medicine

4 Medical Director, Pediatric Intensive Care Unit

5 Naval Medical Center San Diego

6 San Diego, California

7

8 **Mary Majumder, JD, PhD (Acting Consumer**

9 **Representative)**

10 Assistant Professor, Department of Medicine

11 Center for Medical Ethics and Health Policy

12 Baylor College of Medicine

13 Houston, Texas

14

15 **Lynn D. Martin, MD, FAAP, FCCM**

16 Director, Department of Anesthesiology & Pain

17 Medicine

18 Medical Director, Bellevue Clinics and Surgery

19 Center

20 Seattle Children's Hospital

21 Seattle, Washington

22

TEMPORARY VOTING MEMBERS (CONTINUED)

Donald R. Mattison, MD, CAPT
US Public Health Service
Epidemiology Branch
Division of Epidemiology, Statistics and Prevention Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
Bethesda, Maryland

Craig J. Newschaffer, PhD
Professor and Chairman
Drexel University School of Public Health
Department of Epidemiology and Biostatistics
Philadelphia, Pennsylvania

Daniel A. Notterman, MA, MD
Vice Dean for Research and Graduate Studies
Penn State University College of Medicine
Hershey, Pennsylvania

TEMPORARY VOTING MEMBERS (CONTINUED)

Mark S. Schreiner, MD

Associate Professor of Anesthesiology and Critical Care

Children's Hospital

Philadelphia, Pennsylvania

Philip Shaw, MD, PhD

Staff Clinician

Child Psychiatry Branch

National Institute of Mental Health

National Institutes of Health

Bethesda, Maryland

Sulpicio Soriano, MD

Professor of Anesthesia

Harvard Medical School

Boston, Massachusetts

TEMPORARY VOTING MEMBERS (CONTINUED)

Ezra Susser, MD, DrPH

Professor of Psychiatry and Epidemiology

Mailman School of Pubic Health

Columbia University

New York, New York

Susan Swedo, MD

Chief of Pediatrics and Developmental

Neuroscience Branch

National Institute of Mental Health

National Institutes of Health

Bethesda, Maryland

Loise Swisher (Patient Representative)

Ambler, Pennsylvania

TEMPORARY VOTING MEMBERS (CONTINUED)

Audrey Thurm, PhD
Staff Scientist
Pediatrics and Developmental Neuroscience Branch
National Institute of Mental Health
National Institutes of Health
Bethesda, Maryland

Joseph R. Tobin, MD
Professor and Chairman
Department of Anesthesiology
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Vesna Jevtovic-Todorovic, MD, PhD, MBA
Professor of Anesthesiology and Neuroscience
Department of Anesthesiology
University of Virginia School of Medicine
Charlottesville, Virginia

TEMPORARY VOTING MEMBERS (CONTINUED)

Steven Weinstein, MD

Professor of Clinical Pediatrics

Weil Cornell Medical College,

New York Presbyterian Hospital

New York, New York

Athena Zuppa, MD

Assistant Professor of Pediatrics

University of Pennsylvania

Children's Hospital of Pennsylvania

Philadelphia, Pennsylvania

GUEST SPEAKERS (NON-VOTING, PRESENTING ONLY):

K.J.S. Anand, MBBS, D.Phil.

St. Jude Chair for Critical Care Medicine

Professor of Pediatrics, Anesthesiology, &

Neurobiology

University of Tennessee Health Science Center

Memphis, Tennessee

John W. Olney, MD

Professor of Psychiatry and Neuropathology

Washington University

St Louis, Missouri

FDA MEETING PARTICIPANTS AT THE TABLE (NON-VOTING)

Bob Rappaport, MD

Director, Division of Anesthesia and

Analgesia Products (DAAP), CDER, FDA

Rigoberto Roca, MD

Deputy Director, Division of Anesthesia and

Analgesia Products (DAAP), CDER, FDA

Arthur Simone, MD, PhD

Medical Officer, Anesthetics

Division of Anesthesia and Analgesia Products

(DAAP), CDER, FDA

R. Daniel Mellon, PhD Pharmacology Toxicology Supervisor Division of Anesthesia and Analgesia Products (DAAP), CDER, FDA

Merle G. Paule, PhD, Fellow Academy Toxicologist Sciences (ATS) Director, Division of Neurotoxicology National Center for Toxicological Research, FDA

C O N T E N T S

AGENDA ITEM	PAGE
Call to Order and Introduction of Committee	
Jeffrey Kirsch, M.D.	15
Conflict of Interest Statement	
Kalyani Bhatt, B.S., M.S.	21
Welcome and Introduction	
Bob Rappaport, M.D.	25
Anesthetic-Induced Neurodegeneration: Update of Pre-Clinical Data since 2007	
Daniel Mellon, Ph.D.	31
Ketamine Anesthesia and Long-Lasting Cognitive Deficits in Rhesus Monkeys	
Merle Paule, Ph.D.	78
Anesthesia-Induced Neuroapoptosis and Oligoapoptosis in the Developing Primate Brain	
John Olney, M.D.	99
Translating Developmental Time from Experimental Species to Humans	
Barbara Clancy, Ph.D.	114

C O N T E N T S (continued)

AGENDA ITEM	PAGE
Review of Clinical Data	
Arthur Simone, M.D., Ph.D.	128
Ketamine and the Neonatal Brain: Rat Pups vs. Babies	
K.J.S. Anand, MBBS, D.Phil	159
What Is Our Professional Responsibility? Focus on Research and Risk Communication	
Robert Nelson, M.D., Ph.D.	180
Follow-Up Questions to the Presenters	190
Open Public Hearing	216
Discussion and Questions to the Committee	227
Adjournment	328

P R O C E E D I N G S

(8:00 a.m.)

Call to Order and Introduction of Committee

DR. KIRSCH: Good morning, everybody. I'm a bit disappointed this morning because it's raining, and I was trying to leave Portland to get away from the rain. And my sense is that here in D.C., they do less well with the rain than we do in Portland. So I'm sure people will be trickling in. And I understand there is an accident on the Beltway. We don't have a beltway in Portland, so it's not a big deal.

Well, good morning. If everyone could please take their seats, we can get started. I'd like to remind everyone present to please silence your cell phones, Blackberrys, pagers and other devices, if you have not done so already.

We'll get started by going around the table and introducing ourselves, and we'll start with Dr. Tortella.

DR. TORTELLA: Bartholomew Tortella, Industry Representative, Pfizer.

DR. IKONOMIDOU: I'm Chris Ikonomidou. I'm a child neurologist from Madison, Wisconsin, University of Wisconsin.

DR. SCHREINER: I'm Mark Schreiner. I'm Associate Professor of Anesthesia and Pediatrics at Children's Hospital Philadelphia, University of Pennsylvania.

DR. TOBIN: I'm Joe Tobin, the Chairman of Anesthesiology at Wake Forest and immediate past president, Society for Pediatric Anesthesia, and consultant to the committee.

DR. WEINSTEIN: I'm Steve Weinstein. I'm a Professor of Neurology and Pediatrics at Weill Cornell Medical College.

DR. NEWSCHAFFER: Good morning. I'm Craig Newschaffer. I'm professor and chair of Epidemiology and Biostatistics at Drexel University in Philadelphia.

DR. JEVTOVIC-TODOROVIC: Vesna Todorovic, anesthesiologist from University of Virginia.

DR. SUSSER: Ezra Susser, Columbia University, Professor of Epidemiology and

Psychiatry, direct the imprint center for genetic and environmental life course studies.

DR. SORIANO: Sul Soriano, pediatric anesthesiologist at Children's Hospital Boston, and Professor of Anesthesia at the Harvard Medical School.

DR. NOTTERMAN: I'm Dan Notterman. I'm a pediatric intensivist, Professor of Pediatrics and Molecular Biology at Penn State.

DR. MARTIN: I'm Lynn Martin. I'm a professor of Anesthesia and Pain Medicine at the University of Washington, department director at Seattle Children's Hospital, and the president for the Society for Pediatric Anesthesia.

DR. KON: I'm Alex Kon. I'm a pediatric intensivist at the Naval Medical Center in San Diego, and I've also done quite a bit of work in pediatric ethics.

DR. CLANCY: I'm Barbara Clancy. I'm associate professor at the University of Central Arkansas.

DR. FLICK: Randall Flick, associate

professor of Anesthesiology and Pediatrics, Mayo Clinic.

DR. ADAMS: Jane Adams, Professor of Psychology, University of Massachusetts-Boston.

DR. KIRSCH: I'm Jeff Kirsch. I'm the chair of the Department of Anesthesiology at Oregon Health Sciences and associate dean for Clinical and Veterans' Affairs.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm with the Division of Advisory Committee Consultants Management.

DR. INDER: I'm Terrie Inder. I'm a professor in Pediatrics, Neurology and Radiology at Washington University in St. Louis. I'm clinically a neonatologist and a child neurologist by practice.

DR. THURM: I'm Audrey Thurm. I'm a child clinical psychologist and a staff scientist at the National Institute of Mental Health.

DR. DIEKEMA: I'm Doug Diekema. I'm a pediatric bioethicist at Seattle Children's Hospital, where I also practice pediatric emergency

medicine.

DR. MAJUMDER: I'm Mary Majumder. I'm the acting consumer representative, and I'm from Baylor College of Medicine.

DR. SWISHER: I'm Lois Swisher. I'm an emergency medicine physician. But my daughter had a variety of medical issues. She was 1 pound 2 ounces at birth and then at 5, she had a malignant brain tumor and has a variety of anesthesia and sedation procedures in her history.

DR. PAULE: Merle Paule, director of the Division of Neurotoxicology at the National Center for Toxicological Research, FDA.

DR. MELLON: Dan Mellon, pharmacology/toxicology supervisor for the Division of Anesthesia and Analgesia Products, CDER, FDA.

DR. SIMONE: Arthur Simone, medical officer, Division of Anesthesia and Analgesia Products at the Center for Drug Evaluation and Research, FDA.

DR. ROCA: Rigo Roca, deputy division director in the Division of Anesthesia and Analgesia Products, FDA.

DR. RAPPAPORT: Bob Rappaport, director of the Division of Anesthesia and Analgesia, FDA.

DR. KIRSCH: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only when recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about the

proceedings. However, FDA will refrain from discussing the details of this meeting and with the media until its conclusion.

For the convenience of the media representatives, I would like to identify the FDA press contact, Jeff Ventura. If you are present, please stand.

There he is in the back. Okay.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you. I'll pass it to Kalyani, who will read the conflict of interest statement.

Conflict of Interest Statement

MS. BHATT: The Food and Drug Administration, FDA, is convening today's meeting of the Anesthetic and Life Support Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government

employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special

government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of updates regarding neurodegenerative findings, findings related to degeneration in the nervous system, in juvenile animals exposed to anesthetic drugs, as well as to be provided with the results from human epidemiological studies using anesthesia in children; information related to studies of pattern causes of diseases; the relevance of these

1 findings to pediatric patients; and, provide
2 guidance for future preclinical and clinical
3 studies; and, three, the potential implications of
4 these data upon the practice of pediatric
5 anesthesia, as well as communication of the risks
6 of sedative anesthetic agents to prescribers and
7 parents.
8 This is a particular matters meeting during
9 which general issues will be discussed.
10 Based on the agenda for today's meeting and
11 all financial interests reported by the committee
12 members and temporary voting members, no conflict
13 of interest waivers have been issued in connection
14 with this meeting.
15 To ensure transparency, we encourage all
16 standing committee members and temporary voting
17 members to disclose any public statements that they
18 have made concerning the issues before the
19 committee.
20 With respect to FDA's invited industry
21 representative, we would like to disclose that
22 Dr. Bartholomew Tortella is participating in this

meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Tortella's role at this meeting is to represent industry in general and not any particular company. Dr. Tortella is employed by Pfizer, Incorporated.

We'd like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. KIRSCH: Thank you. Our first speaker is Dr. Rappaport.

Welcome and Introduction

DR. RAPPAPORT: Good morning, Chairman Kirsch, members of the committee, invited guests. Thank you for joining us today as we address a

public health matter of considerable importance to the medical community and to the parents of children undergoing anesthesia and sedation for medical, surgical and diagnostic procedures.

In March of 2007, we held the first meeting of the committee to discuss the neurotoxicity seen in juvenile animals exposed to certain anesthetic and sedative drugs and the implications for pediatric patients.

At that time, the first report of neurotoxicity in juvenile monkeys exposed to ketamine in vivo had been published by our FDA colleagues at the National Center for Toxicological Research. We also published an article that summarized the data that was available at that time and called upon the anesthesia community to pursue the necessary research to understand the implications of the animal findings for children.

After hearing presentations from the leading researchers in the field, this committee called for a research agenda and concluded that there was insufficient data to determine whether any of the

1 animal findings could be extrapolated to the
2 setting of pediatric anesthesia. However, the
3 members did recommend that elective surgery in
4 children 3 years of age and younger be deferred
5 whenever possible.
6 There have been numerous additional animal
7 studies conducted since that time and some clinical
8 studies, mostly epidemiological in design, have
9 been undertaken as well. A recent study published
10 by Dr. Paule and colleagues at NCTR demonstrated
11 long-lasting deficits in brain function in monkeys
12 that were exposed to a single 24-hour episode of
13 ketamine anesthesia, occurring during a sensitive
14 period of brain development.
15 But the results of other recent animal
16 studies suggest ketamine and dexmedetomidine may
17 mitigate the neurotoxicities seen following
18 cerebral ischemia and reperfusion, and after
19 repeated painful stimulation in newborns.
20 While some of the epidemiological studies
21 that have been published found learning and
22 behavioral abnormalities in children who had

1 undergone multiple surgical procedures requiring
2 general anesthesia, clearly, there are numerous
3 confounding factors that cannot be fully addressed
4 in epidemiological studies, and other studies have
5 not shown any differences in specific educational
6 outcomes between children exposed to anesthetics
7 and matched controls.
8 It's important to note that at this time,
9 there is no conclusive evidence that would link
10 exposure to anesthetic or sedative drugs in early
11 childhood to neurotoxicity or neurodevelopmental
12 abnormalities. Clearly, additional work will be
13 necessary to further explore the many unanswered
14 questions raised by the animal findings.
15 The vast majority of these drugs were
16 approved decades ago, long before studies
17 demonstrated safety, efficacy and appropriate
18 dosing in pediatric patients were required. And
19 clearly, their use is not optional in most
20 situations. Clinicians only perform procedures
21 requiring anesthesia or sedation when they are
22 necessary for a child's health and wellbeing; and,

the procedures cannot be undertaken without these drugs, as they are essential both for the child's safety and comfort.

Pain itself can result in neuronal abnormalities and behavioral disorders in infants and young children who receive inadequate analgesia, and it would be unethical to allow a child to undergo a frightening medical procedure without adequate sedation.

Today we are going to hear from experts in this field who have a variety of perspectives on the animal data, the epidemiological data, and the implications of these data for the practice of pediatric anesthesia. We will then be asking you to consider the available data, suggest a research agenda, and discuss the most appropriate level of risk communication.

As many of you know, under the FDA's critical path initiative, we have entered into a public-private partnership with the International Anesthesia Research Society, named Strategies for Mitigating Anesthesia-Related Neurotoxicity in

Tots, or SmartTots.

The primary goals of the SmartTots partnership are to bring together all of the many stakeholders from academia, government, industry, and patient advocacy organizations to address the scientific and clinical research gaps and to find the best minds to conduct that future research and raise the funds necessary to see that research through to completion.

Your recommendations regarding where to focus future research will be an important complement to the work that the IARS will be undertaking as they develop their research agenda for the SmartTots initiative. We greatly appreciate your participation today and look forward to hearing your discussion and recommendations.

DR. KIRSCH: Thank you, Dr. Rappaport. Before we go on to the next part of the agenda, I'd like to introduce Dr. Zuppa. Go ahead and introduce yourself.

DR. ZUPPA: Good morning.

DR. KIRSCH: You've got to say where you're from.

DR. ZUPPA: Sorry about that. It's a long ride from Philly. My name is Athena Zuppa. I am a pediatric critical care doctor and clinical pharmacologist at the Children's Hospital Philadelphia.

DR. KIRSCH: Thank you. Next, we'll ask Dr. Mellon to come up.

Presentation - Daniel Mellon

DR. MELLON: Good morning. My task this morning is to try to provide you with a whirlwind tour of the nonclinical information, focusing primarily on information that has been generated since the 2007 ALSDAC Committee meeting.

In order to put those data into perspective, I will be providing you with a broad overview of some of the key findings that led up to the initiation of the 2000 meeting and to try to put the findings into a more broader picture.

I will acknowledge that there is a tremendous amount of research that has taken place

on this particular subject, so I will not be able to go into extensive detail in terms of all of the publications. However, I do think that we will be able to provide some insights into this particularly challenging topic.

So the story for the Food and Drug Administration actually was initiated with the publication of a paper in Science from the laboratory of Dr. John Olney, who is here with us today. This particular publication, first authored by Dr. Ikonomidou, who is also fortunately with us here today, was able to start looking at the impact of the glutamatergic system on brain development, and specifically they were looking at the impact of NMDA receptor antagonists on the developing brain during a critical period of brain development, typically referred to as synaptogenic period.

The model that they were utilizing was a postnatal day 7 rat model, and the drug that was the predominant compound utilized to try to understand this particular phenomena was a drug called MK-801. MK-801 is an NMDA receptor

antagonist. It's a very potent NMDA receptor antagonist. It is not approved for use in humans. However, it was actually under investigation for a while for its potential utility in terms of trying to prevent stroke-induced ischemic neurotoxicity.

The data that we will look at, and I'm sure many of you have seen this particular slide before, is actually a coronal section of the rat brain. And you'll have to forgive me, I can only point to one of these screens. I can't point to all of them. So I will try to use the front one.

The panel on the left is actually a coronal section from the rat brain of a saline-treated animal. And what we can see here is that this particular brain slice is actually stained using the tunnel method, which is a method to try to evaluate the effects -- or to look for cells that are undergoing apoptosis.

What we can see, to orient you, in case you're not as familiar looking at rat brain slices as you are human brain images, this is actually the cortical regions of the brain. There's the very

pretty picture of the hippocampus. And you can see that using the tunnel staining method, there is a light black stippling pattern within this particular region. That is not uncommon, actually, because as it turns out, during this rapid period of brain growth, there are certain neurons that are actually eliminated because they're not deemed necessary. So it is not too surprising to see that there is a little bit of light stippling pattern in the control animals.

What was remarkable about this particular image is the panel on the right, and that is the animals that were treated with MK-801. Now, you can see the much darker areas that are actually cells that are undergoing degeneration and apoptosis. And these particular cells are actually found throughout the regions of the brain, including the hippocampus and the cortical regions.

What was of note of this particular publication is that the studies also utilized a drug that is approved for use in humans, and that is ketamine. The dosing administration was 20

milligram per kilogram, a total of seven different injections spaced over 90 minutes in order to try to provide a more prolonged exposure to this particular anesthetic. And the paper reported that very similar results were obtained utilizing ketamine.

The agency actually became aware of this particular publication in the context of looking at a protocol that was submitted to try and understand and obtain pharmacokinetic data in pediatric patient populations. And in order to try to better understand the potential implications of this particular finding, the agency repeated the studies. And in fact the goal was to repeat them and provide some additional information in order to try to obtain exposure levels in these particular animals to try to put the pharmacokinetics, to some extent, into comparison with the pharmacokinetics associated with when ketamine is utilized in children and to also try to identify a no adverse effect level, if you could, a dose that does not produce this type of phenomenon.

So in this particular chart, we've actually been able to extrapolate, to some extent, try to put these findings into perspective.

So the regimen that was initially studied was the exact same regimen that was reported in the Ikonomidou paper, and it is 20 milligram per kilogram of ketamine, seven injections.

Certainly, in this particular publication, which was studies conducted by CDER, with some input from our colleagues at NCTR, we were able to reproduce the findings that were reported in terms of the evidence of neuroapoptosis. And measuring the plasma levels in those animals shortly after the last injection provided information that the exposure levels that were obtained were actually about sevenfold higher than the levels that had been reported in the literature of ketamine that are necessary to produce actually an anesthetic state consistent for use in major surgery, which is about 2 microgram per mL.

So this is really a worst case scenario with ketamine as a sole anesthetic agent. What was

interesting about the study, as well, is that the same regimen, seven different injections, but only a 10 milligram per kilogram dose of ketamine, did not actually produce evidence of increased apoptosis. The exposure levels in these particular animals were approximately equivalent to that 2 microgram per mL, suggesting that the use at comparable levels, at least within this model, did not necessarily produce evidence of apoptosis.

Looking at a single dose of ketamine that was not actually repeated, so a shorter duration of exposure, actually also did not produce evidence of neuroapoptosis, and the plasma levels that were present shortly after that last injection were about threefold higher than that 2 microgram per mL.

The group in Dr. Olney's laboratory has been doing considerable work to try to understand the impact of various exogenous compounds on brain development, and one of the areas where they have been contributing to the science is actually in the field of fetal alcohol syndrome.

These particular authors also noted that ethanol, which actually happens to be an NMDA receptor antagonist, as well as a drug that potentiates GABAergic systems, is well known to have impact on brain development, with the ultimate phenotype being the fetal alcohol syndrome.

In this particular publication in Science in 2000, they were able to compare the effect of ethanol with MK-801, again, that NMDA receptor antagonist, as well as phenobarbital, which is a drug that has the ability to potentiate GABAergic systems, a barbiturate. There is actually some data in this paper, as well, utilizing diazepam, which is a benzodiazepine.

Look at the information that came out of this particular paper, and if you look at the top panel, you will see that it actually looks very similar to the slide that we just looked at. This is MK-801 and the darker stippling pattern suggests that there are a large number of cells that are undergoing apoptosis. This actually is with a silver stain, so it's more of a basic degeneration

stain. But nonetheless, there are cells that are undergoing neurodegeneration within the exposures to MK-801.

In panel C, you actually see the effects of phenobarbital. And so clearly there are a large number of neurons and cells within this brain slice that are indicating that they are undergoing apoptosis.

What's interesting is that the pattern of the darker areas is actually very different between the GABAergic drug, phenobarbital, and the MK-801 drug. Then if you look at the effects of ethanol, you see a broader region of cells undergoing neurodegeneration that actually, if you looked at the two and you compared them, some of these regions actually start to overlap, suggesting that perhaps ethanol is having its effect by modification of both of those transmitter systems.

This is actually illustrated even more distinctly in the anterior thalamus, where again this is the control slice. This is the area of MK-801, and you can see the darker regions of cells

that are undergoing neurodegenerative changes.

Phenobarbital actually has a slightly different region within this particular portion of the brain undergoing degeneration. Then if you look at the ethanol, you see that they actually overlap. You can pretty much take this slice, this slice, overlap it, and get that one.

So clearly what's happening here is that we're seeing that several different neurotransmitter systems that upon activation or blockade will actually result in evidence of degenerative changes in the brain.

What's interesting about this publication as well is that they were looking at that window of vulnerability to this particular phenomena. So to orient you, again, this is actually data with ethanol. On the X-axis, we see the developmental age. So this is from embryonic day 17 out to postnatal day 21 in the rat. And the publication actually broke down the regions of the brain based upon, in part, the time periods during that brain growth spurt within the rat, which is believed to

be from embryonic 17 and birth out to about postnatal day 14, to see where the structures may have been more susceptible during that time period.

You can see that in the cells that are deemed -- the group of structures that are more susceptible in the early phases of that brain development period include structures such as the ventral medial hypothalamus and the ventral thalamus.

Cells that were in different regions of the brain seemed to be more susceptible in terms of the middle portion of that brain growth spurt within this region, and that includes some areas within the hippocampus. And then regions of the brain that are more susceptible later during the brain development period in these animals were actually some of the more cortical structures, and you can see that those actually peak at around postnatal day 7.

But for the most part, you can actually see that most of the neurodegenerative changes that were noted were pretty much gone by postnatal

day 14. There are still some effects, but, clearly, the broadest area of vulnerability is within that first 14-day period.

The next paper that actually raised a lot of concerns and questions was actually a publication in collaboration with Dr. Olney's lab from Dr. Vesna Jevtovic-Todorovic, and she was actually publishing in 2003 a study that looked at a common anesthetic regimen, a combination of drugs.

As we know, anesthetics are rarely used in isolation, and thus this particular study was designed to try to mimic that cocktail and the use of nitrous oxide, which is an NMDA receptor antagonist, isoflurane, which is a GABAergic potentiating drug, and midazolam, which also has GABAergic properties as a benzodiazepine.

Again, this is in a neonatal rat model at postnatal day 7, a 6-hour exposure worth of anesthesia. The real unique aspect of this particular paper is, in part, the behavioral testing that was conducted in animals that were allowed to mature.

The histopathology looks very much like the histopathology that we just looked at, but I'd like to focus the attention on one of the behavioral paradigms that were tested in this particular study, and that's the Morris water maze results.

Now, for those of you who may not be familiar with this particular assay, I tried to include a diagram here to help orient you to how this study is actually conducted.

This is actually a large pool of water. And if you place a rat in a pool of water, they will swim around and seek ways to try to get out and escape from that water. The way that the assay is done, there's actually a submerged platform that will allow -- that once the rat finds that platform, they were able to get up and get out of the water, which certainly most of us would try to do if we were thrown into a pool of water as well.

But the unique aspect of this particular paradigm is that you can actually make the water opaque by putting in powdered milk, so that you can't see that submerged platform. So the animal

actually needs to learn where that platform is located, and they do that by orienting themselves to external cues. There are various external cues surrounding this particular pool. And you can actually measure and quantitate how well the animal performs in learning where that platform is by including a video camera above and actually measuring the distance that the animal swims in terms of being able to obtain and find that submerged platform.

You could almost think of analogous situation of where you park your car in the parking lot outside of the mall, and if you park in the same place all the time, you generally have a faster pace to get to that particular car. But if you don't park in the same place all the time, sometimes we find ourselves roaming around looking for the car.

So what this particular diagram actually illustrates is the distance that the animals traversed in order to obtain and reach that platform. And as the animals are exposed to this

paradigm over and over, what you can see -- and the control animals here actually were treated with DMSO as the vehicle for midazolam that was used in the darker areas. And the first few times that the animals were exposed to this, they traveled a certain distance in order to find that platform. But eventually they figured out where it was and that distance was shortened tremendously, in order to be able to locate where that was by using the cues surrounding them. So they learned where that platform was.

What's interesting about the study is that the animals that were exposed to an anesthetic cocktail actually did not quite find that platform and learn where that platform was as rapidly as their control counterparts. So that they fell behind, to some extent in their ability to complete and learn this task, although initially -- and these are animals that were at postnatal day 32, after, of course, their exposure at postnatal day 7. Eventually, those animals did catch up and performed comparably to the animals in their

control group.

Further studies were actually conducted, and the submerged platform was moved to see whether or not at postnatal day 131, the animals were able to perform as well within this task. And what this particular diagram illustrates is that the control animals performed at a fairly reasonable level. The animals who were exposed to the anesthetic regimen back at postnatal day 7 did not quite perform as well within this task.

To see whether or not they were able to eventually catch up again, as they did earlier, the training sessions were extended out for almost 10 days. And what was interesting is that the animals never did appear to really catch up in this particular study.

So the functional consequences of the histopathological changes that were reported with this particular drugs actually was illustrated in this and several other studies, which is part of the reason why this paper actually drew quite a bit of attention.

So trying to translate the timeframe and that window of vulnerability in the rat to the human is a challenging task, and Dr. Clancy will be providing some insights into some newer methods to try to gain insight into that.

But one of the biggest challenges and questions that were raised by this growing body of animal data was the knowledge that the rat brain actually develops in a fairly short window. That brain development is believed to occur from approximately birth to about postnatal day 14. And so that's a shorter window.

So one of the questions that was raised about these findings was, well, perhaps the exposure to the anesthetic agents took up such a larger portion of that 14-day period that it was really not mimicking what would happen, since the human brain develops over a much more broader timeframe.

Our understanding, based upon crude brain weight and assessments in the human brain, that period of rapid brain growth in the human is

1 believed to occur largely within the third
2 trimester out to approximately 3 years of age. So
3 one way to try to put the rat data into perspective
4 is to repeat some of these observations utilizing a
5 nonhuman primate model. And so the National Center
6 for Toxicological Research, in conjunction with
7 CDER, actually undertook events to try to
8 characterize it in the rhesus monkey.
9 Understanding that the monkey brain
10 development, based upon several pieces of
11 information, are believed to -- that the brain
12 development is really occurring, again, within that
13 third trimester and slightly before, in terms of
14 the primate brain, out to about two months. So
15 it's a much more extended developmental period, and
16 such that a certain amount of anesthetic exposure
17 may represent only a smaller fraction of that
18 development.
19 Prior to and shortly before the meeting in
20 2007 was a publication that came out of that, which
21 were the first histopathological evaluations in
22 primates. And Drs. Slikker, Paule and Cheng Wang

and their colleagues at NCTR conducted studies using a rhesus monkey model. They utilized the NMDA receptor antagonist ketamine at a dose which was given IV for approximately 24 hours at a dose which was able to maintain a light plane of anesthesia.

The animals were not exposed to any type of surgical procedure, but nonetheless, they were infused with ketamine during this time period. They were dosed at three different time periods of development. The moms were actually dosed in their third trimester at gestation day 122; and in the primate, the full gestational period is about 165 days. So this is within that third trimester, if you would. And then the offspring were actually exposed as well on postnatal day 5 and postnatal day 35 to this 24-hour exposure to ketamine.

An additional group of animals who were 5 days old were actually exposed to a shorter exposure period of ketamine, about three hours. Now, the doses of ketamine that were necessary in order to maintain this anesthetic plane were about

20 to 50 milligram per kilogram per hour. Now, it's interesting that the postnatal day 35 animals actually required larger exposures to ketamine in order to maintain that same anesthetic plane.

So the next diagram here is actually an image to quantitate the cells that are undergoing degeneration and that were evaluated histopathologically, and this is utilizing a Fluoro-Jade stain, which is not specific for apoptosis but can pick up cells that are undergoing apoptosis, as well as necrosis.

What this diagram actually shows is that the animals who were exposed in utero at gestational day 122 for that 24-hour exposure to ketamine actually had an increased incidence of cells undergoing degeneration. They also conducted studies using caspase-3, which is a specific marker for apoptosis, and the image pretty much looks the same as these here.

The animals that were exposed at postnatal day 5 for that 24-hour exposure period also had an increased incidence of cells undergoing

degeneration. What's also interesting about this particular study is that when they were exposed after postnatal day 35 for even the same 24-hour exposure period, they did not have increased evidence of apoptosis. And the animals that were exposed for only that 3-hour period also did not show any evidence of enhanced apoptosis.

So undertaking the same exercise to try to determine what these exposure levels were, because pharmacokinetic information was obtained in these animals, we can actually try to put these data into perspective, again, comparing it to that worst case scenario of about 2 microgram per mL dose of -- or plasma levels of ketamine that are necessary for the human neonate.

The plasma levels that were noted here, we can look at the postnatal day 5 animals and the gestational day 122 animals, where there was evidence of enhanced neurodegeneration, we actually see that the plasma levels were about 10 to 15 microgram per mL.

This actually, again comparing to 2,

provides a pharmacokinetic exposure of about five to sevenfold over what a human neonate would be exposed to under the same type of scenario. But what's interesting is that from a pharmacodynamic perspective, this actually is the dose that's necessary to produce that same level of anesthesia. So from a pharmacodynamic exposure margin, it's really equivocal.

The animals that did not show evidence of enhanced neurodegeneration included the 24-hour exposure at postnatal day 35, and as indicated, it actually took about 25 microgram per mL levels of ketamine in order to actually maintain that level, which would be, from a pharmacokinetic perspective, about 12-fold higher in the human, but certainly, again, equivocal to the dose that's actually necessary to produce that anesthetic state.

The postnatal day 5 animals were about 12 microgram per mL with the 3-hour exposure regimen, which did not show evidence of apoptosis. That's about sixfold higher than the levels that are necessary in the human, but, again, about

equivocal in terms of the pharmacodynamic endpoints.

So knowing that the histopathology data in the primate was actually showing that and reinforcing some of the findings that have been reported in the rodents, the agency felt it important to try to summarize some of the information that it was accumulating to date and, in large part, these findings were what we felt was necessary in order to gather this particular committee together to have this conversation, very similar to the one we're having today.

In this particular publication that was published in Anesthesia and Analgesia, we noted that this really was a communication to help open the dialogue with the anesthesia community to try to address this particular issue.

The document also notes that there is a lack of information to date that early precludes our ability to say that any one particular anesthetic agent or regimen was safer than any other, but we anticipate further working with the anesthesia

1 community and the pharmaceutical industry to
2 develop strategies to try to assess this and the
3 impact of anesthetics in neonates and young
4 children, and ultimately to try to provide data to
5 help guide clinicians in interpreting the
6 nonclinical studies and in their abilities and the
7 challenges that they have to try to make the most
8 informed decisions possible when choosing
9 anesthetic regimens in pediatric patients.
10 In large part, this was a call to open up
11 that dialogue even further, and, as a result, when
12 we discussed all of these findings in 2007, as
13 Dr. Rappaport indicated, one of the discussion
14 items was the question, "Are there sufficient data
15 to apply the findings in animals to humans?"
16 Based upon the information that we just
17 described, in large part, 14 out of the 15 voting
18 members responded no. The one individual who did
19 not respond no actually felt that with ketamine at
20 least, there was a pretty significant amount of
21 information to help try to apply that to humans;
22 but for any other compound or for combinations,

that the answer was still no. However, all of them agreed that the data were worrisome and that more studies were needed, and that this really should be deemed a high priority issue.

So at this point, what I'd like to do is talk about some of the studies from a very high level that have been published since then. And as you can imagine, the ALSDAC committee meeting in 2007, as well as the publication of the document in Anesthesia and Analgesia, and Dr. Slikker's work in the primate, actually sparked a tremendous amount of additional research in this particular area. And there are some very interesting findings that have come out of that research that we feel are very important and contribute to our particular discussion today.

These are in no particular order, so don't assume that these mean that some of them have any particular differential level of concern. Nonetheless, the first finding that I think we will be discussing, and this will be presented in far more detail by Dr. Merle Paule in the subsequent

discussion, are the data that have come out of the functional studies in primates. At that point in 2007, we only had histopathological data.

We had none of those long-term behavioral assessments that were described in the studies conducted in Dr. Todorovic's laboratory. So those data actually have recently been published and Dr. Paule will present that information to you.

As you look at that data, I do ask that you think about how that data compares to the information that we have seen to date in the rodent, and we only looked a little bit at it this morning, and to think about those data also in the context of some of the clinical information that is coming to light as well as we start to explore this particular challenge. And Dr. Simone later this morning will present some of that information to you.

I do think it's very important to also think about which endpoint is actually the most sensitive endpoint. When we think of risk assessment, we really think of trying to identify the adverse

consequences at the lowest doses, and it is actually a challenge right now to be able to say whether or not the histopathological findings or the functional changes actually show greater sensitivity, which is a unique challenge to the field.

The second finding that I'm not going to go into in great detail today, because we are fortunate enough to have Dr. Olney here to present those findings, are some work that's coming out of his laboratory that suggests that in addition to neuronal apoptosis, there appears to be evidence that immature oligodendrocytes are also susceptible to anesthesia-induced apoptosis. Dr. Olney will present this information.

As you look at that data, we need to ask ourselves some questions. Do the oligodendrocyte data actually have the same window of vulnerability as what we have looked at in terms of neuronal damage? What are really the long-term clinical implications, if any, of these particular findings? And if there are implications, what clinical

endpoints should we look for and when would we actually expect to see them?

A third finding -- and, again, I'm kind of breaking these into larger picture subjects -- are interesting studies that have looked at synaptic architecture. So instead of looking at neuronal apoptosis or neuronal necrosis, looking at more subtle changes within the brain, and there are several publications that have started to contribute to this particular arena.

What's interesting is that they're looking at a slightly delayed time period compared to what we've been looking at in terms of the apoptosis. So we'll look at a little bit of data from the laboratories of DeRoo and Briner, that have actually looked at postnatal day 15 and 20 anesthesia exposure and are looking at the architecture of the neurons within the brain to see whether or not the anesthetics could actually have some impact on some of these particular effects in terms of development.

The significance of these findings are not

exactly clear at this point of time, but one of the questions that we need to ask is, "Do these data actually broaden our perceived window of vulnerability in terms of overall brain development?" And even a bigger question, "Are these findings adverse or are they adaptive," and understanding what the implications are is very challenging.

So we're going to look at a little bit of those data, and I'm going to show you some images from the paper published by DeRoo and colleagues. This is a group in Switzerland.

Their particular model and their objective here is to try to understand really what the impact is on the synaptic growth. We discuss this vulnerable period as the brain growth spurt or the period of synaptogenesis. This is a period when the brain is growing, because new connections are being formed. Neurons are gaining connections with other neurons. They're establishing the neuronal circuitry. And to be able to try to understand what impacts anesthetics may have in this

1 particular model, they actually utilize an
2 interesting model in mice that were expressing
3 yellow fluorescent protein specifically in layers
4 5B of cortical neurons.
5 The exposure periods were at postnatal day
6 15, 20 and 30, again, outside of that previously
7 perceived window of vulnerability for apoptotic and
8 neurodegenerative changes. They looked at the
9 compounds midazolam and propofol, which have
10 GABAergic properties; ketamine, which is an NMDA
11 receptor antagonist, as we know; and, they utilized
12 doses that were appropriate in order to provide
13 deep sedation in those particular animals for about
14 approximately five hours.
15 So some of the findings -- and we can only
16 look at some of them today, but what this image is
17 here and on the left in panel A is actually a
18 three-dimensional volume rendering based upon
19 images obtained via confocal microscopy to look at
20 the dendrites of neurons within the somatosensory
21 cortex.
22 As we know, neurons communicate with other

neurons via synapses that come through that dendritic tree that is formed and allows the neurons to actually receive communication from other regions of the brain. And what this renditioning actually illustrates is that in the saline-treated animals, you can see these dendritic protrusions, and these are areas where potentially other neurons can synapse and form communication patterns with this particular neuron.

When the animals were exposed to either propofol or ketamine, what was interesting is that when you looked at postnatal day 15 and postnatal day 20, there actually was a greater number of dendritic protrusions, suggesting that the exposure to the anesthetic actually altered the dendritic tree to some extent, that would allow potentially the formation of new neuronal connections.

So these particular findings were quantified basically based upon protrusions per micron, and both drugs at postnatal day 15 and 20, when there was no evidence of apoptosis, actually led to alterations in synaptic architecture.

So these findings actually are much more subtle changes, but also we need to think about it in the context of do they actually change our perceived window of vulnerability; how do these particular time periods in the rodent compare to human brain development, which is a very challenging question.

So I'd like to shift to another subject, which I have described as neurogenesis, and there are some interesting studies in the literature that have actually tried to look at the impact on the formation of new neurons in the brain; again, looking at additional endpoints.

This particular diagram, which I borrowed from the Internet, actually describes the fact that in that brain growth spurt, new neurons are formed and new cells are formed within the brain from stem cells that ultimately differentiate into oligodendrocytes, astrocytes, and neurons.

One way to try to look at the effect of anesthetics on the formation of new neurons is to do what is very much equivalent to a proliferation

assay. And the study that I'm going to show you a little bit of information from is published from a group in Sweden just last year looking at isoflurane anesthesia.

What was interesting from this study is that they were actually utilizing, again, a postnatal day 14 animal, a time period where you would not expect to see apoptosis, and were comparing that to animals that had actually aged and following exposure at postnatal day 60, and I'll show you a diagram of the dosing regimen. They were using isoflurane, an exposure of only 35 minutes per day for four days, and started looking at some additional endpoints in this particular paradigm.

So the top panel here actually describes the dosing regimen. So the way they measured proliferation, very much akin to the older method using tritiated thymidine, which is of course still used today, but utilizing BRDU, which is a means to actually establish the cells that are proliferating, they dosed the animals with BRDU at day 14, 15, 16 and 17 or postnatal day 60, 61, 62

and 63. The isoflurane, as we indicated, were just a 35-minute exposure per day over that time period, and they were able to measure the amount of proliferation that was taking place in the brain.

So in this particular panel, which we've labeled "proliferation," what it illustrates is that looking at the BRDU labeled cells, that the exposure to isoflurane actually reduced the level of proliferation in the animals that the exposures were initiated at postnatal day 14. This effect was not noted in the more adult animals.

To try to understand which cells are actually proliferating, they co-labeled the cells with NEUN, which is a marker for neurons, and were able to show that actually it was neurons that were not proliferating in this particular -- in various regions of the brain following exposure to isoflurane compared to the control treated animals.

There actually was a subtle effect as well in the older animals, and this actually does suggest that even at this age, there is some level of proliferation, and there was a slight subtle

change that was at least statistically significant in this particular diagram here.

An interesting aspect in this paper as well is that in contrast to neurons, astrocytes actually appeared to be increasing in terms of proliferation, utilizing a specific marker for astrocytes. Again, this phenomena was also evident in the animals that were aged out to 60 years.

So it suggests that exposure to the anesthetics could have impacts beyond that initial period of apoptosis.

What was interesting as well in this paper is that they actually tried to use some specific markers to try to identify and detect neuronal stem cells, and this is particularly within the granule cell layer of the hippocampus. And although neurogenesis largely occurs during the brain growth spurt, there are regions of the brain that actually have neurogenesis taking place even in adulthood. One of those regions is the hippocampus.

What's interesting about these findings is that the exposure to isoflurane appeared to reduce

the number of stem cells within this particular region more predominantly when exposed here during this particular time period, and no effect was actually noted on that population of cells that were older.

So, again, different endpoints, additional endpoints giving us more information regarding what types of impact anesthetics may potentially have in developing brain.

I'll shift to what I refer to as finding number 5, and that's spinal neurons. There have been several publications who, in addition to some of the high regions of the CNS, have looked at the spinal column to see whether or not exposure to anesthetics actually led to changes within those regions as well.

A study by Sanders, et al., actually reported that an exposure systemically to isoflurane and nitrous oxide actually increased neuroapoptosis within the dorsal horn of the spinal column. And there were two papers that were recently published coming out of Tony Yaksh's lab

1 looking at the spinal administration of drugs.
2 They compared both ketamine and a separate study
3 looked at morphine, and they actually noted and
4 reported that spinal administration of ketamine in
5 neonatal rats was able to demonstrate evidence of
6 neurotoxicity with the ketamine, but they did not
7 see evidence of neurotoxicity following
8 administration of morphine, which is certainly a
9 very interesting finding.
10 There are some limited functional data that
11 exist in these manuscripts, but certainly the
12 impact of a reduced number of neurons within the
13 dorsal horn does make us wonder, do these
14 particular cells follow the same window of
15 vulnerability. The early data actually suggests
16 that this is earlier, at around postnatal day 3,
17 where, at least in terms of ketamine,
18 susceptibility seems to be showing up, which is
19 consistent with the data that we saw with ethanol,
20 that different regions of the brain have different
21 windows of vulnerability.
22 Certainly, we need to ask ourselves the

1 question, do we actually have any data with local
2 anesthetics utilizing this particular spinal model,
3 and I'm not aware of any studies that have actually
4 done that. Certainly, there are data that suggest
5 that some of the anticonvulsant compounds, which
6 are sodium channel blockers, also can contribute to
7 neuronal degeneration, but certainly we've never
8 really looked to see whether or not there's any
9 evidence about local anesthetics, which are also
10 sodium channel blockers.
11 The effect of pain is a very big question,
12 and Dr. Anand will provide you with a lot more
13 information on this. So I'm not going to go into
14 great details. But Dr. Anand will be able to show
15 you some data that suggests that an analgesic dose
16 of ketamine actually blocks pain-induced
17 neuroapoptosis.
18 So we need to ask ourselves the question,
19 "Would an anesthetic dose produce the same
20 response?" Most of the animal models that have
21 been reported to date really have not incorporated
22 either a painful stimulus or an adverse stimulus in

order to see what the interaction is in those particular phenomena on brain development.

There is at least one paper by Dr. Stratmann, et al., who had looked at a tail clamped method in the rat model in order to maintain a painful stimulus throughout the procedure and establish the dose that was necessary in order to maintain that anesthesia, although in that paper, they actually still reported some long-term cognitive defects. So clearly that is an area of further research that would be useful.

Are there better options? There are actually studies in the literature that suggest that dexmedetomidine, which is an alpha-2 agonist and approved for a sedative agent in adults, did not produce neuroapoptosis in the brain.

There are data reported in Rizzi, et al., in a guinea pig model with fentanyl that suggests that the fentanyl did not produce anywhere near the type of changes that were noted with isoflurane. And morphine has also been reported to not produce these responses.

There are publications in the literature that are starting to suggest and compare two different drug regimens. One that we'll look at in just a second compares isoflurane to sevoflurane, and Dr. Olney will actually show you some data comparing ketamine and propofol to isoflurane. So there are some suggestions in the nonclinical world that suggest that perhaps all of these compounds do not necessarily behave in the same way.

Will these findings be observed in primates? Should they be repeated in primates? What would the impact of these findings be in terms of trying to understand how to utilize these compounds in the most effective way? Certainly questions for discussion this afternoon.

I do want to note that there are reports of opioids having different effects on neuronal development in the literature. Dr. Anand is very familiar with these data as well, including the effect that exposure to opioids early on in life may change your susceptibility to pain later on, at least in animal models, and may actually change

your sensitivity to opioid administration later on in adulthood.

So when we say that the opioids do not necessarily produce neuroapoptosis, that's just that one endpoint. So I do think we need to keep that picture in mind, as well.

These are the data with sevoflurane, and this particular group was actually trying to maintain a .5 MAC level of sedation. And they actually noted that with that same level of sedation, the isoflurane treated animals actually had much higher levels of cells undergoing apoptosis as measured by caspase-3 compared to sevoflurane, which I think is one piece of information that's providing us with some additional insights.

The final topic that I'd like to bring up is there are a lot of data actually that have been looking at ways to try to prevent or ameliorate this particular phenomenon, and this actually presents some very unique challenges in terms of trying to understand how to extrapolate the

histopathological findings in animals to potentially a clinical study.

How could we potentially study this to try to understand whether or not these same type of regimens would translate into a clinical setting? Would animal efficacy data have an impact on the practice of medicine if those data were obtained? And ultimately, if yes, should they actually be conducted in primates in order to provide the best model that we have in terms of neuronal development? And then how should we be able to communicate these findings to clinicians and the public?

The data that have been out there -- and this is I think a pretty comprehensive list -- suggest that there are studies using estradiol. There have been data that have looked at the effects of melatonin. Xenon, which is an anesthetic gas, although not approved in the United States, has been looked at. It does not seem to produce apoptosis and it seems to be able to block the effects of other anesthetics.

L-carnitine has been looked at in the context of studies through the National Center for Toxicological Research. Lithium and hypothermia data have been coming out of the laboratory of Dr. Olney, as well as dexmedetomidine has been reported by Sanders, et al., that it has the ability to ameliorate, although not completely block some of the effects of other anesthetic agents.

So from a nonclinical perspective, the information that we've seen so far suggests that the data in the primates so far is supporting the findings in rodents, and you will see more of that this morning; that, clearly, the research in rodent models is far outpacing our ability to conduct the studies in primates, obviously due to the longer developmental period in the primate, the cost, and not all laboratories are able to actually do studies in primates. So we actually are providing much more information from the rodent world.

Clearly, I think, from a histopathological perspective, the drugs that have an NMDA receptor

antagonist property seem to be not necessarily producing the same type of damage in terms of where the damage is showing up in the animal models to the GABAergic modulators, and I think that's very important to keep in mind as well as we start thinking about some of the clinical findings that we are seeing.

But clearly in the rodent models that are existing to date, there are more subtle changes that are being reported, including changes in synaptic architecture and neurogenesis, and that these changes are actually occurring a little bit later in development compared to the apoptosis, which do suggest that perhaps there may be age-dependent changes in terms of the endpoints that we look at and build into some of the clinical studies that we're looking at.

I do have a couple considerations to suggest regarding future nonclinical studies. One of the challenges from the regulatory world is to really be able to try to identify drugs that don't produce this response. We recognize that journal editors

like to see positive findings, but from a regulatory perspective, it's very helpful to know what doses do not produce this response. We encourage people to gather and report information on pharmacokinetic exposures that are obtained in the models that they're looking at, as well as pharmacodynamic endpoints to be able to look at compare these findings to humans.

Further studies on the comparative toxicological assessments I think are very warranted to help put the findings into perspective across the various drugs that we're looking at. And the general rule of thumb in the nonclinical world is to try to mimic the clinical setting as closely as possible.

The challenge in extrapolating information from animals to humans is that there are indeed a lot of variables that can contribute to the findings, and people have gone through extensive efforts to try to mimic and understand the conditions at which the animals are exposed to these compounds.

Clearly, the information that we have, it's very clear that surgical stress and pain sand psychological stress can have a negative impact on brain development. We are just beginning to understand how brains actually develop in the first place, and a lot of these studies that are being conducted can shed some light on just the basic understanding of brain development across species.

The data that we're seeing suggest that anesthetics can have, under certain conditions, adverse effects in animal models on brain development. We're just beginning to consider the overlap of these two particular paradigms in trying to understand how this particular phenomena is taking place.

There actually are data that there are doses and durations and information that suggests that there are levels that we can use that do not produce this effect. And ultimately, our overall objective, which I think we're all in agreement, is that we are using these anesthetics to try to prevent many of these adverse consequences, but

maybe we can learn more about particular anesthetics in order to maximize the benefit and really tip the scales in terms of obtaining the most amount of benefit with a minimization of risk as we proceed forward, and I think the nonclinical studies can provide some additional insights into that perspective.

So I thank you very much.

DR. KIRSCH: Thank you. I'd like to take a minute and ask Drs. Markman, Deshpande, Swedo and Mattison to introduce themselves.

DR. DESHPANDE: Jay Deshpande. I'm the chief quality officer, Arkansas Children's Hospital. I'm an anesthesiologist and pediatrician.

DR. MARKMAN: John Markman, from the Department of Neurosurgery, neurologist, director of translational pain research and neuromedicine pain management at the University of Rochester School of medicine.

DR. MATTISON: Don Mattison, Child Health Institute, NIH.

DR. SWEDO: Sue Swedo, National Institute of Mental Health, pediatrician and head of pediatrics and developmental neuroscience.

DR. KIRSCH: Thank you. Our next speaker is Dr. Paule.

Presentation - Merle Paule

DR. PAULE: Well, good morning. And thanks very much, Dan, for setting this up and giving us such a nice background discussion.

As he mentioned, I'm going to be talking to you today about the behavioral effects we've observed in primates. And just to sort of reiterate, we have determined that the sensitive period for the induction of nerve cell death in the monkey includes the middle of the third trimester, around gestational day 120 to postnatal day 5, and we see no effect in PND-35 offspring.

We used the 24-hour exposure initially as our benchmark. We have found that three hours' exposures to ketamine IV does not appear to be sufficient. Nine hours does appear to be over the threshold, and Dr. Olney's group recently has

demonstrated five hours of ketamine exposure is sufficient to be over the threshold.

Interestingly, perhaps, we find that cell death in the monkey is both apoptotic and necrotic, whereas in the rat, it is primarily apoptotic. So there are species differences in the effects of these compounds.

So given that ketamine also causes significant abnormal cell death during the brain growth spurt period, as we see in rodents, we also wanted to find out whether there were associated functional consequences as had been reported in the rodent model.

So the goal then was for us to make predictions -- this is always our goal, of course, make predictions about the effects of developmental exposures to ketamine, in this case, on cognitive function in humans. And ideally, to do this, we need data from laboratory animal models, well controlled experiments under known conditions of exposure. Using the appropriate animal model is critical.

In this case, we feel that the closer to humans, the better; therefore, reliance on the rhesus monkey. And relevant endpoints, we think, decrease the uncertainty in extrapolating our findings from the animal model to the human situation. And when you can utilize identical endpoints, obviously we think that's the best, because then you don't have to try to determine what the difference is from that point of view.

So I'm going to be talking today about a procedure in which we exposed postnatal day 5 and 6 rhesus monkeys to 24 hours of IV anesthesia with ketamine. We then weaned the animals at six months of age. We begin cognitive function assessment of these animals at about seven months of age in daily sessions, Monday through Friday, 50 minutes each.

The initial intent was to monitor these animals for at least two years, but currently we've been testing them for over 760 daily sessions, 150 weeks, or over three years of testing, and the animals are now about 4 years of age. So we actually began these studies about the same time

that the last advisory committee met.

The instrument that we utilize to assess cognitive function in these animals was called the National Center for Toxicological Research Operant Test Battery. Operant simply means you operate something in an environment, which means in this case, press a button or push a lever. And we have, as part of this battery, tests which we feel assess aspects of motivation, color and position discrimination, learning and short-term memory, and I'll briefly describe those for you.

So this is a caricature of the intelligence or behavioral panel that we use. We use exactly the same panel for children that I'll talk about in a little while. So we utilize press plate manipulanda here that we can illuminate from behind with colors or geometric symbols, depending upon which cognitive function task we're asking the animals or subjects to perform.

We utilize retractable levers that can either be extended or retracted, depending upon which task we're asking the animal to perform. We

give them information about whether they made an incorrect response or a correct response, and then, in some cases, how many more responses they need to make in order to obtain their banana-flavored food pellet, which is delivered down here in the reinforcer trough. We also pipe masking white noise into the testing chamber so that they won't be disturbed during the testing period, given the background level of noise in the laboratory.

So briefly, for the motivation task, we only utilized the far right retractable lever. It's extended. Quite simply, the subject has to press the lever more and more times in order to get its food pellet. So, for example, the first food pellet cost two lever presses, the second cost four, the third cost six, and so forth. And so in a very short period of time, you ramp up the work requirement necessary for the food pellet, basically asking the animal how much effort they're willing to put forth for that particular reinforcer.

We think it's very important to understand

the level of motivation of the subjects, because if they're sick or they're not hungry, then that can severely impact, as you can imagine, their willingness to work for food.

For our color and position discrimination task, we utilized the press plate manipulanda. So initially, we illuminate the center press plate with a red, yellow, blue or green color. The subject responds to it, says, "Yes, I see it." It immediately goes out. Its two side-keys are illuminated white. If the color had been red or yellow, a left choice is correct. If it had been blue or green, a right choice is correct. A very simple task. You get a lot of data very quickly. You get reaction time measures, accuracy measures, and so forth.

For the short-term memory and attention test, we also utilize the press plate manipulanda. In this case, we utilize geometric symbols, where we illuminate the center panel with a sample stimulus. Let's say it's a triangle. The subject indicates, "I've seen the triangle," pushes it,

everything is dark. And then after a delay of random duration, they are presented with three choices. If they remember that the triangle was the sample stimulus and they match it, then they get their banana-flavored food pellet reinforcer.

By looking at the accuracy of matching as a function of delay, you get very nice forgetting function. So it's a very nice metric for short-term memory.

For the learning task, we utilize all four retractable levers. They're extended and we use the serial position indicator lights here to indicate how many more correct presses they need to make. Quite simply, the animal's job is to figure out the correct sequence of lever presses for this particular session. They can't predict from day to day what the sequence is going to be. They must learn a new sequence every time they go into the chamber.

Initially we start with a one-lever sequence. So they have to figure out which of the four levers is correct. Once they do that, they

have to go to a two-lever sequence, three-lever sequence, and so forth.

So in a single testing session, we can actually generate several different learning curves. For those of you familiar with the game Simon that our kids play, this is the monkey version of Simon.

So initially, we've been using this instrument now for probably over two decades. Initially, of course, one of the things we wanted to determine was how do children perform the same task. And here you can see the actual panel itself. Instead of working for banana-flavored food pellets, we drop nickels down in here. So the kids are working for money, positive reinforcement, again. And kids are actually quite nice because all you have to do is show them a videotape instruction set as to how to play the games and you can start generating data from kids relatively quickly, in fact, right away.

So one of the things that's nice about being located next to Children's Hospital is that we had

access to a cohort of low birth weight pre-term infants, a group of 115 of them. So each data point here represents a single child. And we simply asked the children to perform these tasks and see how that performance related to IQ.

So what you see here is accuracy of responding in that very simple color and position discrimination task, and you can see as IQ goes up, so does performance in that task in a very positive and highly significant manner. And probably not surprising, you see a similar phenomenon with the learning task, the Simon game that the monkeys play.

So these are really nonverbal metrics of certain aspects of intelligence. And in fact, you can predict the intelligence of children, within 10 or 15 points anyway, based upon solely their performance on these operant tasks. So we think it's a very relevant measure.

We also of course wanted to compare how do kids do compared to monkeys. So these data here show accuracy of choice in that short-term memory

task. Now, this is irrespective of delay. So we're not looking at decay curves here, but just accuracy of responding.

These are children from 4 to 13. The Ns per cell are down below. You can see that 4-year-old kids are about 70 percent accurate and they increase very rapidly as they age out and probably asymptote around age 11 to 13. And here you can see that monkeys are just as good at performing this task as 4-year-old kids, same task.

If you look at how fast they're making their choice -- so the higher number here represents slower responding; this is the animal or the human making its choice after presented with the sample stimulus -- you can see that kids are pretty slow at 4 years of age, but then they rapidly decrease their ability to make that choice. And here, monkeys are just as fast as 13-year-old kids. Remember, though, they're only as smart as the 4-year-old kids.

So depending upon the metric you use, it's virtually indistinguishable sometimes to tell the

performance of children versus monkeys, and this is exemplified in this particular slide, where here, now, we're actually looking at decay curves. So this is the delay in seconds over which they have to remember the sample stimulus.

The solid line here represents the data for monkeys and the line right on top of it is data for 4-year-old kids. So you can see that, initially, at very short delays, they're about 70-80 percent accurate and they decay, their memory decays with a certain slope that's no different from that of monkeys.

Of course, as kids get older, they get better at encoding information, so they remember more and they forget less over a short period of time. But here is just an example of virtually no difference in performance between monkeys and children.

We were also curious of course to determine how predictive the monkey model was, where we could find data on drug exposure. So this is just simply a list that we compiled some years ago showing the

compound of interest, the primary acute drug effect, and then the references showing what that was.

So, for example, delta 9-THC, the active ingredient in marijuana smoke, very significantly causes monkeys and humans to overestimate the passage of time. So if they're asked to time a 10-second interval, they'll say eight seconds is 10 seconds, and monkeys do exactly the same thing.

If you give marijuana smoke, on the other hand, so it's got THC in addition to a whole bunch of other stuff of course, you see that the short-term memory is impaired, and that's a very well known phenomenon of people who smoke marijuana, their short-term memory is out to lunch, and we see the same thing in the rhesus monkey.

I'm not going to go through the rest of these, but do want to point out that where we have long-term chronic administration of marijuana smoke, we find an amotivational syndrome in a bottle of teenagers. We used teenaged monkeys, had them smoke marijuana every day, and they don't want

to work so much. And so that's also been reported in human teenage populations, not so much in adults.

So where we have data -- and, granted, the human data here were not from the operant test battery, but they were from clinical instruments designed to measure the same sort of cognitive functions -- we see that the monkey is an incredibly good predictor of drug effect.

So this is a picture of the testing pods we use for the monkey behavioral laboratory. In each one of these chambers, there is one of the intelligence panels that I mentioned. And so they go in there for their 50-minute session every day. And unlike children, who you can simply show the videotape instruction set and say "This is how you play the game," we have to spend a lot of time training monkeys, weeks to months, literally, in order to get them to understand what the rules are in order to play these games.

So we use that to our advantage and actually capture that training data as a measure of how

smart they are. And so what we see here in this particular slide are training scores that we have arbitrarily assigned as a function of training over weeks. So this represents really over three years of training. And each dotted line represents what we consider performance of at least the right topography of a given task.

So, for example, let's take the learning task, that lever task where all the four levers are out. If you put a monkey in front of a panel and four levers are sticking out, the chances that a monkey is going to press one of those levers is incredibly high. By accident, they simply do that.

So almost without exception, within one test session, we can get animals to press levers for food. Now, they don't have any idea what the rules of the game are, but that's how we go about training the animal.

So after they start pressing levers for food, then we start using the method of successive approximations to shape the behavior closer to the one that we really want to look at. So after they

start lever pressing, then we start deactivating levers, such that they're just pressing one lever or following a lever around and so forth.

So this bottom line here indicates that after a training score of 5, we have assumed that they have met the response topography for the learning task. There should be an IRA here indicating incremental repeated acquisition or learning task, but it just fell off the slide. So after a training score of 5, we believe that the animals are actually playing the equivalent responses for the learning task, even though they don't quite yet understand the rules.

Another two points are given for acquisition of performance under that progressive ratio or the motivation task. We assign them another 10 points for learning how to follow the rules for the color and position discrimination task, and we assign another 10 points for them learning the concept that they have to match the sample stimulus.

After they've matched the sample stimulus with zero delays, that is, instantaneously, then we

start adding delays in groups, such that the final delays are out to 82 seconds. And so the maximum score that a monkey can use in this situation is 36.

The important point of this slide is that after -- we can see the ketamine animals and control animals track each other until we start to ask them to learn the concept of matching. Now, in monkeys and a lot of animals, the tendency is to non-match. So, for example, if you show an animal a symbol and then you show them a representative -- other symbols, their tendency is to move away from the one they're already familiar with and choose a non-matching symbol. So it's a difficult concept. A non-matching example would be much easier to train.

So what we're seeing here is actually a pretty severe deficit in the ketamine animals in order to learn that concept of non-matching. In fact, it makes them significantly worse than the ketamine animals over about 10-month period until they finally catch up some more down here.

So now what we're going to do is to look at performance at each one of these tasks right here. So we're going to look at performance in the learning task after they have figured out the kind of response that they need to make. So these data here now are how much of the learning task they finished in the timed session that they were given to perform the task.

Now, you can see, early on, the animals in both groups track together pretty nicely. But after a couple of months, we see that the control animals clearly outperform the ketamine animals in how much of the task they finish. We see that part of that reason is because the ketamine animals are not able to solve that puzzle as rapidly as the control animals. Remember, this data spins over about three years here. You can see the ketamine animals never appear to catch up.

If you look at the accuracy, this is their ability to correctly solve that puzzle, the control animals significantly outperform the ketamine animals for what seems like forever. The ketamine

animals don't appear to be ever catching up.

If we look at the color and position discrimination task, we have a little bit different picture here. The controls outdo the ketamines for a while, but for the last year and half, they've been basically finishing the same amount of the task, even though the ketamine animals are still performing less rapidly than the control animals. And the accuracy in this particular -- remember, it's a very simple task, red, yellow, blue or green choice, you can see that they're tracking right together.

In terms of the motivation, we also see that the ketamine animals either are not as motivated to perform for the food as the control animals or they are, for some reason, unable to perform as rapidly. It could be a motoric effect; we don't really understand it yet.

Then, interestingly, even though they had a very difficult time with the concept of matching, their short-term memory actually is intact. So by using this instrument, we can get at very specific

aspects of cognitive function. But the troubling thing, of course, is that the ketamine animals don't ever catch up to the controls in a lot of very important tasks that we think are certainly relevant to intelligence in humans.

So I think these data sort of prove the concept at least that exposure to these kinds of agents can alter very important cognitive functions significantly and perhaps permanently.

We certainly have a lot of questions that remain. We don't know yet what the threshold duration is to cause the functional deficits. Dan mentioned this already. We don't know what's the most sensitive measure. Is it the histological pathology or is it the functional aspects? Are they the same as that for causing abnormal cell death or even the spine issues that Dan mentioned? Unknown. How long will the functional deficits manifest? It appears at least so far that they never go away.

We're still following these animals and challenging them in other ways to see if we can get

at other aspects of cognitive function, such as timing behavior and so forth.

Then we really don't know the exact period of sensitivity to these effects. We don't know how much earlier than gestational day 120, for example, in utero these animals are going to be sensitive to it. We know that somewhere between postnatal day 5 and postnatal day 35, the sensitivity goes away, but we don't yet know exactly where that is. And then, of course, the big question is we need to know how this relates to human development.

Then can we come up with other markers that we can use to monitor in vivo without -- using perhaps new imaging techniques like MicroPET. So, for example, in the rodent, we've come up with some markers that we think label apoptosis that allows us to look at the time course of apoptosis after a single administration of one of these compounds.

We have yet to find a compound that will work in the primate, because the primate blood-brain barrier seems to keep things out that get in the rat brain. But that would be really ideal if

we could come up with a marker that we could follow non-invasively, even in human subjects, for some of the pathology that we're seeing in these animals.

Then, of course, Dan already alluded to what are some of the strategies for preventing or ameliorating these effects and he mentioned some of those possibilities. And then which drug combinations or clinical manipulations make the situations worse? I think Dr. Olney is going to talk a little bit about that in his presentation.

Then very importantly, and I think Dr. Anand is going to address this issue, how will these findings relate to the use of anesthetics in actual surgical or painful, stressful circumstances. These animals were not surgicated, they were not stressed in any way. They were simply anesthetized. How is that going to impact actual surgical procedures that we know are also bad?

So there are a lot of questions that remain and a lot of work to be done, but I think that the primate model does give us pause for concern that a single episode, albeit a long-term one of 24 hours,

does in fact seem to permanently affect the ability of their brains to work.

Thank you.

DR. KIRSCH: Thank you. Our next speaker is Dr. John Olney.

Presentation - John Olney

DR. OLNEY: Good morning. I'm going to address anesthesia-induced neuroapoptosis and oligoapoptosis in the developing primate brain. And most of the data I'll discuss were developed as a collaborative project between researchers at Washington University and the Oregon Health and Science University, and the experimental procedures were performed at Oregon National Primate Research Center. And the brains were then shipped to my laboratory for analysis.

This research is supported by three NIH grants of which I'm the principal investigator, and also a center grant, Intellectual and Developmental Disabilities Research Center, of which Terrie Inder, who is over there on the committee, is the principal investigator and director.

So the protocol for our primate research is to expose fetal or neonatal research of rhesus monkeys to isoflurane, ketamine, or propofol for five hours and examine the brains three hours later for histological documentation of apoptotic cell death.

The fetuses are exposed in utero by administering the drug to the pregnant dame. The fetus is delivered by caesarean section, then immediately is euthanized. So it's three hours after five hours exposure to anesthesia that the fetuses are euthanized.

The anesthetic drug is administered to the dame or neonate in an amount sufficient to maintain an intermediate surgical plane of anesthesia. That's defined by using a hemostat pinch at hand and foot and determining that there is no movement or less than a 10 percent increase in blood pressure or heart rate.

Ansgar Brambrink, professor of anesthesiology at OHSU, personally supervises the administration of anesthetic drugs, and all the

procedures are approved and are in full accordance with the PHS, Policy on Humane Care and Use of Laboratory Animals.

I'll show you first our isoflurane data in P6, postnatal day 6, rhesus neonates. The neuroapoptosis response is here, and that bar represents approximately a 13-fold increase over the control level. The control level is the rate of apoptosis that's occurring naturally in the developing brain.

We also saw a glial apoptosis response, which was almost of identical magnitude to the neuroapoptosis response. And histologically, this is what the neuroapoptosis response looked like in the no anesthesia control brain. There's a sprinkling, random sprinkling and very sparse distribution of apoptotic neurons.

The method we use for detection is activated caspase-3 immunohistochemistry. And in the isoflurane exposed animal, what I'm showing you here is the visual cortex. The effect was very prominent in the somatosensory cortex, the temporal

cortex, and the occipital cortex, where the primary visual cortex is located.

You see that the pattern of apoptotic cells is highly organized and it does reflect the location of specific neuronal populations that are in layers 2 and 5 of the visual cortex. These other layers which you see here, those are layers 2 and 5, also. It's just that the convolutions of the brain, as it's cut in cross-section, gives that kind of pattern.

The glial distribution, again, for the no anesthesia control, it's a sparse, scattered distribution, which does pretty much conform to the location of white matter areas. And then in the isoflurane exposed brain, you can see that it's much more dense concentration, again, conforming to the outlines of the white matter.

The type of glial cell, then, we used fluorescent co-labeling methods to determine that. Over here, I'm just showing what the activated caspase-3 stain looks like in black and white when you're staining neurons that are dying and then

when you're staining the glial cells. They look very different. And just on the basis of morphology, we can distinguish them from the dying neurons. But they also are located in the white matter. So that's a second method of distinguishing that they are glial.

This is the activated caspase-3 stain. We also view silver staining, and this is what the silver stain looks like for the glial. Then we used double-label fluorescent methods. And the red cell here is stained by activated caspase-3, and the green stain is GFAP, which is a marker for astrocytes. You can see that the three astrocytes there are labeled with a GFAP stain, but there is no co-labeling with this cell that is dying and is stained by the AC-3 method.

Down below here, the green represents an antibody against a component of myelin, and the red is the AC-3 stain, showing that this cell is dying. The green forms a rim around the dying cell, that represents this myelin component which is in the plasma membrane of the dying cell, and that of

course is a characteristic of oligodendrocytes, because they are responsible for myelinating axons, and they elaborate the myelin in their plasma membrane and then wrap it around the axon. So that's how we've identified the dying glial cell as an oligodendrocyte.

So the potential significance of this phenomenon we would suggest has to do with the oligos being vulnerable during the stage when they are just beginning to myelinate axons that interconnect neurons throughout the CNS, and deletion of oligos at this critical stage may disrupt myelin formation, which could potentially have adverse long-term neurobehavioral consequences that might be additive to the potential consequences of isoflurane-induced neuroapoptosis.

If the window of vulnerability for oligoapoptosis stays open longer than for neuroapoptosis, which we suspect may be the case based on studies in rodents, this may extend the period of risk for brain changes that could have adverse neurobehavioral consequences.

Now, I'm going to show you a sort of summary slide that pertains to all of the nonhuman primate data that we've generated so far, and it pertains to exposure of both fetal and neonatal rhesus monkeys to isoflurane, ketamine, and propofol.

We evaluate the toxic impact on the brain by counting the number of cells, both neurons plus glia, that are deleted from any given brain. So we're giving here the mean number deleted from the brains of any given treatment condition.

You can see that for isoflurane, this is the magnitude of the effect in the fetus. But in the neonate, it's much greater magnitude. But for ketamine in the fetus, this is the magnitude. And in the neonate, this is the magnitude. Over here it's represented a little more clearly for isoflurane in the fetus and here for isoflurane in the neonate. But for ketamine, it's a criss-cross. It goes from a higher value to a lower value with advancing age.

For propofol, there wasn't very much difference from the fetal to the neonatal period,

and propofol was least toxic at either age.

So summing up, the primate brain seems to be quite sensitive to brain cell death induced by alcohol -- that's a separate study which we've published recently, down here, or anesthetic drugs. And which anesthetic drug is most toxic depends on the age at time of exposure. Ketamine appears to be most toxic for the fetus. Isoflurane appears to be most toxic for the neonate, and propofol is least toxic at either age.

I want to briefly discuss then the window of vulnerability based on the brain growth spurt period, which would be the data of Dobbing and Sands. The brain growth spurt for monkeys is precocious compared to the human, so that about 75 percent of the brain growth spurt occurs for the monkey prior to birth, but for the human, about only 25 percent occurs prior to birth and 75 percent after birth.

What I am showing here are the areas under the curve for the monkey represents the period when we treated monkeys. G120 is the gestational days,

gestational age that we treated the fetuses, and P6, postnatal day 6, is the day that we treated the neonates.

So the area under the curve there represents the period that our study covered in the monkey. If you just move that area under the curve over here to the human curve, then that would give you the comparable time or age for the human that our monkey study pertains to.

So if, in the monkey, ketamine was the most toxic in this fetal period, that would be over here, for the human, perhaps a 10-day-old human, when ketamine would be most toxic. But for isoflurane, it was most toxic on P6, which would, for the human, be over here around 4 to 6 months of age.

But that isn't the main reason that I'm showing these brain growth spurt curves. The main reason is that I want to point out that the first half of the brain growth spurt is a blind spot for us. We haven't really studied that period, and neither has the Food and Drug Administration.

Their studies also -- the earliest period that they've studied is G120.

So this whole first half of the brain growth spurt hasn't been looked at; and in the human, that would be the case, also. We don't have any data that we could even extrapolate from the nonhuman to the human primate for this first half of the brain growth spurt. And that's important, it's an important deficiency in our data, because this period, the first half of the brain growth spurt, is the period which, on the NICU, premature infants are being exposed to anesthetic drugs and a lot of other drugs at the same time, and we just simply don't have any data for how these drugs interact with respect to these toxic parameters.

I wanted to just mention then that there is evidence suggesting that drug combinations containing both an NMDA antagonist and a GABA agonist may be more toxic than either agent alone, and alcohol, which acts through both NMDA and GABA receptors, is quote toxic in mice, monkeys, and humans.

But there's also evidence that other types of drug combinations may increase the toxicity of anesthetic antiseptic drugs. And what I mean there is that agents that are not anesthetics, but are being used together with anesthetics, can perhaps also augment the neurotoxicity of the anesthetic drugs.

I'm going to give you an example that we have just hit upon. We found that caffeine potentiates the toxicity of both NMDA antagonists and GABA agonists, and caffeine is used in very high doses to counteract apnea in premature infants who are simultaneously being exposed to anesthetic drugs.

I'm going to show you some data here pertaining to PCP. We started out studying PCP because I have a grant from NIDA and they want to support research on drugs of abuse, but I also like to kill two birds with one stone, and PCP is an anesthetic drug also. It was introduced into human medicine back in the 1950s and then rapidly withdrawn because of its hallucinogenic properties.

1 But it is a potent anesthetic.
2 What I'm showing here is that caffeine by
3 itself has some apoptogenic properties, and the
4 dose of PCP we are using has approximately the same
5 amount of apoptosis. If you combine the two, you
6 get a much increased apoptotic response.
7 What I've done here is I'm subtracting out
8 now the saline component and representing over here
9 the bars without the saline, so that each bar
10 represents just the drug-induced apoptosis. You
11 can see that caffeine is causing about 200 density
12 points, and if you were to add that on top of the
13 PCP effect, this is the additive, theoretical
14 additive effect that you would expect. But we're
15 seeing a much greater effect, which we're calling
16 supra-additive or potentiation.
17 That's PCP as an NMDA antagonist. We also
18 have studied that then for GABA agonists. And here
19 I've already subtracted out the saline control
20 component. So caffeine is causing here about 125
21 density points; diazepam causing quite a bit more.
22 But if you add caffeine to diazepam, it should give

you this amount if it's an additive mechanism, but instead it gives you this supra-additive effect. For example, this is about 125 points. If you start here, add that, you get that, but if you really look at what you're getting here, it's about 1,250 instead of 125 that's being -- about 750 that's being added instead of 125. The same thing we found for isoflurane and caffeine. It seems to be a supra-additive effect when you combine those two agents.

Histologically, this is what it looks like. The control brain has a sprinkling of apoptotic cells. Isoflurane brain has an increased density of apoptotic cells. And the caffeine-plus isoflurane has a markedly further increased amount of apoptosis.

So the situation is that caffeine is administered prophylactically in the NICU to apnea-prone premature infants to stimulate respiration, which reportedly reduces risk for cerebral palsy. In fact, recently, caffeine has been called the silver bullet of neonatology because of its

beneficial effects.

Premature infants that are treated with caffeine and in the NICU are also exposed semi-chronically to anesthetic drugs, and our preclinical findings suggest that while caffeine is protecting against hypoxic, which I like to call excitotoxic cell death, it may combine with anesthetic drugs to potentiate apoptotic cell death.

So under some circumstances, minimal anesthesia, for example, the effect of caffeine may be beneficial, and under other circumstances, for example, maximal anesthesia, it may be detrimental. And unfortunately, and this is, I think, an important point, the detrimental effect can happen very quietly without waving red flags. We really don't know what's going on inside that brain.

So I wanted to leave you then with an interesting paradox. Our infant model studies support the following conclusions: caffeine stimulates respiration, enhances brain oxygenation, counteracts hypoxia, and prevents excitotoxic

neurodegeneration.

Isoflurane at 75 percent MAC suppresses respiration, renders mouse pups apneic, hypoxic and cyanotic unto death within about less than two hours.

If we co-administer caffeine with isoflurane, the mouse pups are pink, healthy and happy at two hours. When we examine the brains, the pale cyanotic pups exposed to isoflurane alone have a modest amount of neuroapoptosis, whereas the pink and happy caffeine-plus-isoflurane pups have a massive display of neuroapoptosis.

So I want to leave you with this question. What is caffeine trying to tell us?

Thank you.

DR. KIRSCH: Thank you, Dr. Olney. Before going on to the next speaker, I'd like to have Dr. Shaw introduce himself.

DR. SHAW: My name is Dr. Phillip Shaw. I'm a psychiatrist at the Child Psychiatry Branch of the National Institutes of Health.

DR. KIRSCH: Thank you. Our next speaker is

Dr. Barbara Clancy.

Presentation - Barbara Clancy

DR. CLANCY: Thank you. I appreciate this opportunity to tell you about the research that I do with my colleagues, primarily Barbara Finlay and Dick Darlington.

Barbara Finlay is an evolutionary neuropsychologist, and Dick Darlington is a statistician, which is why I say we are taking an interdisciplinary approach to address a critical question that we've all faced, how to translate developmental time from experimental species to humans.

We know we have to use model systems. They're required for good reasons, and we can divide them into precocial species and altricial species, precocial born relatively late in development, at least somatic development, and that would be macaques, cats, guinea pigs, spiny mice. But so much of our work is done on the altricial species, particularly the rats and mice. If you'll notice that middle column, gestation is literally

all over the place. These species are born at different neurodevelopmental times. So birth we know is not necessarily a good milestone for comparisons, and we don't know for sure that gestation percentages would be.

There have been many ways we've tried to address this challenge in the past using proportions of development, some kind of gap between conception and eye-opening, or using anatomical comparisons. Bayer and colleagues have some beautiful comparisons between rats and humans, or Carnegie stages, which are actually based on somatic and not neural, and we're concerned primarily here with the neural development.

So we do a lot of work based on vulnerability patterns, initiated by Dobbing back in the '70s, in that brain growth spurt. And I was taught a rule of thumb, that a rat brain, postnatal day 5 to 7, was equal to a human newborn brain.

We all know these comparisons are vague. They're often restricted to rat and human or primate and human. What I think might be the

biggest problem is that all the neural regions are grouped together, and it's very likely that there are different vulnerability patterns for different brain regions.

The comparisons using these kinds of anchor events, some kind of interval between conception and eye-opening, if you're trying to predict then when something that you have found in the empirical literature in a rat might equate to a time in human, it's basically just stretching the interval out like on a rubber band. So we can find when the corpus callosum occurs in a rat brain and then try to stretch that interval so that we can predict when it will happen in a human brain.

We suggest a novel approach for this challenge using evolutionary principles. Development is constrained to a curve in a very well described pattern across all mammalian species. Neurons have to be born before they can connect, before they can synapse. And so we are using a principle that was derived to understand how brains get bigger. Why is a rat brain so much

smaller than a human brain?

Back in 1995, Barbara Finlay and Dick Darlington were looking at this and they could describe the relationship between development across mammalian species because there's a striking conservation in the order of neural development as the log of a post-conception day minus a constant would equal a species score plus a structure score.

Many mathematical models were tested before that and many have been tested since. What we've found works best is a general linear model, such that those scores I mentioned are derived from regression coefficients, which basically quantify the goodness of fit in this model.

The events that occur late in development, the neurogenesis of the rods in a retina would score high, while the events that occur very early would score low. Species that develop slow like humans would receive a high score, and hamsters, which develop relatively quickly, would get a low score.

We have to express the post-conception days

in this kind of model on a log scale, which means multiples don't work. It's a lot more complicated. Dog years won't work.

We have to adjust using a constant, which right now is 4.34, because it's likely in mammalian development, some events that occur very early occur in the same amount of time, blastulation, for example, in all species. And I'm not a statistician, but for the statisticians, we predict why using dummy variables, such that the event or species of interest receives a 1 and all the other scores would receive a zero. So the log of a post-conception day minus a constant will equal a species score plus a structure score.

When we began -- or when I began working on this in 2000, we had nine mammalian species and 90 different neural developmental events all gleaned from the empirical literature. Currently, we have 11 mammalian species and 225 different development events, and counting.

The beauty of this kind of model is that instead of looking at the relationships as though

we're stretching out intervals on a rubber band, the model takes the relationship between every number in the database and every other number into account. So it's a big columns-and-rows problem really, where all the known empirical literature can be plugged in, and then using that formula, we can extrapolate from known events to predict when events are going to happen in another species.

So, for example, we can take that columns-and-rows problem, plug in our model and predict when the corpus callosum does appear in a human. When we look in the empirical literature, Ashwell reported it occurred on post-conception day in human 88. Our model predicts 91, which is pretty close, and likely some of the discrepancy is based on it's very hard to predict the actual date of conception in a human or establish that I guess.

We have put all of this information to date up on a website, translatingtime.com, where you can go to the 2ebsite, put in a rat or whatever species of interest, date in development, translate to a human or to any other species, something that's

very important, because so much of the previous work was done on rats, but a lot of the newer work is being done on mice. At the website, you can also put in a specific neuro event, if it's in our database, and we can predict when that's going to happen in your model of interest.

So what can these translations from an experimental species tell us about anesthesia and about human brain development? One question we ask is, is modeling useful or perhaps even preferable for humans? Are primates different? Does somatic development detach from neural? And how do we relate the anesthesia ages and timing? Are there different times for different brain regions?

We argue that modeling is not only useful, but actually may, in many cases, be preferable for humans, because of the variability in conception dates, the restrictions due to sampling intervals, and the lack of controls in human experiments. And although we have many examples, our best example is eye-opening -- eye-opening, which occurs in a mouse at about 12 to 13 days, a rat at about 15 days.

Our model consistently was predicting in the early times that the eye-opening in a human would happen at about 22 weeks. But in the empirical literature at that time, 28 weeks was all we could find.

But when 4D sonogram imaging came into use, the model had been right. The statisticians would call this the bootstrap effect. The idea that the more data points that go into our model, the more errors will average out, such that the predictions might actually be more reliable than in the empirical literature, at least for species that cannot be sampled at every interval.

We have consistently found that primates are different. The graph here is just showing a plot of model-produced dates before we made an adjustment to it. The yellow dots are critical events. The triangles are limbic events, just in primates.

If our model was predicting everything accurately without any adjustments, all of those would cluster around the zero line on that graph. But cortical events are above the line, limbic

below, indicating in primates cortical events occur a little bit later than they do in rodents, and limbic events occur a little bit earlier. The beauty of this kind of a model is that we can, by adding or subtracting from the model prediction, actually adjust for that.

One thing we found just very recently is primates are different in their GABAergic system, also. The modeling we're working on right now we hope will allow accurate translations, but the table there just lists some GABAergic events, the empirical days in the literature in the middle column. But what our unadjusted model would predict, again indicating that the model is predicting that they occur earlier, this is just in primates once more, indicating that GABAergic events in primates occur later than they do in rodents. So those vulnerability patterns or brain growth spurts are actually acting on different systems at different times.

We know not everything fits the model and that some can be adjusted; limbic and cortical,

we're working on GABA. Some events cannot be included, at least in this particular model. Birth, as I mentioned, is variable. The synaptogenesis surge that accompanies birth also does not fit into this model and weaning doesn't fit into the model. And our model at this point cannot take into account differences in maternal and fetal interactions, and these are all things that of course we have to consider.

We're right now looking at how to expand our model. It ends currently at eye-opening. That's when very specific neural events we could capture and actually plug into the model. Postnatal, it's more difficult. So we're looking at reflexes, we're looking at different behaviors. We're actually asking if somatic development detaches from neural.

We're testing the onset of crawling, the onset of social play, and onset of walking, a beautiful experiment by -- or I guess I will say modeling experiment by Garwicz in 2009 showed that the onset of walking is very predictable if

conception is used as a starting point, and it's very predictable from brain size.

The onset of walking it looks like does fit into our neural model, although sexual maturation, something that I know has been used frequently, may not fit, certainly may not fit as well for females as it does for males.

We're of course at this meeting very interested in anesthesia intervals, and I would call your attention to the picture, the sonogram of the human, with a mouse and a rat. Those neural events that are happening in those three species at that point are happening similarly. So a mouse postnatal 11, a rat postnatal 13, and a human prenatally, and, of course, divided into three because of the limbic and cortical differences.

We can't say the brain is exactly the same. What we're saying is that the neural events that occur at that time are similar. And I put in some of the data points that had been reported for the readings for this meeting, post-conception now into the first column there, the table at the bottom,

and translated them into macaque and human time, because we may be trying to equate ages and brain regions that are not exactly similar or not exactly at similar stages of development.

There is some impact on the timing of exposure to such things as anesthesia, because in a rat, between post-conception day 20 and birth, just a matter of hours; in a human, that time during neurodevelopment might correspond to over a wee, so of course something that we have to keep in mind. Our model right now does take into effect metabolic development, but that's something that we hope to in the future.

So this kind of modeling is very useful for predicting similarities and differences across any species and in any process that's constrained to occur in a sequence. So the next steps are to put in metabolic rates, to put in male/female differences certainly in behavior that's indicated. So likely we will find similar differences in development. And in those critical windows, where do they indeed fall based on these offset patterns

of development?

We're putting in gene expression patterns right now, ages from birth through puberty. We've just put in heart, lung and kidney development to see if indeed somatic detaches from neural, because in so many species, we will not have neural development milestones to put in, but perhaps we will have somatic data. So if we can find that they fit with some adjustments into this model or fit into a different statistical model, we're very hopeful for being able to add those. And of course we're testing the new systems, the GABAergic and the NMDA. Certainly, the variability in those receptors across development should be in this model.

We can then test for individual events -- do they fit -- in addition to finding out if any system is different. We are quite sure the visual system would be different across these mammalian species, because the visual system between rats and primates appears to be so different, but the development of the system appears to be constrained

to occur in the same order and at about the same time. And, again, we're just now finding that the GABAergic system may be different, and we're hoping to test other systems, the dopamine cholinergic system.

So in addition to using a modeling approach to find primate and rodent similarities and differences and the disparity in development of the brain regions and the comparisons between motor and somatic, this type of research can save us a lot in time and funding.

We know what we're producing, our approximations at that website I mentioned. We also have confidence intervals. We know their approximations, but currently we realize that there are few other options. And we have a lot of optimism that with enough of a database from the information from this meeting and from all we can find in the empirical literature, and with the proper mathematical analyses, we will be able to produce the comparisons that are so needed to address this important issue.

I'd like to thank a lot of people, but in particular, my students, James Hyde and Brandon Kersh, who helped to get that website up and running.

Thank you.

DR. KIRSCH: Thank you. We'll now take a short 10-minute break. Committee members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with other members of the audience. We will resume at 10:20.

(Whereupon, a recess was taken.)

DR. KIRSCH: Our next speaker is Dr. Simone.

Presentation - Arthur Simone

DR. SIMONE: Good morning. I've been tasked to update the committee on what's occurred in the clinical arena since our last meeting in 2007. And I just want to make clear that this presentation is limited, first of all, to information that's in the public domain or about to be released into the public domain, and that the FDA hasn't reviewed either the protocols or the data that are

1 associated with these studies. And, therefore, my
2 mission is not to critique them in any way, shape
3 or form, just to help focus the clinical discussion
4 that will ensue.
5 A number of investigations have occurred
6 since 2007, two overseas and a number here in the
7 U.S. The retrospective epidemiological studies
8 have had some reported outcomes. There's a
9 prospective epidemiological study and an actual
10 randomized controlled study that are underway or in
11 the process of going underway.
12 In Denmark, Hansen and his colleagues
13 reported in Anesthesiology a study that they are
14 about to undertake or have undertaken, looking at
15 children less than 1 year of age who were exposed
16 to anesthetic and comparing their non-IQ academic
17 achievement with that of the background Danish
18 population.
19 They're looking at the years from 1977 to
20 1990, which there are over 45,000 children that
21 have met their criteria. And their project is
22 utilizing a number of registries that provide

information on demographics, medical background, and academic achievement. The results from this group are still waiting to be published.

In the Netherlands, Bartels, et al. have published some data that they have generated which looked at twins. And they had a hypothesis that anesthesia administration sometime during the first three years of life resulted in late or learning disabilities. And they were also concerned that children who need surgery early on in life may have medical problems that provide them with a vulnerability to such learning disabilities.

So what they did was take the young Netherlands twin registry and they were able to identify over a thousand monozygotic twin pairs that were born between 1986 and 1995. They took those who were gestational age of 32 weeks or more and weighed 2,000 grams or more.

What they looked at were children who had anesthetic, based on parental surveys, prior to the age of 3 years and then again between the ages of 3 and 12 years old. And then they went on to look at

learning disabilities that were assessed at 12 years of age, and they used two measures for this. One was educational achievement and another one was a teacher-reported cognitive problem survey.

The twins were categorized in two ways. They were looked at in terms of their anesthetic exposure, whether they were concordantly exposed or unexposed, and then discordant in terms of their anesthetic exposure. And then they looked at those that were administered an anesthetic prior to the age of 3 and those who were ever exposed to anesthesia at some point before age of 12 years old.

What they found were those that were exposed to anesthesia prior to the age of 3 had either lower educational -- well, they had both, actually -- lower educational achievement scores and significantly more cognitive problems than twins who were not exposed to anesthesia. More interestingly, they found that in the twins who were discordant for anesthesia exposure, the

unexposed did not differ from the exposed twin for either educational achievement or cognitive problems. The results were the same whether they looked at children who had anesthesia exposure prior to 3 years of age or ever prior to 12 years of age.

They also found that males who were exposed at any point in time had a slightly but significantly lower educational achievement score than their non-exposed colleagues. And for females, there was a slight difference in the same direction, but it didn't achieve significance. They also noted that cognitive problems were not significantly different between those who were never exposed and those who were ever exposed.

Based on these findings, they concluded that monozygotic twins who were discordant for having received an anesthetic nonetheless had equivalent levels of learning-related outcomes, and they said that this data provides evidence against a causal effect for an anesthetic effect on cognitive functioning. They also said that this type of a

1 study, which they described as genetically
2 informed, offers a different conclusion in the work
3 of Wilder, et al., which we'll get to in a minute.
4 Their thinking was that the vulnerability
5 for learning disabilities may already be present at
6 the time a child presents for surgery and that
7 perhaps some type of screening process should be
8 put in place to identify these children beforehand
9 and deal with them accordingly.
10 They noted, too, that their study was
11 limited in at least two ways. One was that they
12 did not assess the children directly for learning
13 disabilities. Rather, they looked at their
14 learning capabilities based on the outcomes. And
15 it also didn't assess for the specific types of
16 anesthesia that the children were exposed to.
17 At Mayo Clinic, Dr. Flick, who is on our
18 committee, and a number of his colleagues have
19 performed several studies that have been reported
20 in the literature. The first one I'm going to talk
21 to relates to neuraxial anesthesia and analgesia
22 that's used for labor for vaginal delivery. And

while this doesn't apply directly to some of the drugs that are under consideration today for their either GABAergic or NMDA inhibitory effects, it does reflect on concerns for anesthesia exposure in this vulnerable period.

Specifically, they thought that reducing stress associated with delivery by using neuraxial anesthesia might somehow impact on neurodevelopmental outcomes later on. And they used a population-based birth cohort that's in Olmsted County, surrounding the Mayo Clinic, and this cohort has been used for all their subsequent studies.

What they looked at were children who were vaginally delivered between 1976 and 1982 and who were still present in the county up until at least the age of 5, and they followed them out to age 19 as best as possible.

What they looked at was whether or not neuraxially-administered analgesia was used and whether they were able to identify learning disabilities in this population, and they evaluated

it using a Cox proportional-hazards regression.

What they found was that there were over 45,000 vaginal deliveries, and about a third of these were to patients who were administered a neuraxial labor analgesic. And looking at the hazard ratio, they found no difference in those children who were born to mothers that either had or had not had a labor analgesic. And they concluded that neuraxial analgesia during labor in vaginal delivery was not independently associated with any type of learning disability that was diagnosed prior to the age of 19.

This database was then used to look at children who were born out of C-section and looked at them for learning disabilities down the road. As I mentioned, the database was the same as that which was used before, and, again, they used a Cox proportional hazard ratio to look at learning disabilities for those who were born either vaginally delivered or Cesarean delivered with general or regional anesthesia.

In all their 5,320 children in this cohort,

of whom less than 10 percent were delivered by Cesarean section, and in those, there were more so delivered by regional anesthesia than general anesthesia.

It was noted that children delivered by Cesarean section under general anesthesia had lower mean birth weights, gestational age, and Apgar scores at one and five minutes. Their mothers were also more likely to have experienced complications associated with pregnancy and delivery, such as hemorrhage and eclampsia or preeclampsia. And an emergency indication was seen for twice as many patients that were delivered by C-section under general anesthesia as under regional anesthesia, which is not surprising.

The results of this study, using vaginal delivery as the reference, showed that those children that were born by Cesarean section under general anesthesia had no difference in terms of later developing a learning disability compared to those delivered vaginally.

Interestingly, though, those who were

delivered by Cesarean section under regional anesthesia appeared to be less likely to develop a learning disability later on. These ratios were adjusted for several factors that can affect learning disabilities or a tendency towards them, including gender, birth weight, gestational age, exposure to anesthesia prior to age 4, and maternal education.

This graphically shows the findings from this study, with the dark line representing the vaginal delivery, and the one slightly above it that's following it closely is general anesthesia used for Cesarean sections. And then the one below it, interestingly, is the regional anesthesia for Cesarean section.

The authors concluded that exposure to anesthesia for Cesarean section didn't lead to a greater likelihood of developing a learning disability compared to those children who were delivered vaginally. Likewise, their data suggested that a brief perinatal exposure to anesthetic drugs doesn't seem to adversely affect

1 their neurodevelopmental outcome, and that the risk
2 of a learning disability may actually be lower in
3 children delivered by Cesarean section for mothers
4 who had regional anesthesia in place.
5 They noted that the population in this
6 county was primarily white and middle class, so the
7 generalization of these results is somewhat limited
8 perhaps, and that the incidence of Cesarean section
9 in the series was considerably less than is
10 currently the case. And it's not known whether the
11 changes in indications for a Cesarean delivery now
12 may affect the results. Also, based on the date
13 that this was done, halothane and methoxylflurane
14 were inhalation agents that were used in many of
15 these mothers, and these are no longer available.
16 In a third study using the same database,
17 they looked at children who underwent general
18 anesthesia for any type of surgical or diagnostic
19 procedure before their 4th birthday, and again they
20 looked at educational and medical records to
21 identify those children with learning disabilities;
22 and specifically they looked for reading, writing

and arithmetic skills or disabilities and diagnosed them using formulas that they have generated which utilizes IQ scores and achievement test scores.

Again, a Cox proportional-hazards regression was used, and they adjusted for gestational age at birth, gender of the child and birth weight. And these individuals, too, were followed out to age 19, where possible.

In all, they had 8-and-a-half thousand children that were born during the period. Over 5,000 could be included in the cohort. In that group, just under 5,000 had no anesthesia exposure, and just under 600 had received a general anesthetic before the age of 4. Most of those, it was a single anesthetic exposure, but they were also able to identify those who had two anesthetics and those who had three or more.

They noted that those who had an anesthetic before 4 years of age compared to their unexposed cohort had lower birth weights, lower gestational ages, were more likely to be male, and had higher levels of maternal education. The analysis they

conducted was able to adjust for the first three differences or the first three exposure comparisons. They couldn't adjust for the higher levels of material education because of the data that would have to be excluded from the study. They also noted that Apgar scores and peripartum complications, which were reported for just a small segment of the population, didn't appear to differ between the two groups.

Furthermore, they were able to look at the physical status of these children, and this is using the American Society of Anesthesiologist Physical Assessment, where a number 1 represent a healthy patient, 2 suggests someone that has mild systemic disease, 3 someone with moderate, and 4 even worse. And what they noted here was that there was a difference between those who had three or more exposures compared to those who had a single or two exposures to anesthetic, and that those children with three or more exposures tended to what would appear to be sicker than the others.

In a univariate analysis that they looked

at, however, there was no difference in terms of learning disabilities in those who were rated higher for their ASA physical status than those lower. And when they removed those sicker children in the ASA classifications 3 and 4, they found no difference between treatment groups in terms of learning disabilities.

Overall the study showed that for a single anesthetic exposure, there was no difference compared to those children who were unexposed. However, with the second anesthetic, there was a significant difference in terms of learning disabilities later on, and that number increased substantially when the anesthetic exposures were three or more.

They went on to look at duration of anesthesia exposure, breaking it down into 30-minute intervals, and they found that for those children who had an under 30-minute or 30-minute duration of anesthetic exposure, there was no difference in learning outcomes compared to their confreres who had not been exposed at all.

However, two or more hours of anesthetic exposure was associated with a significant increase in learning disabilities.

This is graphically represented, where the bottom two curves have a solid line showing children who had a single anesthetic, which closely parallels that to the dotted line with no anesthetic exposure and compares that to the multiple anesthetic exposures, three or more, the dark, bolded line above.

They concluded that a single anesthetic exposure was not a risk factor for developing a learning disability later on in life, at least not through age 19; that multiple exposures, however, were a significant risk factor, but that the data don't discern whether it's the anesthesia that contributes to the learning disability or whether it's a marker for other factors that do.

Specifically, you can't distinguish between the potential effects of an anesthetic itself and those factors associated with it, such as the need for a surgical procedure or the stress response to

the procedure itself. You cannot discern if children requiring surgery differ from those who do not in a way that affects the risk for learning disabilities. And it cannot exclude for the requirement of multiple anesthetics as being a marker for children whose health is such that they would be at risk for learning disabilities anyway.

They also suggested that children with repeated exposures may have a higher burden of illness that can increase the risk of likelihood of learning disabilities. And as mentioned before, their area is predominantly a white, middle class community, so that limits the generalization of the results.

Also, it's not clear whether learning disability is itself a relevant outcome measure for assessing the neurotoxic effects of anesthesia, an issue that's still sort of being worked out in the animal studies that were presented.

Lastly, they went to further assess the possibility that co-morbidities could affect learning following an anesthetic, and this is a to-

be-published paper that we were permitted to look at for this advisory committee meeting.

Again, it was the same database as before. This time the anesthetic exposure was limited to children who received an anesthetic below the age of 2, and they identified 350 such subjects. They matched these two each for an unexposed control based on the risk factors for learning disabilities that are known, gender, mother's level of education, birth weight, and gestational age. And then they adjusted for co-morbidities. And this time, they used the ASA physical status system that was previously used, but also included the Johns Hopkins adjusted clinical group's case mix system, which looks at clusters of ICD-9 codes that would suggest possibility for other systemic diseases or health conditions that might affect learning later on.

The educational records were looked at for these children to identify those who were diagnosed with a learning disability, those who required an individualized educational program at some point,

and also to look at tests of cognition and achievement. And the individualized education programs were further subdivided into those that had emotional behavior disorders requiring such intervention and those with speech and language impairments.

What they found is when you looked at the emotional behavioral disorders, children that had a single anesthetic exposure were no different than the unexposed children, and they were unable to identify any who had more than two anesthetics that had any type of emotional behavior disorder that required an IEP.

In terms of speech and language problems, children with a single anesthetic exposure also did not differ from their unexposed colleagues, whereas those who had two or more anesthetics did substantially differ, substantially and significantly.

So, again, they concluded that multiple exposures to anesthesia can result in or it can be associated with some type of learning disability

later on. This time it was prior to age 2 for these multiple exposures, and that the association with learning disabilities appeared to be more with speech and language, but not for emotional or behavior disorders.

They also noted, too, that group administered tests of cognitive ability which were examined in this study, as well as group administered tests for achievement were consistent with but didn't seem quite as sensitive as the results of individual testing.

Again, there is still the possibility for unknown or unmeasured confounding factors to affect the outcome. And despite their more rigorous evaluation of the health status of the children, there might still be something going on that's not assessed with their two measures that could potentially affect the outcomes.

They do have some upcoming work. They're continuing to use this database for two other outcomes. One is to look at autism and the other is to look at attention deficit and hyperactivity

1 disorder. Those will hopefully be reported in the
2 not too distant future. And they're also planning
3 on looking at neurodevelopmental outcomes for
4 children who are exposed to modern anesthetics
5 prior to the age of 2.
6 At Columbia University, Charles DiMaggio and
7 his colleagues, including Lena Sun, who is here
8 today, developed their own database of patients to
9 look at neurodevelopmental outcomes for children
10 undergoing surgery and anesthesia, and they did a
11 retrospective cohort analysis for children born in
12 the three-year period between 1999 and 2001 who
13 were also enrolled in the New York State Medicaid
14 program. And they were able to develop a cohort of
15 383 children who underwent inguinal hernia repair
16 during their first three years of life, and they
17 compared these to a random sampling of children who
18 were matched for age and lack of history of hernia
19 repair before age 3, and that comparator group
20 consisted of more than 5,000 children.
21 They used ICD-9 coding to determine exposure
22 and they allowed for both inpatient and outpatient

herniorrhaphies. It could be a principal or secondary procedure for them. And the outcomes for learning abilities or disabilities was based on diagnostic codes that were either for unspecified delay or behavioral disorder. They also looked at autism, mental retardation, and speech and language problems. They were able to control for age, gender and complicating birth-related conditions, such as low birth weight.

In the two groups, they found there was no difference for age or loss to follow-up. For the exposed group, however, versus the unexposed group, they were mostly male, black, and diagnosed with other conditions at birth, including GI disorders that could account for the hernia, as well, CNS anomalies, low birth weight, and perinatal hypoxia.

The diagnosis of other problems at birth and male gender are commonly associated and would be expected to be seen with groups of children presenting for inguinal hernia repair. It's not clear about the slightly more likelihood for a black race.

But if you look at this table, which reports the results, you'll notice that in terms of race, the factor really isn't terribly significant. It just hits unity as opposed to crossing it, as does age. However, gender and birth complications are significantly higher for the group undergoing inguinal hernia repair, which, as I said, is not to be unexpected. However, the hazard ratio for anesthesia exposure is also significant, with those undergoing the hernia repair being more than twice as likely to have a learning disability diagnosed at some point after surgery.

They concluded that hernia repair prior to the age of 3 is associated with an increased risk of subsequent diagnosis for a behavioral or learning problem. It could not be explained by confounding either due to low birth weight, co-morbidity, or demographic characteristics, at least not those that they were able to look at within their database, and they said further studies are needed.

They do point out that the database they

1 have is a relatively blunt instrument to use to try
2 to establish a possible association between
3 anesthesia and related developmental outcomes.
4 In particular, because of the type of
5 anesthetic was used, either drugs, route type of
6 doses that were used or not available, they
7 couldn't distinguish the effects from anesthesia
8 from those due to surgery, and that the diagnosis
9 of learning disabilities is susceptible to bias
10 based on how these things are reported to the
11 Medicaid database.
12 There's also the potential for bias from
13 unmeasured cofounders, such as the reasons for
14 prematurity or resulting low birth weight. And
15 there's potential for differences between children
16 in the Medicaid group versus the general
17 population. Also, they only followed these
18 children for a couple years, so any long-term
19 effects are not discernible from this study.
20 In a second study, they looked at a birth
21 cohort of twin pairs, and they had nearly 6,000 to
22 do this with. And, again, they wanted to assess

1 the risk of anesthesia exposure before age 3 and
2 the development of either learning or behavioral
3 disorder.
4 What they looked at from these twin pairs
5 were people that were also in the New York State
6 Medicaid system between 1999 and 2005. This time
7 they followed them up to 6 years of age. It was
8 for any type of surgical procedure, not just hernia
9 repair, prior to age 3, and, again, they used the
10 ICD-9 codes to look for developmental and
11 behavioral outcomes.
12 What they found were of the 11,600-plus
13 children that were studied, only 6 percent were
14 exposed to anesthesia at least once by age 3.
15 During that time period, 19 percent were diagnosed
16 with developmental or behavioral disorders. Most
17 of these were -- a vast majority of these actually
18 were unspecified developmental delay.
19 The incident rates looking at exposed and
20 unexposed children were 34 and 16 cases per 100,
21 respectively, which led to an accrual relative risk
22 ratio of 2.5, which was significant. And after

adjusting for birth complications and gender, the risk ratio went down slightly, but it was still significant, and they're continuing to analyze this data as we speak.

Based on their analysis so far, they decided that children who were exposed to anesthesia are more than twice as likely as their peers to be subsequently diagnosed with a learning disability, and that the excess risk cannot be fully explained just by birth complications alone, and further studies are needed.

Also, coming out of Columbia is a study that's being spearheaded by Dr. Lena Sun, who is in our audience. This is the PANDA study, which refers to the pediatric anesthesia neurodevelopmental assessment study. It's a large-scale, multisite, strictly within the U.S., study. It's ambidirectional, where they're taking a retrospective cohort of children and following them out prospectively. And what they want to do is enroll a thousand children and use siblings as comparators and do direct neuropsychological

assessment on them. Exposure, again, is for inguinal hernia surgery prior to the age of 3.

So far, they have identified eight sites, all in the eastern half of the United States that will be participating. They're going to be looking at healthy children, relatively healthy with ASA physical statuses of 1 and 2, born after 36 weeks gestation, and who have only had a single anesthetic exposure for that hernia repair. The siblings will be matched within 3 years of age of the exposed child, and the children have to be between 8 and 15 years of age to participate in the study.

At this point, they've taken care of some of the paperwork in terms of developing a case report form and a means for capturing the neuropsychological tests. They've identified seven cognitive domains that they want to assess. They're looking at memory, motor skills, language and speech, visual-spatial, attention, behavior and IQ, and they've chosen 16 instruments that will be used to assess these. They also have some upcoming

1 works that are in press. One is looking at labor
2 analgesia and the developing brain, and a second
3 one is also looking at a sibling birth cohort for
4 effects of anesthesia exposure and, down the road,
5 learning disabilities.
6 Lastly, there is one randomized control
7 trial that's prospective and is ongoing as we
8 speak. This is referred to as the GAS study. It's
9 an international trial. Children's Hospital of
10 Boston is the U.S. sponsor and Dr. Mary Ellen
11 McCann who spearheads that effort is here with us
12 today as well.
13 A number of English-speaking countries are
14 involved and one non-English-speaking, Italy. And
15 what they're looking at, it's a non-inferiority
16 trial, it's observer blinded, and they want to
17 assess whether regional or general anesthesia
18 differ from each other, for children undergoing
19 inguinal hernia repair anyway, for
20 neurodevelopmental outcomes. And as a secondary
21 objective, they also want to look at apnea during
22 the post-operative period for both these anesthetic

1 techniques.
2 They've defined the types of anesthesia to
3 be used very specifically. Regional anesthesia is
4 to be bupivacaine only, up to 2.5 milligrams per
5 kilogram. It's administered in one of four
6 methods: caudal, subarachnoid, combination caudal-
7 subarachnoid, and subarachnoid and ilioinguinal
8 nerve block.
9 General anesthetic is to be limited to
10 sevoflurane, which is to be used for induction and
11 maintenance up to 8 percent inhaled concentration.
12 However, in addition to the general anesthetic,
13 bupivacaine can be administered, again, up to 2.5
14 milligrams per kilo via, either the caudal route or
15 the inguinal nerve block route for post-operative
16 analgesia.
17 In all, they wanted to include 660 infants
18 presenting for herniorrhaphy into the study.
19 Inclusion criteria are rather broad. It can be
20 unilateral or bilateral inguinal hernia repair,
21 with or without circumcision. The children have to
22 be at least 26 weeks gestational age, and no more

than post-menstrual age of 60 weeks.

The exclusion criteria include any reason to not randomize a child to either a caudal, spinal or general anesthetic; inability to follow-up; previous exposure to a volatile anesthetic or benzodiazepine agent; need for ventilation, mechanical ventilation prior to surgery; and any one of a number of other factors that would predispose these children to a learning disability separate from their need for inguinal hernia repair.

Their primary outcome measure is the Wexler scale for intelligence. That will be performed or assessed at 5 years of age. Secondary outcomes include the Bayley neurodevelopmental scale, which will be assessed at 2 years corrected age, and then they're just going to go ahead and characterize the apnea in the immediate post-operative period.

At this point, they have enrolled more than 400 subjects so far and they expect enrollment to be complete either later this year or early next year. So the Bayley scores should be reported

sometime in 2014 and the Wexler scores sometimes in 2017 when the study is complete.

So in summary, we have a number of nonclinical findings that were presented today, and these indicate that there's mounting evidence for anesthetic-induced toxicity both on a histopathological level and in the behavioral level following exposure to these drugs.

There's also some sunlight on the horizon there, because some of the studies have shown and suggest that there's possible safety margins that may exist between exposures used in animals and those which are used in the clinical setting. Also, there are some drugs that may not be associated with such findings.

On the other hand, we have clinical findings which come only from epidemiological studies so far, and these have conflicting results for single exposures. And regardless of the outcomes from these studies, causality, at least in terms of anesthetic exposure, cannot be established based on these kinds of studies.

There are prospective epidemiological studies and one clinical trial underway which will hopefully add to the information we have. But clearly, at this point, although a lot has been done, it's not enough to make any definitive conclusions or to fully resolve this issue.

Part of what will be important later on is the ongoing discussion among committee members for what type of clinical trials should be used in the future, and, in particular, designs, populations to be studied, especially now that we see that there's changes in terms of patient vulnerability or at least animal vulnerability, depending on their level of development and time of exposure.

Then there's also the issue that was raised by Bartels and colleagues about the possible potential need to do a pre-operative evaluation for neurocognitive function in patients presenting for surgery, if indeed their underlying problem is what's leading to the learning dysfunction as opposed to the exposure to anesthesia or the stress of the surgical procedure. And also is there a

need for children that do present for surgery and anesthesia to follow them more carefully and perhaps intervene more rigorously based on the animal data and limited human data to date.

Thank you.

DR. KIRSCH: Thank you. Our next speaker is Dr. Anand.

Presentation - K.J.S. Anand

DR. ANAND: Good morning. Delighted to be here today. I thank Bob Rappaport and his colleagues at the FDA for inviting me as a guest speaker. I'm going to only talk about one anesthetic -- ketamine -- and not across the preschool age span, but only in neonates. I want to focus primarily on the comparisons between rat pups and humans, although other species that serve as model animal species have similar findings.

So about 20 years ago, we published a clinical trial in the New England Journal where babies who were undergoing cardiac surgery were randomized to two different groups, one standard anesthetic, halothane-morphine versus hydro-

sufentanil, and we found important differences in mortality, the post-operative mortality in those babies.

After the study, there was a reduction in mortality following cardiac surgery, and this study really changed the paradigm in terms of focusing on the need for anesthesia. And the evidence for the need for anesthesia in neonates has accumulated over the past 20 years, so much so, as summarized recently by Frank Weber. But there's also an accumulating literature on the use of analgesic and sedative drugs in the neonatal ICU. And my colleagues in Switzerland and I published this review article where we tried to integrate the clinical trials and the lab data.

About 10 years ago, Frank Scalzo and I were thinking about this problem, and we've tried to see if -- we asked the question, "Do adverse neonatal experiences alter brain development and subsequent behavior?" And we came up with two different models or two different sets of experiences that neonates were being exposed to.

They were separated from their mothers, which we thought would lead to a lack of NMDA receptor activity and increase the rates of apoptosis. They were being exposed to repeated pain, which we thought may lead to excessive NMDA activation and lead to excitotoxic damage. Given this was very simplistic and 10 years ago, there's been a substantial amount of data that has now added to these hypotheses. Of course, the landmark article by Dr. Olney and his colleagues at Wash-U really focused attention on the potential toxicity of NMDA receptor antagonists and their effects on neuroapoptosis.

My colleagues and I at Arkansas Children's, here's Adnan Bhutta, Cynthia Rovnaghi and others, we took a different view, and we said that there are significant differences between human and rodent brains. We felt that there were very high doses that were used or high concentrations maintained in in vitro studies. There was a prolonged duration of anesthetic exposure, and all of this was done in the absence of any stimulant,

such as surgery or inflammation or other things.

Of course, I'm sure you're familiar with the ontogeny of NMDA receptor subunits, nicely summarized by Haberny and colleagues from NCTR, where, if you look in the cortical areas of the rat brain, basically, in the neonatal period, there's mainly the expression of the NRA1 and NR2B subunits of the NMDA receptor.

In the human neonatal brain, in contrast, there is the NR1 subunit, but there is an expression of NR2A, 2C and 2D, less expression of NR2B. So there are some basic differences between rodent and human brains that would change the calcium currents that are generated and the downstream effects on the cellular neurophysiology.

As mentioned before, we were concerned about the very high doses and prolonged exposures, and I go back to the pharmacologist of ancient times, where all substances are poisons. FDA knows that better than any other agency in the world. But it's the right dose that differentiates a poison from a remedy.

Taking this approach, we designed some studies which have been referred to before. I'll just quickly summarize those.

We took rats who were cross-fostered on the day of birth and were stimulated daily from postnatal day 1 to postnatal day 4. We randomized these rats to four different groups. One was a control group, which was undisturbed; one group received 4 percent formalin injections, one injection given each day into each paw, so four injections at one hour apart on each of those days, total of 16 injections.

There as a third group that received ketamine in two doses that were injected subcutaneously in the interscapular area, 2.5 milligrams for each dose. And then there was a fourth group that got the ketamine followed by the formalin injections. Prior to injection one and injection three of formalin was the ketamine dosing.

We allowed these rats to survive for another 20 hours and then sacrificed them on P5 and then

stained their brains.

So here is a summary of the data. These are cell counts using Fluoro-Jade-B, which is a nonspecific marker for cell death or neurodegeneration. And as you can see, in the cortical areas, compared to the control group, there was about a threefold increase in cell death in the formalin injection group, and this was completely blocked by giving ketamine just prior to the formalin injections. Similar patterns occur in other areas of the brain, although in the habenula, where there are no NMDA receptors, no synaptic NMDA receptors, there was no differences noted.

Several of these rats were allowed to survive to adulthood, and we tested their visual-spatial memory function in an eight-arm radial maze test. And what we find is that the rats who were in the formalin injection group took longer time at each of the events to find the bait as compared to rats in the other three control groups.

So based on this set of experiments, we proposed that injury or inflammatory pain increases

1 cell death in cortical areas about 3.3-fold and in
2 subcortical areas, as well. Could this be due to
3 NMDA receptor mediated excitotoxicity, since it was
4 being blocked by ketamine analgesia and we found no
5 change in apoptotic mediators?
6 We did find long-term behavioral changes in
7 these adult rats, where those exposed to
8 inflammatory pain had higher pain threshold,
9 impaired spatial learning, exaggerated startle
10 responses, and increased anxiety on a number of
11 tests.
12 So following the publication of these data,
13 the big question came, can we extrapolate from a
14 rat or mouse model to the infant who is in the
15 neonatal ICU or the cardiac ICU?
16 We do note that there is significant organ
17 dysfunction, affects all organs following
18 cardiopulmonary bypass, and this affects the brain,
19 as well. We know that the bypass associated injury
20 is mediated through glutamate excitotoxicity and
21 also that immature neurons are potentially more
22 susceptible to excitotoxic cell death.

1 So our hypothesis was that ketamine given in
2 a dose of 2 milligrams per kilo prior to
3 cardiopulmonary bypass will block the excitotoxic
4 neuronal cell death and inflammation and may have
5 some neuroprotective effects for bypass.
6 So we designed this as a placebo-controlled,
7 randomized trial, blinded, for children who were
8 less than a year of age. They had no other
9 chromosomal abnormalities. They were undergoing a
10 single lesion -- repair of an isolated surgical
11 ventricular septal defect. So no other lesions, no
12 cyanotic heart disease, et cetera. They were
13 randomized to two different groups. This was a
14 pilot study. We measured markers of inflammation,
15 NCNS injury at the end of surgery, at 6, 24 and 48
16 hours post-op.
17 Five neonates from each of these groups were
18 taken for MRI and MR spectroscopy before surgery,
19 and then a week later, they were taken back for MR
20 spectroscopy to measure in vivo metabolites in the
21 brain of these children. We also did Bayley infant
22 development scales before, as well as two or three

weeks after the surgical operation.

So just to summarize those data, we found significant differences in the expression of C-reactive protein, with higher levels being found in the control group at 24 and 48 hours as compared to the ketamine anesthesia group. The levels of neuron-specific inlays peaked at about six hours in both groups, although the peak tended to be higher than the ketamine group and the control versus the ketamine.

Looking at the MR spectroscopy data, when we use a short spin echo time, 35 milliseconds, we can measure glutamate and glutamine levels in both white matter and gray matter of the brain. And we took frontal white matter as our representative area, and we found that glutamate levels were lower in the ketamine group versus the control group in frontal white matter and actually decreased from pre- to post-op, post-surgery MRI scans in the ketamine group, whereas there were -- that was not seen in the control group.

Using a longer spin echo time, we were able

to measure other metabolites and found that creatine increases in the control group pre- versus post-surgery, suggesting a greater energy requirement in the basal ganglia, which was our gray matter representative area, which is occurring in the control group, not noted in the ketamine group.

In both the basal ganglia and the frontal white matter, choline levels decreased pre- versus post-surgery in the ketamine group, but there were no such changes in the control group. Choline simply signifies a greater turnover of neurotransmitters in the control group.

So based on this very small pilot trial, we also found differences which were not statistically significant in the Bayley infant assessments, but it was a very small sample.

So these data at least on the pilot study suggest that ketamine given prior to cardiopulmonary bypass can reduce inflammation and neuronal injury during bypass. The MR spectroscopy shows that infants who received ketamine had less

glutamate release, lower choline or neuronal metabolism, and less creatine levels. These are internally consistent findings in the MR spectroscopy.

We did near infrared spectroscopy, which is a clinical monitoring tool post-operatively, and found greater chaos and complexity in the control group versus the ketamine group. And so we have now proposed a large multicenter trial to confirm these results, and this is an application pending with the NHLBI.

However, coming back from the bedside to the bench, there is very clear data from NCTR and other places where the potential neurotoxicity of ketamine occurs following high doses and prolonged exposures, and you need both of those.

With permission of Merle Paule and my other colleagues from NCTR, here are some of the photomicrographs showing caspase-3 expression in a control group -- in the control group following saline injections, ketamine 5 milligrams per kilo, ketamine given at 10 milligrams per kilo times six

1 injections, or 20 milligrams per kilo. So you see
2 only when you give 20 milligrams per kilo, six
3 injections, is when you see increased caspase-3
4 expression.
5 This is neatly summarized in this figure,
6 where the number of caspase-3 positive neurons is
7 increased significantly only when there are six
8 injections given at the highest dose, which is 20
9 milligrams per kilo. This is replicated using the
10 Fluoro-Jade labeling, which looks at apoptotic and
11 non apoptotic cell death. Again, a very similar
12 pattern emerges.
13 So I think when we look at high dose
14 prolonged exposure of ketamine, there are three
15 factors that have not been considered until now I
16 think. One is the effect of ketamine on non-NMDA
17 receptor populations, which is very well
18 characterized. What are the roles of synaptic and
19 NMDA receptors versus the extra-synaptic NMDA
20 receptors, because they have completely opposing
21 downstream genetic and neurophysiologic effects.
22 And what are the effects on neural stem cells,

which has been referred to in a previous talk?

So just considering non-NMDA receptor effects, ketamine has agonist activity on dopamine D2 receptors, the serotonin receptors, as well as your mu and kappa opioid receptors. So we need to dissect out where the cellular and neurophysiological effects are occurring from the high doses of ketamine.

There's also a noncompetitive antagonism of nicotinic acetylcholine receptors, which, as you know, these are receptors involved in a number of cellular processes, including survival, including learning and memory, and other functions.

So very recently, Hardingham and Bading published this review in Nature Reviews, where they said that there is a longstanding paradox in that NMDA receptors both promote neuronal health and kill neurons, and the recent study showed that these NMDA receptor-induced responses depend on the receptor location.

Stimulation of synaptic NMDARs acting through nuclear calcium signaling leads to the

buildup of a neuro-protective shield, where stimulation of extra-synaptic NMDARs promote cell death. And this is very nicely followed.

The traditional model -- this is taken from a figure in Nature Medicine about 10 years ago -- was that the degree of calcium influx into the cell determines the effect of NMDA receptor activity on that cell. So if there is too little or if there is too much, you get neuronal damage and neurodegenerative changes. However, if there's optimal calcium influx, it promotes dendritic arborization, it promotes a number of other cellular functions.

So this was the traditional model, and this is now being challenged by -- or revised by accumulating data insomuch that where you have, on the Y-axis, a survival-promoting and death-promoting activity, when you follow the increase in NMDA receptor activity, as synaptic and NMDA receptor activity increases, there is more and more cellular functions promoting survival. As extra-synaptic NMDA receptor activity increases, there

occurs a cross-point where the extra-synaptic NMDA receptor activity overwhelms the synaptic NMDA receptor activity and promotes cell death, and that's becoming clear more and more.

We do know that immature neurons, particularly in the perinatal period, up to 75 percent of NMDA receptors are extra-synaptic. The proportion consistently progressively decreases during development into adulthood. These extra-synaptic receptors generate smaller initial calcium currents, but if you only activate the extra-synaptic NMDA receptors or if you activate all NMDA receptors, the synaptic and extra-synaptic, you get the same amount of cell death.

So the way they work is by shutting off the CREB transcription factor and signaling pathway. They decrease the RAS-ERK1/2 pathway. They activate the 4CAD FOXO protein in the calpain pathway, which up-regulates P38 and promotes greater expression of pro-apoptotic factors.

This occurs through importing FOXO across the nuclear membrane. The main players are the

1 FOXO-1 and FOXO-3, which then up-regulates proteins
2 like the thioredoxin-inducing protein, the BCL-2
3 interacting mediator of cell death, and the FAS
4 ligand. And all of these lead to further
5 activation and disruption of the mitochondrial
6 membrane release of cytokine C, finally leading to
7 apoptosis.
8 However, if you have synaptic NMDA receptor
9 activity, there is an activation of the anti-
10 apoptotic genes. There is suppression of pro-
11 apoptotic gene expression. Other survival genes
12 are activated. The glutathione system is
13 activated, which prevents antioxidant effects on
14 the cell, or causes antioxidant effects on the
15 cell. And there is pro-survival gene expression,
16 which leads to an increase in the mitochondrial
17 membrane potential and less disruption of
18 mitochondrial occurrence.
19 So this protects against or builds a
20 neuroprotective shield. And this is very
21 important, because if you look at the clinical
22 situation, babies are undergoing surgery or pain or

they're getting repeated procedures performed which activate NMDA receptors, only those NMDA receptors that have an open channel, ketamine will only bind to NMDA receptors with open channels. So it blocks the synaptic activity occurring as a result of pain.

If you have high doses of ketamine and prolonged blockade of those synaptic NMDA receptors, there will be constitutive release of glutamate, which causes a spillover from the synaptic cleft, thereby activating your extra-synaptic pathways and then activating the multiple pathways leading to apoptosis, which I've referred to already.

Your synaptic NMDA receptors will activate the PI3 kinase pathway, increase AKT, and then this results in exclusion of FOXO1 and FOXO3 from the nuclear membrane, whereas the extra-synaptic NMDA receptors promote this entry into the nucleus, which then binds to the FOXO binding side and leads to the transcription of a number of factors promoting apoptosis and cell death.

So the third thing that I want to focus on is the effect of this drug, ketamine, on neural stem progenitor cells. And this is data from my lab, where we take cells from embryonic brain at E17. We culture them in monolayers, as well as neurospheres, and we can characterize those cells using nestin staining over here and TUJ1 staining to characterize their lineage into neurons and astrocytes.

So here we've looked at proliferation assays. We've looked at differentiation of these neural stem progenitor cells. And then by exposing these in vitro cultures to different concentrations of ketamine, we can look at their impact on subsequent development.

We've also characterized NMDA receptor subunits in these NSPCs. So this is taking the ventricular and subventricular zone, and we can show the expression, abundant expression of the NR1 receptor, and over here, very little expression of the NR2A receptor, but abundant expression of NR2B, which is characteristic of rodent brains.

So here is some of that data. When you expose different concentrations of ketamine for 24 hours and then we fix and stain these cells, we find no increases in apoptosis up to about 50 micromolar concentrations. Only at 100 micromolar concentration did we find a significant change from control. We also looked at necrotic cell death and we find no changes in these cells just being exposed to ketamine.

We looked at a time response. So we take 10 micromolar of ketamine and expose these cells for a number of hours, and all the way up to 48 hours, we found no increases in cell death. We also looked at the LDH assay to look at apoptotic versus necrotic cell death; again, no differences between control and ketamine.

We do find, as do Stratmann and others, that exposing these cells, neural stem cells to ketamine, there is an inhibition of their proliferation. So we do that by exposing them to ketamine plus BRDU 10 micromolar, and we find that at all of the concentrations that we tested from 1

micromolar to 100 micromolar, there is a suppression of neurogenesis. But BRDU stains only the S phase of dividing cells, and if you look at a much more representative marker, it is at the higher concentrations, 20 to 100 micromolar, KI67 stains all phases of cell division in these neurons.

So there is a suppression of proliferation. We characterize this even more in detail in the ventricular zone and subventricular zone, showing that the BRDU positive cells are decreased at the higher concentrations of ketamine both in the VC and the SVC separately.

We found that prolonged exposure of ketamine at 10 micromolar with the BRDU results in differences at 24 and 48 hours, looking at BRDU incorporation or KI67 staining only at 48 hours. So prolonged exposures, 24-48 hours, will inhibit the proliferation of these neural stem cells.

Like others, we found that ketamine promotes differentiation of these stem cells into the neuronal lineage rather than the astrocytes or

oligodendrocytes, and this is seen at all concentrations that were tested from 1 to 100 micromolar.

We also found that when we used 10 micromolar ketamine, since that is the clinically relevant concentration, we find that there is an increase in differentiation into neuronal cells, seen after about 10 or 12 hours of exposure. So this promotes greater production of neurons from these stem cells.

So to conclude from these studies, we've shown that neural stem cells are resistant to the neurotoxic effects of ketamine at low or clinically relevant high doses. The proliferation of NSPC is inhibited by ketamine in a concentration and time-dependent manner, and this was confirmed from in vivo and in vitro experiments; and, that ketamine enhances neuronal differentiation of neural stem cells, again, in a concentration time-dependent manner.

So I'll close at this point. I urge the committee -- thank you for your attention. I urge

the committee to consider this question really seriously. The lives of our children are at stake in terms of the long-term outcomes following surgery with lack of or inadequate anesthesia as opposed to the anesthetic exposure required for surgical operations.

Thank you.

DR. KIRSCH: Thank you. Our last speaker before lunch is Dr. Nelson.

Presentation - Robert Nelson

DR. NELSON: This will be a bit of a change of pace. I've been asked to provide some ethical reflections on the questions that are before the committee today, and I've chosen to organize my thoughts using the categories made infamous by Donald Rumsfeld contained in the quotation that's cited in the slide.

In addition to his three categories, the known knowns, the known unknowns, and the unknown unknowns, I'm also going to add a fourth one and I'm going to call it the "unknown knowns." And I trust that my use of these categories will

hopefully become clear as I move through my presentation.

So the first is the known knowns. So the committee is being asked to discuss the nonclinical and clinical data that's been presented today, and I will say it is an overwhelming amount of fairly complicated data.

In other words, answering the question of what we know is a necessary prelude to discussing what we don't know. One would hope that we can come to some agreement about the facts. The problem is that each fact is shaped by the investigational context within which it was established. It has attached to it a measure of certainty or uncertainty about the truth of that fact.

As a result, factual agreement may be a necessary first step, but it may also be a limited step when we begin to address question 1, whether or not these facts can be applied to the clinical setting.

In a clinical setting, we would like to know

the probability of either harm or clinical benefit from a prospective proposed intervention for that specific individual set within the context of their disease process and of any available alternatives.

Even if we achieve an accepted degree of scientific certainty about the truth of a given hypothesis, using, for example, a classic prospective, randomized, controlled trial as the gold standard, with a p-value of less than .05, this information tells us we can at least be 95 percent confident that the results of the experiment did not occur by chance. But it does not inform clinical decision-making.

So even if we can agree on the scientific facts as currently known, these facts will not easily translate into the clinical setting.

So now to the known unknowns. Question 2 asks the committee to discuss and propose a research agenda that would address important unanswered questions about the use of anesthetic and sedative agents in pediatric clinical practice. For example, and these are some that I came up

with, you've seen a number of other questions on the presentations this morning, what's the role of surgery or pain in mitigating the potential for developmental anesthetic neurotoxicity? Is that toxicity linear, as it might be with lead, or nonlinear, with perhaps a threshold of anesthetic exposure below which there is no neurotoxicity?

Can we achieve a more nuanced understanding of exposure response with appropriately designed clinical trials using nonhuman primates or other animal models? How do these animal models translate into the human clinical environment? Can we establish noninvasive biomarkers of anesthetic neurotoxicity that can be adopted for use in human clinical trials?

These and other questions that the committee may identify are best understood as known unknowns in that the question can be identified and a scientific protocol designed to answer that question.

Towards the end of my remarks, I will comment on our ethical framework for conducting

1 pediatric studies. Here I simply want to point out
2 that a research protocol will require a document
3 and process for obtaining parental permission.
4 So how does one describe the research
5 question to a parent who is being asked to permit
6 their child to be enrolled in such a protocol?
7 Does one simply describe the known facts and
8 present the research question without passing
9 judgment on the importance of the risk reduction
10 strategy contained in one treatment arm of the
11 protocol? Would parents preferentially select the
12 risk reduction strategy if it is available outside
13 of the protocol?
14 Presumably, the risk reduction strategy may
15 have its own set of risks, even though it may be
16 avoiding the risk of anesthetic neurotoxicity. How
17 are these different risks presented in a way that
18 allows for a meaningful choice?
19 In effect, the decision to enroll in a
20 clinical protocol that tests a risk reduction
21 strategy is to take an action in the face of
22 uncertainty.

I will offer some thoughts on this difficult question under the category of unknown unknowns, which may be a bit of a stretch to maintain the categories. But before doing so, I'd like to touch briefly on the new category that I'm proposing of unknown knowns. And in that category, I would ask the question, is ignorance of the known facts an option. Should what we know be kept from others, since we don't know what to do with the data, besides more research, or how to describe the risks in a meaningful way?

What is our professional responsibility to educate others? Personally, I do not believe that ignorance remains an option.

In addition, it will be hard for us a professional community to motivate others to contribute to a research agenda, whether through providing financial resources or enrolling their children, if, at the same time, we are counseling parents not to worry about these findings. We can't have it both ways.

Unknown Unknowns. So how do we incorporate

1 this information into our clinical practice of
2 informing parents of the risks of anesthetic and
3 sedative agents? Risk is usually understood as the
4 probability of a specified harm. Are we currently
5 able to specify the probability of neurotoxicity
6 based on the level of anesthetic or sedative
7 exposure?
8 Do we have an understanding of the magnitude
9 of that neurotoxicity and how it may impact on the
10 performance of cognitive and behavioral tasks?
11 Absent that information, how are we to
12 effectively communicate these concerns to parents
13 in a way that enables them to incorporate it into
14 their decision-making, or are we simply asking
15 parents to be aware of these issues even though
16 there is no obvious way that this information can
17 be incorporated into current decision-making?
18 Absent a clear alternative, are we left with
19 simply assuring parents that we will minimize
20 anesthetic and sedative exposure as far as
21 possible?
22 One can expect that parents will incorporate

1 this information differently. Decision-making in
2 the face of known risks is difficult enough. Other
3 than avoiding surgery, which in most, if not all
4 cases, may be not an option, it is difficult to see
5 how this information can be translated into
6 actionable knowledge.
7 Now, some comments on the ethical framework
8 for research. So in approaching the necessary
9 scientific protocols, we already have a fairly
10 robust ethical framework for conducting clinical
11 research involving children. What are some of the
12 principles that we should keep in mind as we design
13 these protocols?
14 First and hopefully most obvious is that any
15 research protocol enrolling children must offer a
16 direct clinical benefit that is comparable to the
17 non-research alternatives. Practically speaking,
18 any modifications of the usual practice of
19 pediatric anesthesia should be designed to mitigate
20 the risk of neurotoxicity.
21 Interventional studies designed to establish
22 the level of anesthetic exposure necessary to

induce neurotoxicity under different conditions will need to take place in animal models.

As such, these animal models need to be developed to inform clinical practice and to serve as the initial platform to explore mitigating strategies or early phase antidotes for developmental neurotoxicity.

There is, of course, a role for human clinical studies of different risk reduction strategies. Although important, these trials may be of limited significance if we discover that the neurotoxicity from anesthetic exposure is not linear, but has a threshold below which such toxicity does not occur. In other words, we may have negative findings in research where the exposure does not exceed that threshold.

Although clinical trial are usually designed to answer an efficacy endpoint, there is no a priori reason why a clinical trial cannot be designed to answer a safety endpoint, provided that we're not doing anything to intentionally increase the risk exposure within the clinical trial.

Given the uncertainty that remains about the applicability of the nonclinical and existing clinical data to current anesthetic practices, it remains reasonable to test risk reduction strategies against standard anesthetic practice.

So let me end with some thoughts on professional responsibility. The pediatric anesthesiology community has had a longstanding commitment to the continued improvement in the safety and efficacy of anesthetic practice. It can point with pride to the decreased morbidity and mortality associated with the provision of general anesthesia over the past several decades.

I'll also say that pediatric critical care and neonatology community can also I think point with significant improvements in the morbidity and mortality of the provision of intensive care over the last several decades as well.

We are now faced with a new challenge. Rather than short-term and overt adverse drug reactions, such as chest wall rigidity or post-operative nausea and vomiting, we are now faced

with a potential long-term and silent adverse drug reaction that could be resulting in significant neurobehavioral toxicity. Tackling the complicated questions that we are now facing will require partnerships, resources, and commitment.

Thank you.

Follow-Up Questions to the Presenters

DR. KIRSCH: Thank you. Those were extremely helpful comments. Thank you.

So now we have a few minutes before lunch to have the members of the panel ask questions of any of those who made presentations this morning. I'd ask for members of the panel to, if you have a question, raise your hand and we have a list here that we'll write you down in order.

I'd also ask you, when you make a comment, try not to be redundant from comments that were previously made or ask questions that have already been asked and answered. And if I believe that the question has been asked and answered or your comment is redundant, I'll ask to go on to the next person, to try to be efficient with everyone's

time.

So with that said, are there any questions for any of the presenters this morning? Dr. Soriano?

DR. SORIANO: Sul Soriano from Boston. I agree that these preclinical data are certainly convincing and definitely have been duplicated by several laboratories. But the issue is what role does plasticity have to play in this?

I like to point out the study by Andreas Loepke from Cincinnati Children's Hospital, where he did the same model, exposed neonatal mice to isoflurane for a prolonged period of time, got the neurodegenerative changes as well as caspase-3 activation in the acute setting, but allowed some of these mice to grow to adulthood, and did some neurobehavioral testing, where he found no changes, no differences in their neurobehavioral scores. And they had I think about a battery of four or five different tests.

Furthermore, he did neuronal counts of these adult mice who were exposed to these anesthetic

drugs, as well as no drugs at all, and found that there was no decrease in the neuronal counts.

If you look at some of the data on injuries, injury paradigms exposed in neonates, you can see that a lot of them all have some recovery. Unfortunately, there's no developmental neurobiologist on this panel.

I was wondering if anyone here can comment? Perhaps Vesna or Dr. Ikonomidou, discuss some of these issues, specifically the role of -- the question is, what is the role of plasticity, and is it something that we're missing in some of these studies? Is it something that has to be examined? It's a known unknown, I guess, if you want to categorize it the way Skip has in his presentation.

DR. KIRSCH: Please use your microphone.

DR. IKONOMIDOU: I'm Chris Ikonomidou from UW in Madison.

I don't think we have enough data, I believe, that I'm aware of, that we can answer the question how plasticity modifies this. The fact that plasticity, especially in early childhood, can

counteract, to a great extent, developmental insult, it's a well documented fact.

We see that in children with cerebral palsy, I see that in children with traumatic brain injury. But to what extent developmental plasticity will counteract neurocognitive deficits resulting from exposure to anesthetics or antiepileptic drugs, I'm not aware of any studies to address that.

Now, would it be reasonable to do these kind of studies? Certainly. I think though that if we are to prioritize things, perhaps this would not be the first one to put on.

DR. KIRSCH: Dr. Flick?

DR. FLICK: This question relates to the concerns that I think were nicely outlined by Dr. Anand, about the effects of anesthetic exposure in the absence of pain.

I'd just ask the folks at NCTR, when you instrument these rhesus macaques for your studies, can you tell me how exactly you instrument them? Are there invasive monitoring lines placed? What is exactly the process that goes into monitoring

these animals?

DR. PAULE: So for the monkey studies, usually there's an initial injection, IM injection of ketamine to induce anesthesia followed by a central line put for the drip, and then the animal is maintained in an incubator to maintain body temperature and the like.

DR. FLICK: How is the central line placed? Is that percutaneously or is it using a cut-down approach?

DR. PAULE: Percutaneously.

DR. FLICK: And is that the only monitoring line, that's where you get your blood gases and those sorts of blood samples?

DR. PAULE: Yes.

DR. FLICK: Is there an arterial line placed, as well?

DR. PAULE: No.

DR. KIRSCH: Dr. Inder?

DR. INDER: Thank you. I was wanting to follow-up on one of Dr. Anand's clinical studies, as well, and perhaps to draw some further

discussion. In a lot of what we're viewing, we're viewing everything from sedative medication, anesthesia exposure for a variety of conditions, and then anesthesia exposure and perhaps really the ketamine story, he's getting at neuroprotection in the case of cardiopulmonary bypass with a cerebral insult. And I think each of these things are very distinct and different, and if we lump everything together in this way, we may be oversimplifying grossly what's a very complicated story.

I wonder if you feel that ketamine in this role is really neuroprotective in the setting of cerebral ischemia associated with cardiopulmonary bypass rather than confusing it with the issue that has been for the rest of the day, that of anesthesia exposure as a risk for neuroapoptosis.

DR. KIRSCH: Dr. Anand, if you could come up to the microphone here, it would be great. Thank you.

DR. ANAND: Terrie, thank you for bringing that up. You're absolutely right. The excitotoxic damage that occurs as a result of cardiopulmonary

bypass is because of a number of factors. There's microemboli, there's hypothermia, hypoxia, ischemia during the aortic cross-claim time and things like that.

What's sort of surprising, although not very surprising, is that the differences that we found between the groups were at 24 and 48 hours after the surgery, or the neuron-specific inlays was at six hours after the surgery. So I think what's activated is an inflammatory cytokine response as a result of non-pulsatile flow and exposure to extracorporeal membranes, et cetera, which then leads to the ongoing vulnerability.

So I think as a clinical model, we could choose this or we could choose, like the PANDA study has done, a simple inguinal hernia operation. I think it depends on how you want to assess the effect of your treatment.

DR. INDER: I just think it's a very important point, and the same thing holds, for instance, for the antiepileptic drugs in the setting of either an ischemic cerebral insult,

where you are trying to down-regulate excitotoxic, or a non-ischemic cerebral insult setting, which is the vast majority of surgical exposures for children. So I think they are very important differences for us to be cognizant of.

DR. KIRSCH: Dr. Diekema?

DR. DIEKEMA: I'm not sure if anybody can answer this or not. But the scope here is clearly on early childhood, and I understand that that's because we have this major expansion in the brain architecture at that point in time. But it seems like we're learning that a similar expansion occurs during adolescence, with significant increases in myelination and prefrontal cortex development, laying down of tracks between brain regions.

So I guess my question is whether we should also be concerned about the impact of anesthetics and these sedative agents at that particular age group.

DR. KIRSCH: Would any of the speakers like to comment on that question?

DR. PAULE: I think it's clear that puberty

needs to be another huge concern, and we're trying to follow the animals that I discussed today through puberty to find out if there's not going to be some new surprise that happens during development at that point.

We know for certain that at least nonhuman primates are differentially sensitive to a series of psychotropic drugs, for example, the amphetamine class. You can pour cocaine and amphetamine into an infant monkey and nothing happens. You take 1/10th or 1/30th of that in an adult and they'll be bouncing off the walls.

So there are huge differences during development and I think puberty has got to be a definite consideration.

DR. KIRSCH: Dr. Majumder?

DR. MAJUMDER: I was going to ask about adolescents, and in the interest of not duplicating, I'm searching for something else. And I did have one other question.

I was looking at the minutes from the 2007 meeting, and there was a bullet about looking at

potential gender differences and susceptibility to neurodegeneration. So maybe just in a slightly different direction, has the research turned up anything on that front?

DR. KIRSCH: Would any of the speakers like to address the question?

DR. PAULE: I think any gender differences are obviously important. We don't really have enough in our cohort to tease that out, because we have a small number of animals. But it certainly is I think a big consideration.

DR. KIRSCH: Dr. Weinstein?

DR. WEINSTEIN: I think Dr. Anand has done some of that work.

DR. ANAND: I was waiting for permission. So basically, we've done the same sort of experiments and looking at long-term outcomes using morphine, a two-by-two factorial design, and looking at the long-term effects.

So morphine in male rats seems to protect against some of the long-term neurobehavioral consequences of repetitive neonatal pain. Ketamine

has that effect in female rats, and that's what we've noted in a couple of papers published.

There are also important differences in early life in terms of the cellular mechanisms that are somewhat accentuated. So this is the data of Bob Clark and colleagues from Pittsburgh, where they've shown that immature brains, female brains will respond to an insult like hypoxia or hypoglycemia with increased apoptosis, whereas male brains will respond to the same insult with greater excitotoxicity.

How that impacts anesthetic neurotoxicity remains to be explored.

DR. KIRSCH: Dr. Swedo, do you have any comments? I'm sorry.

DR. WEINSTEIN: Go ahead. My ignorance.

DR. KIRSCH: Dr. Swedo? Excuse me. You had a comment related to the specific question that was being asked? Okay.

Dr. Weinstein?

DR. WEINSTEIN: My ignorance. I listened to the threshold phenomena, and I'm trying to

1 understand whether people believe that everybody,
2 every animal, every human, is affected by the
3 particular agent of interest and has a little bit
4 or a little bit more, or whether there truly is a
5 threshold within which you -- below that, nothing
6 happens and you cross that line.
7 For those people that are studying the
8 primates and the humans, the question, are there
9 biomarkers or some sort of marker of susceptibility
10 to injury with exposure of something. We talk
11 about looking for malignant hypothermia and looking
12 at muscle. Is there something comparable that one
13 can look at in terms of EEG frequency, biomarkers
14 of inflammation, whatever, what else? Is this an
15 all or none, everybody has a little bit or is it
16 truly two different populations?
17 DR. KIRSCH: Dr. Paule or Dr. Olney?
18 DR. PAULE: Well, I don't think we have
19 right now any good markers to a priori identify
20 animals that are going to be more or less
21 susceptible to the phenomenon. We certainly know
22 that some animals are more sensitive than others

after the fact, but we don't know yet, at least I don't know of any information that would allow us to make that prediction.

DR. WEINSTEIN: But if you look after the fact and say these are the differences between those who are affected and those who are not, can you take those data and begin to apply them prospectively to see what happens?

DR. PAULE: I think that's a perfectly good suggestion, and I think we should try to pursue that, even by looking at genetic differences or something like that. And we could certainly do that. We could look for snips and so forth and to see if there is some way to differentiate that group of animals. We simply haven't done that yet, but one of the good things about keeping our animals around for a long time is we can now go back and ask those kinds of questions.

Also, with the newer imaging techniques, we can do MRS on these animals and see if there are some noticeable differences in basic brain metabolism, for example, and that might give us

some issues, too.

So, yes, I think those are avenues that we absolutely need to look at, and the more suggestions we can get, I think the better off we're going to be.

DR. KIRSCH: Dr. Ikonomidou?

DR. IKONOMIDOU: I wanted to ask something about the phenomenon of oligoapoptosis. John, that's for you.

This is a very interesting phenomenon, especially given the fact that in premature infants, we have the problem of selective white matter injury, periventricular leukomalacia.

So I wanted to ask if there are any areas of predilection in the brain, in the primate brain, where this injury is being seen, or is this just a generalized phenomenon?

DR. KIRSCH: Dr. Olney, could you come to the microphone, please?

DR. OLNEY: The damage that we see in the nonhuman primate brain -- we are studying both fetuses and neonates. The damage in the fetal

brain is both age-specific and agent-specific, and the regional distribution of the degeneration is agent-specific and age-specific.

So in the fetal brain, for example, we see a great deal of damage in the basal ganglia and thalamus, which I think is concerning, because you have published data showing that antiepileptic drugs cause neuroimaging evidence of decreased neuronal mass in the basal ganglia.

It is well known that in the fetal alcohol syndrome, it has been reported repeatedly that there is a decrease in neuronal mass in the basal ganglia following fetal exposure to alcohol. And in the neonatal animals that we're exposing, for example, to isoflurane, the regional distribution of the lesions are quite different from the neonatal animals that we expose to ketamine.

Ketamine doesn't have the effect that I showed in the primary visual cortex or the temporal cortex. At the same age, the two drugs are causing a different pattern of degeneration.

There's also some overlap in the patterns.

For example, in the fetus, the basal ganglia lesions that I referred to, all three of the agents we've studied in the fetal period do seem to have an affinity for damaging the basal ganglia.

DR. KIRSCH: Thank you. Dr. Susser?

DR. SUSSER: To me, there seems to be a striking imbalance both in the readings we were given, in the talks, and in the whole field in the sense that 90 percent of it is animal models and 10 percent are human studies.

There is just so much that could be done in human studies that isn't being done. I don't know why. We don't even know, for example -- well, let's start with the gender question. We know males are more likely to get neurodevelopmental disorders in general than females, often by ratios of 4 to 5 to 1. But we know that already. That has many implications to the animal studies.

But we don't even know what the variation in practices is for the use of anesthetics in young children across regions, across social classes, across communities, across countries. And you can

assume, based on every other study that's been done of clinical practices, that it varies enormously. But we haven't looked at that yet, and that would be a clue that we could start with to see what is the impact by looking at different places that are using different procedures and so forth.

Secondly, there are whole populations that one can study nowadays, the Scandinavian countries, Israel, other places. There are pregnancy cohorts of size 100,000 and so forth, where the children are now growing up. There are all these opportunities where you can implement really rigorous designs, and we haven't heard anything about it, just a few good studies that are now coming out of two places, Mayo and Columbia.

It's very difficult for me to see how we'll ever answer these questions without turning to these human study opportunities that are right at hand. And I guess it's more a sociological question.

My question is, why is that? Why is there so much focus on the specifics of the animal

studies and so little on human studies?

DR. KIRSCH: I think that's actually what the FDA is looking for us to suggest this afternoon in one of the questions. So keep those thoughts in mind and we'll make those suggestions so that funding opportunities will become apparent for those kinds of studies.

Dr. Swedo?

DR. SWEDO: I had a question for Dr. Mellon, and that was because you did such a beautiful review of the nonclinical literature for us.

How do you reconcile that, which seemed to suggest that ketamine is quite problematic, with Dr. Anand's findings that it may be protective? I just don't know enough about how these are impacted.

DR. MELLON: The challenge of extrapolating animal data to humans is obviously a large one and from a regulatory perspective, we frequently try to establish and use the information from the nonclinical studies to be able to come up with exposure margins that would say this dose is

problematic, this dose is not.

I think that part of the data that we're actually generating with ketamine, in large part, through the work that NCTR is doing, is starting to define more for that particular compound the durations and the doses which seem to be correlating with adverse consequences and defining that window of vulnerability. That part, at least in the absence of an overt surgical stimulus or painful stimulus, has provided a lot of information particularly for that compound. But, unfortunately, we don't have a lot of information for all the others.

One of the best things that we can do when we try to design the nonclinical studies is really that key point, try to mimic the clinical setting as closely as possible. That's a very challenging thing to do, and a lot of animal care and use committees are actually not real inclined to accept and allow some of those studies to take place due to some of the ethical concerns of providing a painful stimulus in the absence of treating the

pain in the animals.

So I think, though, that clearly we can try to extrapolate as much as we can from the data in the absence of a surgical stimulus, but additional studies to try to put that into perspective, I think are one of the things that we could really use, and there's very limited information there, to try to see whether or not these types of interactions could counterbalance each other, and in reality perhaps the anesthetic is the helpful agent.

But once you know those doses and durations and thresholds, I think it will help us eventually try to put those findings into context and perhaps even choose compounds that are less likely to cause problems, and perhaps eventually we'll have enough information to be able to make and inform those decisions.

I'm not sure if that answered your question.

DR. KIRSCH: Yes, Dr. Swedo?

DR. SWEDO: I had a second question and comment that's on the clinical side, and that was

following-up on Dr. Nelson's knowns, unknowns, and known knowns. But the epidemiologic literature that we have is a good start, but it's extremely limited, and I'm frankly quite anxious about the upcoming study from that Mayo sample looking at autism, because they've defined the sedation as the risk, and I would have defined the autism as the risk for the sedation, since we know that children with autism spectrum disorders have to be sedated for dental procedures, for EEG lead placement, for dozens of things that healthy, typically developing children don't.

So I think in our afternoon discussion, it would be really helpful to think about some of these confounds that are known quite well, and that's the biggest limitation that I can see so far in the data that have been reported is they might look at a couple of perinatal factors, but they're not looking at the fact that children who have multiple anesthetics would be expected to have some speech and language delays, because they're getting those for ear tube placement. So trying to do a

better job of separating the reasons these kids are having the anesthetic to begin with might be helpful.

DR. KIRSCH: Dr. Flick?

DR. FLICK: Let me just respond to a couple of those points; the first point, the question of autism. That study is done using a different cohort than the cohort that we've used for our other. We have an autism cohort. It's relatively small. If memory serves me correctly, it's about 125 kids.

Now, we have the advantage of having essentially complete medical records and school records of all of the children that we study. That study is actually completed. We have those data, and what we find is really no difference in those groups, except in one unadjusted analysis based on duration of exposure.

We made a decision as a group not to publish those data because of our concern that they didn't make a significant contribution to the literature and may tend to be misinterpreted. We certainly

would revisit that decision, but autism is a highly emotional problem and we did not want to muddy the water with that.

With regard to your example of myringotomy, that question was raised in letters to the editor after our first -- The Wild publication.

There are a couple of points that need to be remembered. Number one, myringotomy has never been shown to be effective in reducing the incidence of hearing problems. Number two, hearing problems are poorly correlated with learning disability. Three, if one thinks of the kids who are exposed to anesthetic and got to myringotomy, those would be the children who would most likely do better because their hearing problem was addressed as opposed to the children who had myringotomy and didn't get -- or had chronic ear infections and didn't get treated.

My point is that that's a very complicated question. I personally reviewed every one of the records in the study that's unpublished and counted every episode that a child encountered a physician

for ear infection, all 700 records, and we entered that into the model. That's not included in the publication, but it didn't make any difference. The number of encounters for myringotomy or for ear infection had no impact on outcome.

DR. KIRSCH: The last question before -- or last comment before lunch is going to be from Dr. Anand.

DR. ANAND: I just wanted to respond to a couple of the questions that were asked.

With regard to oligoapoptosis, we had done a randomized control trial in pre-term babies who were randomized to placebo, low dose morphine, or low dose midazolam, and this was published in '99. In the low dose midazolam group, there was a very high incidence of periventricular leukomalacia in these. These were all babies less than 30 weeks of gestation. So they were the micro preemies.

In regard to Dr. Susser's comment, I just wanted to mention, the hurdles are well known. It's basically funding, ethics and IRB committees, and it is the regulatory hurdles. My group has

been trying to get an IND for a ketamine randomized trial, and it's two and a half years into this project and we still haven't gotten the IND.

There are some absurd, I feel, forgive my strong language, requirements such that studies have to be done in adults before they can be done in pediatrics or less than a year of age. I mean, it makes no sense from a clinical and a vulnerability point of view. Those studies need to happen now and they need to be done in the pediatric age groups for which this information is relevant.

So I think those are important considerations for the committee in order to help this research really come to light and for the questions to be answered in the human in the clinical situation.

DR. KIRSCH: Thank you. We will now break for lunch. We will reconvene again in this room 45 minutes from now, which is 12:50. Please take any personal belongings you may want with you at the time.

Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, the press, or with any members of the audience.

For members of the committee and consultants, the lunch will be served in 1404 and 1406. Thank you.

(Whereupon, at 12:06 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:50 p.m.)

Open Public Hearing

DR. KIRSCH: We are going to begin the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Speaker number 1?

DR. ANDROPOULOS: I am Dean Andropoulos from

Texas Children's Hospital, Baylor College of Medicine. I have no financial conflicts of interest. I'm also a member of the SmartTots Scientific Advisory Board.

Based on the currently available data, I believe that the clinical practice of pediatric anesthesia should not change at this point and the FDA should make no such recommendations.

First, with regard to the animal data, as we've heard, a major flaw in most all these animal experiments is that they do not include modeling of surgery or painful intervention, which is why these infants and children receive anesthesia.

Seldom mentioned in the reviews and editorials are the published animal model studies clearly demonstrating a neuroprotective effect of GABA agonist and NMDA antagonist anesthetics in models of surgery or pain. Although the issue of surgery, pain and peri-operative inflammation is very complex, I urge animal model investigators to include these factors in future investigations.

Second, with regard to all of the human

epidemiological data, retrospective diagnoses from school district records or Medicaid databases is not equivalent to formal neurodevelopmental testing. These study designs cannot exclude that the need for anesthesia is a marker for co-morbid conditions that are responsible for the neurocognitive changes, and also that it is the surgical experience and not anesthetic exposure that is the cause.

There are two new reports of neurodevelopmental outcomes with regard to anesthetic exposure in the neonatal congenital heart disease population, in a total of 135 patients tested at 12 to 24 months, one of which is our own. The conclusion from these two small studies is that anesthetic and sedative exposure does not affect formal early neurodevelopmental outcomes in this population.

My third argument against changing practice is a practical clinical one of the four to six million anesthetics performed in pediatric patients annually, one-third are inpatients less than 3

1 years of age.
2 In 2010, the faculty in my department
3 performed over 32,000 anesthetics. These ranged
4 from very simple outpatient procedures lasting less
5 than 10 minutes to anesthetics of 12 hours or
6 longer for complicated cardiac or neurosurgical
7 cases. The average anesthetic exposure was 1 hour
8 20 minutes.
9 Over 1,500 of these patients then went on to
10 receive prolonged post-operative sedation and
11 analgesia in the intensive care unit. Almost
12 12,000 of these anesthetics were in patients aged 3
13 years or younger; 23,000 were anesthetics for
14 surgical procedures; and, 6,500 were for
15 radiological sedation.
16 Few, if any, of these procedures could be
17 postponed for years until the perceived effect of
18 anesthetics on the brain is lessened. Of the
19 anesthetics and sedatives used, virtually all are
20 GABA agonists or NMDA antagonists. The use of
21 opioids or dexmedetomidine would be possible for
22 some diagnostic procedures, but the side effects,

1 i.e., respiratory depression, bradycardia
2 hypotension, are far more likely in patients under
3 the age of 3 years.
4 Prematurely or unnecessarily recommending a
5 change in practice will cause practitioners and
6 parents to cancel or postpone needed procedures
7 intended to enhance the health and
8 neurodevelopmental outcome potential of the infants
9 and children receiving the anesthetic.
10 Before recommending any change to current
11 practice, three questions must be answered in
12 properly designed human clinical trials. First, is
13 there really a neurodevelopmental effect of
14 anesthesia in young children? Second, what is the
15 magnitude of the effect? Third, what are the
16 populations at risk for adverse neurodevelopmental
17 effects; i.e., what is the dose and duration,
18 combination of drugs, effective repeated exposure
19 and of co-morbid illness and surgery?
20 We have heard about the GAS and PANDA
21 studies today. Unfortunately, the PANDA study is
22 awaiting funding to begin formal enrollment, so we

are left with only one ongoing prospective study enrolling patients at this moment.

If, after these and similar studies are completed, there is clearly a clinical effect on early human neurodevelopment. We can begin to recommend changes to practice, which would need to be very carefully considered given the potential effects on the overall health of the young pediatric population.

In conclusion, in my position as chief of a large pediatric anesthesia department, a clinical researcher, and a member of the SmartTots Scientific Advisory Board, I urge FDA not to recommend any change in the practice of clinical pediatric anesthesia based on current data.

SmartTots was formed to answer this question and is in a unique position to support this clinical research. I urge the FDA and the public to continue strong support for SmartTots. I believe that SmartTots and other funding agencies should place a high priority on raising and providing funds to prioritize properly designed

clinical studies to determine whether anesthetic neurotoxicity is a clinically important phenomenon.

Thank you very much.

DR. KIRSCH: Thank you.

Speaker number 2?

DR. HOUCK: Thank you. I'm Dr. Connie Houck from Boston Children's Hospital, and I have no conflicts.

I actually am the chair of the American Academy of Pediatrics' Section on Anesthesiology and Pain Medicine, and I'm actually going to be reading a statement that was put together by members of the American Society of Anesthesiologists, the Society for Pediatric Anesthesia, and the AAP's Section on Anesthesiology and Pain Medicine.

"The care of our smallest and most fragile patients is a crucial part of the practice of anesthesiology. It presents distinct challenges. For example, in emergency rooms, imaging suites, endoscopy units, and other settings, young children routinely require sedation or anesthesia for

procedures that could be performed in older children and adults without sedative medications.

Advances I perinatal medicine now allow the survival of newborns with unprecedented prematurity, challenging them with a host of additional threats posed by their early births. Every day of their continued growth is a delicate balance of risk and fortune. These babies are prone to multiple complications of prematurity that demand surgery and anesthesia, and they often have long-term medical conditions that will require repeated painful procedures and surgeries throughout their lives.

Recent studies in newborn animals show that almost all commonly used anesthetic and sedative medications cause injury to the brain with long-term behavioral consequences. Whether these effects are also seen in human infants and young children requiring anesthesia or sedation is a question of utmost importance.

These medicines have been used for many years in the care of many millions of infants and

young children in this country and around the world without apparent harm. Yet, new studies in animals, including primates, suggest the possibility of subtle adverse effects on developing human brains, prompting the urgent need for research to more fully evaluate potential neurologic changes.

Clearly, this research must be a high priority for the specialty in order to provide reassurance that needed procedures can be performed as safely as possible.

Patient safety is the essence of anesthesiology. We take very seriously the faith and trust that patients and their families place on us. For each child who requires anesthesia or sedation, anesthesiologists craft a carefully considered plan using the best, most current information to minimize discomfort and maximize safety.

Unfortunately, the potential for harm exists despite our best efforts and current state of knowledge. We believe that we can best protect our

patients from harm by continuing to pursue the very best science that informs our practices.

If anesthesia is associated with brain injury in neonates and young children, we need to understand the mechanisms of this injury so that we can develop ways to prevent or minimize this damage. This knowledge will help us provide the best possible guidance to our patients and families so that they can make the best choices for their children.

As anesthesiologists, we care for all children as if they are our own. We urge that every effort be made to fund the research needed to ensure the continued safety of children.

The membership of the American Society of Anesthesiologists, the Society of Pediatric Anesthesia, and the American Academy of Pediatrics' Section on Anesthesiology and Pain Medicine are united in our dedication to our patients. We support any and all efforts to better understand and ameliorate any risks that anesthesia and sedation may present to our youngest patients."

This is signed Mark Warner, President, American Society of Anesthesiologists; Constance Houck, Chair, Section on Anesthesiology and Pain Medicine; and, Nancy Glass, President-elect, Society for Pediatric Anesthesia.

Discussion and Questions to the Committee

DR. KIRSCH: Thank you. The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

Before we actually address the questions posed to us by the FDA, I'm going to return to the list of individuals who had questions or comments before our break. So first on the list is Dr. Adams.

DR. ADAMS: Thank you. Yes. There was a comment or a question before the break with respect to the role of studies in adolescents or with respect to the issue of whether or not there might

be an adolescent vulnerability, as well as an infant vulnerability to anesthetic exposure. And so I wanted to comment on that.

I think the field of developmental neurotoxicology has established the adolescent brain growth spurt as another period of vulnerability to the effects of various agents, and I think studies that were directed at that age group with respect to this anesthetic issue could be valuable in two primary ways.

First of all, they would allow pre- and post-evaluation of functioning of the children with respect to neurodevelopmental outcome parameters. And secondly, they would allow studies to be conducted in individuals who do not necessarily have co-morbidities that contaminate the problem.

So there are many adolescents who require surgeries post-accident that wouldn't have a problem such as premature infants with respect to already being at risk for neurodevelopmental compromise.

So I just wanted to make that comment about

the value of those studies.

DR. KIRSCH: Thank you. Dr. Deshpande?

DR. DESHPANDE: Thank you. I'd just like to reiterate the fact that the human studies we've seen so far are association studies and, clearly, we need more realistic study design, as was mentioned earlier by Dr. Swedo and Dr. Mellon.

To me, that includes realistic peri-operative conditions, not only tightly controlled RCTs, because most of us don't practice in an RCT setting 24 hours a day.

The second comment I have is that the medications we've heard as potential alternatives to the ones that have been discussed as potentially harmful are opiates and dexmedetomidine. And the thing that I would ask is that we need to consider, when we decide on a study design, that the medications that are of interest and focus should provide analgesia, amnesia, sedation, and physiologic stability.

If the alternatives that are being brought forth by those who are bringing forth both the

preclinical studies and the human studies are proposing other medications, I would make sure that these mediations provide the total experience of anesthesia rather than just one component.

I do have a question for Dr. Nelson, if I may. I heard in your comments about the time to be -- something to the effect of public awareness or at least making sure that we are forthright about the issues instead of either ignoring or denigrating or downplaying the potential impact of these medications.

My question is how do we, as we go forward, make sure that we are forthright, at the same time, not cause undue alarm, which we, as you know, have dealt with in pediatrics with vaccinations and other medical interventions.

So help us with that balance.

DR. KIRSCH: Dr. Nelson?

DR. NELSON: I thought that was my question to you. I think it's going to be very hard to tread that balance between informing people about the data, translating that into some meaningful

language in a clinical context, which I think would be difficult, and then doing it in a way that doesn't unnecessarily alarm, but also informs people about the need for the kinds of studies that we're talking about. I think that is very tough, and I don't have any great insight into how you're going to do that.

DR. KIRSCH: Dr. Newschaffer?

DR. NEWSCHAFFER: This question, I guess, is for Dr. Mellon, but it could be directed to anybody else who does preclinical work in this area and any of our speakers.

My question has to do with an assessment of the totality of the evidence base in this area. Is this a field -- I don't work in this area -- that is subject to file drawer bias and publication bias? Is what we've seen here what there is?

In fact, I asked this question about the preclinical studies, but Dr. Flick's comment about decision not to publish in a human study raised -- while I understand the complexity of the issues, it goes to some concerns I have about publication

bias. And so I wonder if you could comment on that.

DR. MELLON: I think one of the challenges that we face as an agency right now is that there are a great deal of publications that are coming out, and they are coming from a lot of academic laboratories who are doing a great deal of work.

But one of the things that is challenging is, as I mentioned, a lot of times, journal editors are not real interested in some of the negative findings. So it's possible that there are studies that have been conducted and haven't been published. I would encourage those individuals to let us know about them, but I'm not aware.

There is potentially a challenge in that arena, but I think frequently you can actually get some negative data generally published, as long as it goes along with some positive data. So if you had a dose response, then a lot of times you can actually glean a lot of information from that. But I also recognize the challenge that since right now the funding that is coming to a lot of the

publications that are the groups who are actually studying this, they have limited resources because their money is coming from grants, and they have to try to optimize the bang for their buck, if you would. And so they may not be able to include multiple dose groups, and they may have to be very cautious in terms of how they conduct and design their studies in order to accomplish their objectives.

So I think your point is well taken. It is possible that there may be information out there that we're not aware of. I think, in part, being able to structure and perhaps hopefully eventually fund some very distinct nonclinical studies would provide us with a great deal more information that may not necessarily be as readily available through some of the granting funding options that exist right now.

I would open it up to anybody else who may want to comment on that.

DR. KIRSCH: Next question, Dr. Notterman?

DR. NOTTERMAN: Thank you. I'll turn first

to Dr. Mellon and see if Dr. Anand also wants to address this issue.

Of course, much of the use of these agents occurs outside of the operating room, and some of the speakers have mentioned this. But, of course, in the intensive care unit, when these drugs are used, they're often used for prolonged periods of time, and they're often used in a context in which there's preexisting acute or chronic neurologic injury, either focal or global.

Yet, I don't recall any of the models addressing the physiologic state of the patient either in terms of their cardiovascular or respiratory function or, most particularly, brain function as affecting the response to these drugs. And I wonder if in fact there is a literature that's beginning in that, and if not, if you think it's important to address those issues.

DR. MELLON: I can start that conversation, but there are many people in this room who can actually provide even greater insights.

I think one of the challenges associated

with any animal model is to try to make sure that you maintain the appropriate physiological conditions as you would in an operating room or in a clinical setting.

I do know that certainly the studies conducted through NCTR, and I know great lengths have been taken by Dr. Jevtovic-Todorovic and Dr. Olney to try to make sure that they can measure those parameters. We really didn't discuss those today, but they certainly try to control them within as much of the appropriate ranges as possible to minimize the impact of some of those other circumstances and the contributing factors to those.

I don't know if Dr. Paule or, Vesna, if you would like to comment in that capacity, as well.

DR. JEVTOVIC-TODOROVIC: This is actually an interesting question that we've been asked over and over, over the last 10 years or so. In the anesthesia community, that's a kneejerk reflex. As soon as you put somebody to sleep, somebody else wants to know what is the pulse ox reading, and I

say 02.

We've done a great deal of controlling for these parameters, and the study we did, obviously, with rats and mice, you are limited because it's a tiny animal where you can't really do any thorough invasive monitoring.

What we did in my lab, we used pregnant guinea pigs, and they're about a kilo and a half, and these are large animals where you can do whatever your heart desires, and we've done it all. We put a central line -- to respond to Randy's question, we put an A-line. We intubated, we mechanically ventilated him. We did exactly what we would do in your setting, except for a surgical incision.

DR. KIRSCH: You can follow-up.

DR. NOTTERMAN: Thank you. I think what I'm also asking is whether there is any information on whether the response of the injured brain, for example, the post-hypoxic brain or the brain that's been subjected to closed head trauma, whether the response to NMDA antagonists and other agents is

likely to be any different.

We can imagine, based on what Dr. Anand says, that a dose of ketamine which would be harmful in one context might actually be neuroprotective in the context of closed brain trauma. We can imagine it. I don't know if there's any data.

DR. JEVTOVIC-TODOROVIC: I think, actually, Dr. Ikonomidou can respond to that question better, because my understanding was that that's how they actually basically stumbled upon it by studying it. That was brain trauma you did in 7-day-old rats and found protection on one side and then a different kind of injury on the other.

DR. IKONOMIDOU: May I speak?

DR. KIRSCH: Yes, you may.

DR. IKONOMIDOU: Yes. We did do this type of study. We actually were trying to ameliorate apoptotic neurodegeneration in an infant trauma model, brain trauma model using an NMDA antagonist, and we found that the brain injury is markedly enhanced if we treat the animals with NMDA

antagonists.

We have also done similar experiments in adult animals, by the way. It's a paper that we published I think in '99. We did adult brain trauma, and we did systemic 3-nitropropionic acid toxicity, which is a model for Huntington's disease and one of the older models. And even in this model, we found that NMDA antagonists exacerbate delayed brain injury.

There are studies that we have been doing in seizure models. That's not really related to anesthesia, but we have done studies in the pilocarpine seizure model in young animals and we have obtained data that show that treatment with GABAergic-acting antiepileptic drugs do exacerbate seizure injury.

I don't know of other studies. Actually, I did make a proposal to study these type of questions in infant animals, but my application was not discussed. It will come back to how to fund this type of research, I guess.

DR. KIRSCH: The last comment in this

section will be from Dr. Anand, who wanted to clarify something from a previous comment.

DR. ANAND: Thank you. I just wanted to clarify that the comment I made with regard to getting an IND was for a trial looking at ketamine as a neuroprotective agent, and it is being evaluated by the neurology section at the FDA.

So it's a separate indication than looking at sort of the anesthetic -- sort of toxicity of ketamine, as such. So I just wanted to clarify that.

I also have one question for Dr. Flick. In the epidemiological studies that have been done, have you looked at other drugs that were given, steroids, for example? A lot of children get exposed to steroids. They have clearly apoptotic effects on hippocampal cells and so on.

DR. FLICK: Thanks for the question. It allows me an opportunity to emphasize that the cohort that we study is a cohort of children who are born and raised in Rochester, Minnesota. They are, for the most part, neighborhood, healthy

children. This is not a referral population. It's very different than the populations being studied elsewhere. This is a community population.

Virtually all of these children are ASAs 1s and 2s. And virtually all of them got the same anesthetic. You could hardly design a study with more -- you could not design a study currently with a more uniform anesthetic. All of them got halothane. Virtually all of them got nitrous oxide. So these are healthy children who got the same anesthetic, all of them.

Did we look at other drugs? The answer is yes. Were there any? The answer is no.

DR. KIRSCH: Thank you. We're now going to turn to the questions posed to us by the FDA. And what we'll do is I'll read them, take comments form the panel, and then try to summarize the opinion of the panel for the record.

So the first question is, what is the applicability of the presented data at this time? Please describe what other data would be additionally informative.

1 So I think that we've discussed a lot this
2 morning about the applicability of the data. I
3 think I'd like to concentrate mostly on trying to
4 describe for the FDA what other data would be
5 additionally informative.
6 Dr. Soriano?
7 DR. SORIANO: Thank you. The first issue
8 I'd like to bring up is the whole issue about the
9 dose and duration. Many of these studies have
10 clearly shown in rats and in monkeys that you need
11 a large dose of drug -- and this is for the
12 injectable drug, a large dose of drugs for a
13 prolonged period of time.
14 Now, this is in contrast to some of the mice
15 studies that have been done where a single dose of
16 propofol-ketamine -- induces neuroapoptotic effect.
17 The reason why this differential is important is
18 because when you think about pediatric anesthesia,
19 a large percentage of it is short duration. You
20 use ketamine for induction of anesthesia and that's
21 it, or short duration of the anesthetics; for
22 example, ear tubes, and even tonsillectomies now

take about 20 minutes of time. A small minority of our cases are longer than six hours, that fulfilled the requirement -- the criteria that these studies are done.

Are these findings of a single dose of a drug relevant at all in the whole issue about giving anesthesia and sedation to our pediatric patients? I'd like for the committee and perhaps maybe Dr. Olney to comment on this topic.

DR. KIRSCH: I think that actually Dr. Flick had -- there was data presented from his group about frequency of anesthetic administrations.

Dr. Flick, would you like to comment?

DR. SORIANO: It's not frequency, but the long duration, a craniotomy versus an ear tube placement, for instance.

DR. KIRSCH: Okay. Yes?

DR. IKONOMIDOU: I would just also like to mention, because I think we are not discussing this very much here, we are often giving anesthetic drugs to children and neonates while they are in the intensive care units for days. And many times

the decision is made to even continue the sedation, the deep sedation for over the weekend, because we're afraid of complication. I think this is something that we should also take under consideration when we discuss whether or not we should make this information open to the public.

So although ketamine anesthesia for 24 hours may not be very relevant for a procedural setting, I think comparable situations we are faced with quite often.

DR. KIRSCH: Dr. Inder?

DR. INDER: Thank you. I just wanted to reiterate what I had said earlier, that I think we're dealing with three very distinct issues. One is the issue of sedation, anesthesia -- or analgesia in critically ill children in intensive care units; the second, brief anesthetic exposure, and then the third is complicated, very prolonged procedures. And each of them, they have their own distinct gaps in knowledge at the moment.

For instance, in the neonatal intensive care unit where I practice, there is huge variability in

clinical practice across this nation, of which there is no information available. And it would seem if we were going to be able to know where to prioritize what we should be seeking in terms of additional information from both animal and human studies, it would be highly informative to have some understanding of what the current spectrum of clinical care actually is.

Alongside that, the practice of brief anesthesia -- although I certainly don't want to sound like I'm demeaning the need for children to be not suffering at all, which is, obviously, not my intention at all. But, for instance, MRI imaging we do completely without any sedation or any anesthesia for every MR image for any infant under 4 months. And I've been struck how diverse that practice is, where many radiology units will demand that an anesthesia is given.

So I think there is a lot of opportunity to perhaps tackle some clinical practice guidelines or clinical practice recommendations without making major sweeping statements about critically

important issues related to gaps in knowledge that we still have.

DR. KIRSCH: Dr. Flick?

DR. FLICK: We're being asked to address what is the applicability of presented data at this time, and I think probably one of the questions that I have foremost in my mind is the question of the effect of surgical intervention in these studies.

I guess I need clarification from a clinician's perspective. When we talk about a procedure with -- probably, first, we need to preface this. Dr. Andropoulos defined his practice in which it sounded like about 25 percent of his patients were receiving an anesthetic without a surgical stimulation. So the importance of the surgical stimulation is very clear, but we do lots of anesthesia procedures that don't require surgical stimulation.

But what I don't understand, and Dr. Anand and the folks at the Toxicology Center can maybe help me understand, is what do we mean by surgical

stimulation. The small animal studies frequently require significant intervention to monitor them. Many of these animals are endotracheally intubated. All of these interventions are quite stimulating, in fact, enormously stimulating.

So it's hard for me to separate, from a clinician's perspective, the difference between those two groups.

Can maybe Dr. Anand or Dr. Mellon help me understand that and help the rest of us?

DR. MELLON: I think that's a very excellent point. One of the challenges that we have in this particular field is exactly the fact that there are various levels. I'm sure that clinicians can put a rank, to some extent, by saying that if we do an MRI simply for sedation, there's not going to be necessarily painful stimulus, but there may be some stress, that's more of a psychological stress associated with that procedure.

Certainly, there are various levels. And the really hard part about trying to design nonclinical studies to mimic that is that you could

envision just as broad a type of exposure or painful stimulus or inflammatory stimulus that could be associated with that, and each one of those stimuli presumably will be active in different patterns and pathways within the brain.

So if the drugs are actually having effects across broader regions of the brain, but the painful stimulus is having the counteracting effect, within a certain pathway, how assured are we that we understand what's happening in some of these other regions? Are we looking in the right places?

They're extremely challenging studies to do, and I think part of the way that some of the approaches have been is to try to take the worst case scenario first to either rule in or rule out whether or not something is happening.

So I think it is very challenging to try to do that and part of it -- we can regulate it, to some extent, by trying to understand what the intended use of that product is, whether it's for sedation or whether it's for a surgical procedure,

and then try to mimic the nonclinical studies to pattern it for the intended use.

DR. FLICK: I guess my concern is that the discussion here has treated these things as if they're dichotomous. And as I look at these studies, they don't appear dichotomous to me, dichotomous meaning surgical stimulation or not.

There seems to be a broad range of what we would call stimulation, whether it's an actual surgical incision. But some of these animals have surgical incision to instrument them. I'm not quite sure what the difference is and how great the difference is between the stimulated animals and the non-stimulated animals.

DR. MELLON: I think your point is well taken and the challenge there is that, in large part, the more information that is available to us regarding the process and the procedures that are done on these animals -- which is not always reported in publications and the literature due to page constraints. But the more information we have will provide us with more ability to interpret and

then try to apply those circumstances as we get the data. But I agree with your point.

DR. KIRSCH: Dr. Diekema? Dr. Anand, do you have something different to add?

DR. ANAND: Basically, I think your point is well taken. There are some kids who will be exposed to anesthesia without having a surgical incision. Eighty percent of our population still requires a surgical incision, entry into a body cavity, and things like that, which is far more stimulating than putting in a central line.

So I think the way we need to look at our exposures is both -- it's like area under the curve. So both the dose and the duration have to be taken, and there will have to be some kind of a balance, which clinicians decide routinely in their practice of how much drug to use for what kind of stimulation.

So I think that's where the creativity of our research design and the lab comes into.

DR. KIRSCH: Dr. Diekema?

DR. DIEKEMA: As I looked at the data, there

seemed to be two gaps that I had questions about that struck me, one of which I've mentioned, so I'm not going to spend a lot of time on it, and that's the adolescent sort of from puberty up to 18 or 19 age group and what impact these drugs might have on them.

But the other is particularly since most of these studies involve ketamine, which -- and I would imagine ketamine use probably -- its use in the outpatient setting may even exceed that in the OR. I don't know that for sure, but it's become sort of the drug of choice of most pediatric ERs for things like abscess drainages and fracture reductions, even gyn exams in small children.

The doses we use, probably over the course of even a fracture reduction, don't exceed 2 milligrams per kilo. So they're smaller than what these studies have done. And that, in my mind, raised the question of how this data would impact somebody using these drugs at a lower dose for a shorter period of time in a setting that it's used very commonly.

So I wouldn't want to see that particular setting left out of future studies.

DR. KIRSCH: Dr. Mattison?

DR. MATTISON: I'd like to just focus on additional data in the preclinical domain. It's pretty clear that both rodent and nonhuman primate models have developed data suggesting structural and behavioral alterations. The advantage of these models is that they can allow you to look at a broader range of agents and also get more detailed information about how structure and behavior are altered concomitantly.

In addition, echoing the earlier comments about adolescents, I think the preclinical models would allow greater detail to look at age and regional susceptibility of the brain to damage. So I'd encourage that kind of research.

DR. KIRSCH: Thank you. Dr. Tobin?

DR. TOBIN: Thank you. I'd like to add a comment that adds to the complexity of what Dr. Flick raised, and that regards the level of stimulation that these patients in clinical trials

or these animals in preclinical trials are undergoing.

The difference in the example I'll give is the child who may have acute surgical incision for herniorrphaphy in the operating room which lasts 30 or 40 minutes and that child has undergone a controlled trauma with a peri-operative inflammatory response, whether or not they were intubated.

I contrast that as a very different experience than the pre-term infant who is going to be intubated for three or four weeks of assisted ventilation, with tolerance developing to both opioid and benzodiazepine medications, as the two most commonly used in that circumstance, to doses that are wildly beyond what most anesthesiologists are comfortable with. But neonatologists deal with this all the time, this neonatal tolerance to drugs.

So I add the level of complexity that although I think we need to address the acute model first and find the applicability of that data,

we're going to need a very focused attention to the design of the chronic trials, because these will not necessarily address the issue that is clearly experienced in clinical medicine, which is tolerance even in the very young and developing brain.

If we recognize that even adults who survive acute respiratory distress syndrome are neurologically tested one year out, there is a substantial percentage of those patients who are not back to their pre-acute illness neurologic baseline. They can't perform activities of daily living and many other issues.

So they're neurologically impaired and we don't even have a basal assessment on what we're doing with adults before we start dealing with the developmental issue.

DR. KIRSCH: Dr. Weinstein?

DR. WEINSTEIN: This being Washington, I have to ask a silly question. There's a limited pot of money, and if one's going to divvy up the dollars, where do we get most bang for the buck?

And if we take the most complex patients and try to sort out what happened to them while they're sitting in the ICU, their blood-brain barrier is open, there are drugs going in, wild swings in their physiologic baseline, we'll never get anywhere.

I think I agree with sort of what I'm hearing, which is that the great majority of patients that are exposed to these agents are the ones ultimately that we're aiming to help; that if you have X dollars and you spend it all on 10 patients, is that different than spending it on the 150 patients who come through the ER to get their bones reduced?

So I would certainly vote for -- as thinking through this, forget about the complex ones, forget about the kids that are on the pump for six hours. You're not going to sort it out and nobody is going to believe it anyway. Why don't you show it with the most easiest to study, the patients, the healthy kids?

DR. KIRSCH: Dr. Deshpande?

DR. DESHPANDE: In thinking about the second part of the question about what other data in conjunction with the applicability, I want to echo a little bit what you said and also what Dr. Inder brought up, which is that I don't know that -- I take this as a public health issue, and if this is -- I look at it in two ways.

One is are we harming children for the most -- I look at most of the children that come to our care, are they at risk? That's the first question. Not the ones that have had six operations, 10 operations, because there are multiple underlying issues there. But today, if somebody comes to me, am I harming that patient and does a mother want to know whether I'm harming that patient.

So part of this is what's the threshold for safety for the majority of use. In that, I think that the data we need is to get the scope of the practice. What is the practice for where these medications are used? All of us have talked about the operating room and then mentioned outside of

the operating room and then mentioned the ICU.

Getting the first step, to help public awareness, is to know what the scope of the issue is. And then maybe it's age, dose and duration are the aspects. Somebody had told me, well, a negative study that shows no harm is not helpful. I take it the other way. A study that says that for the majority of patients for which we provide care, if there is no harm or if there are good data to suggest there is no harm, it is public health positive information that we can put out.

So as we look at what information we need, I would say I'd put those three things on the table.

DR. KIRSCH: I'm going to take Dr. Swedo. There are going to be a lot of comments, which I'm going to try to summarize. I'm starting to hear some redundancy. So I'm going to try to summarize it for the FDA, and then I'll open up my summary for further comments.

Dr. Swedo?

DR. SWEDO: I was looking over the answers by the 2007 committee to this question, and at

least on the preclinical side, I would say that at least 90 percent of the things that they had identified would still be true today; that we need more data in the area of currently used agents in real dose situations.

I would like to have sort of the brain behavior literature much more richly described. And I know it's great to keep testing the monkeys, but their error bars completely overlap. So is that just because they weren't very -- the one group wasn't as smart to begin with?

So it would be helpful, I think, to maybe have some focus from those who are using the agents to prioritize in that way.

In terms of clinical data, speaker 1 presented us with a great naturalistic study that could be done and several people have talked about that, that anesthetics are routinely used for sedation for radiologic procedures. There is no pain, other than having to lay still, and they don't seem to mind that.

So the results of those kinds of sedations

in anesthetic events can be compared with the others. Perhaps not, because it's not as deep. I can see him immediately say that. And that would be certainly a huge confound, but probably not as big a confound as trying to compare a group of kids who are having multiple surgeries for the various reasons we've heard about.

DR. KIRSCH: So I'm actually going to pause here and try to summarize what I've heard and then take additional comments for individuals who think I've missed the boat or have something substantial to add.

So I think, as was just eloquently stated, although we've made some progress since the last committee meeting, the progress hasn't been huge, and there's some concern or a suggestion by the panel to the FDA to encourage a survey to first understand where the opportunities are.

So what is the standard -- not the standard practice, but the current practice around the United States and maybe around the world and how these agents are used, so we can better inform

where the low-hanging fruit is, for lack of a better phrase, and focus the research on areas where we'll have the biggest impact on numbers of patients and look, as I think Dr. Deshpande appropriately put, in a dose-dependent fashion on dose of drug, age of kid, duration of exposure to the agent, with the understanding that to be most valuable, measures of preexposure function need to be defined so we really know what impact our intervention, both surgical and anesthetic intervention have on the outcome both short-term and long-term.

So that's my summary. That was what I heard. And if there are strong opinions -- Dr. Notterman?

DR. NOTTERMAN: My opinion isn't that strong, but I would like to make sure that we also address the need for additional studies in animals and not just limit it to clinical.

DR. KIRSCH: My comments did not define animals or humans. They were meant to be broad.

DR. NOTTERMAN: So to that then, I would add

that I think that there's a need for what you could call chronic administration studies in animals beyond several days and in various contexts of brain injury.

DR. KIRSCH: Again, that was in my comments and was focused off the comments made by Dr. Inder to try to understand the scope of where we're administering these drugs so we can be comprehensive in our analysis.

Dr. Zuppa?

DR. ZUPPA: I think there will be some overlap, but I feel that this point is important and it echoes some of the things that were said. But there are definitely different populations where it is important to look. And I feel like there's a population where it's more of an elective procedure versus a population where you have a child that is critically ill. I'd look at a 3-month-old with pertussis who has no respiratory function, needs to be intubated, needs to be sedated. There's really no choice in the matter there.

I also want to go back to the point that a negative study is still an important study. So if you look at a population of healthy young children and infants who have tonsillectomies and adenoidectomies, I think it would be important to know whether inhaled anesthetic versus a ketamine anesthetic versus a whatever anesthetic, neither of them caused harm in that specific setting.

DR. KIRSCH: That was implicit in the comments that were made by Dr. Inder to assess the different venues or different situations where we administer these drugs and understanding where the opportunities are for each of those.

Other comments? Dr. Clancy?

DR. CLANCY: From my perspective, one of the reasons we're struggling with this is that the studies are not -- the animal studies have not been done at all at similar neurodevelopmental ages.

So I would think ways to equate that should be emphasized and that the study should be done instead of -- we have to compare apples and oranges, but we're comparing apple blossoms with

orange juice. We've got to do it at the same age.

DR. KIRSCH: Thank you. Dr. Flick?

DR. FLICK: A couple of comments that I think -- I hope are clarifying.

We talk about negative studies, and I don't think it came out in the presentation today, but all of the studies that have looked -- all of the clinical studies that have looked at single exposure are negative. All of our studies have shown that single exposures, single brief exposures have no measureable effect in the way that we measure, and these are all very complex things.

What is a measurable effect? What measure are we using? Is it the right measure?

Then when we talk about designing clinical studies, we're really talking about two things. We're talking about clinical trials and we're talking about epidemiology. Now, the two folks that are doing clinical trials are here and can address some of these questions, as well, but when we talk about clinical trials, the lead time and the cost of these are extraordinarily expensive.

Now, we've had several different suggestions on what we should study. The cost of those would be enormous and the leads time is great.

Now, we've done several epidemiologic studies -- and, by the way, when I say the single exposure studies are negative, I mean that studies that have differentiated between single and multiple exposures are negative. The studies out of Columbia and other studies have not differentiated single exposure versus multiple exposure or durations of exposure. But when we look at single exposure in our studies, they're negative.

If you look, for example, at the GAS study, when we design a study -- this study will be a single exposure study, a relatively brief exposure -- some of the children in -- and, Mary Ellen, you can correct me, but I think some of the children who will -- in the anesthetic group will get regional anesthesia. So will those children have surgical stimulus the same way as children who don't get regional anesthesia in combination with

1 their general anesthetics? Also, in that study,
2 children are enrolled after 26 weeks.
3 There's a sense that sometimes that clinical
4 trials don't have confounders, and the confounders
5 in these studies, the ability to separate co-
6 morbidity -- the biggest problem we have in the
7 prospective study is trying to separate co-
8 morbidity. And all of these studies are going to
9 suffer from those problems regardless of the way
10 they're designed.
11 DR. KIRSCH: Dr. Susser?
12 DR. SUSSER: I don't think we have
13 definitive answers on any of these questions yet.
14 And I want to underscore something implied in what
15 Dr. Inder said, but didn't come out in your
16 summary, which is the first step, find out what the
17 variability in clinical practice is.
18 The second step, regulate clinical use of
19 anesthetics that are unnecessary, for example, in
20 diagnostic imaging. There are many countries to
21 outlaw it. There are many places across this
22 country that don't use it because they found other

ways to image babies and young children.

I'm sure that when you look at the variability of practice, just across this country, you'll find that people in some places are doing things that people in other places aren't doing and aren't necessary. That would seem like the first step.

DR. KIRSCH: Thank you. Dr. Shaw?

DR. SHAW: Just to address, again, the issue of the applicability of the presented data, I think one shortcoming is really outcome measures that have been used, particularly animal studies. They're really not very applicable to the human setting. They've been largely short-term and largely histological. Clearly, that's not going to really help us very much whenever we look at the effects of potential neurotoxicity in children, where the shift has to be into cognition and behavior.

Just as sort of an example of how much thought I think needs to be put into it, I was noticing that in some of the literature on the

extremely excellent GAS study, the randomized control trial, it is, however, only powered to detect a decrease of an IQ of .05, an IQ score between the group. So that's a decrement that's so large that I think it's the sort of signal that would already have been picked up on in common practice. So I think it really focuses in on what measures should we be looking at.

Secondly, the very interesting preclinical work on oligoapoptosis, and a point that someone else has raised. Myelination is a process that goes on throughout the teens into the 20s. And so how long do we need to follow-up these children, I think, is another sort of important consideration.

DR. KIRSCH: Okay. We're going to go on to question 2. Please suggest an outline of a research agenda in pediatric patients that complements the ongoing clinical and epidemiologic studies. Please include in your response the following things: how to conduct research regarding the commonly used combinations of anesthetic/sedative agents; second, the extent to

which controlled comparative studies should be employed; and, third, an opinion as to whether studies should be conducted in all of the typical settings in which anesthetic/sedative agents are used, including general anesthesia, procedural sedation, and intensive care unit sedation.

So as you can see from this question, there's going to be a lot of redundancy between questions and that's why I'm pushing along, because I think a lot of the comments you'll make for one of the questions are going to be relevant to the other questions.

Comments about this question or suggestions? Dr. Schreiner?

DR. SCHREINER: I wonder if there's been any consideration for extending some of these research questions to the National Children's Study, since we have an ongoing study that is in the process of recruiting 100,000 children, for which we'll have genetic information, environmental exposures, and history through age 20.

It seems to me that since cost is a factor,

that it would be easier to add something to that effort than it would be to initiate something independent.

DR. KIRSCH: Dr. Flick?

DR. FLICK: Mark, we've considered that and I looked a little bit into the National Children's Study. That database does not have the fine data that we would need to be able to address the questions that have been posed around the table.

The unfortunate problem is that we have to have complete access to records to know whether a child actually got an anesthetic. What was in the anesthetic? How long did it last? Did he get one anesthetic? Did he get two anesthetics? Those kinds of things. And I don't think any of that data is available in that study.

DR. SCHREINER: Could I just comment? The National Children's Study has about one amendment per week. So those of us who are on IRBs and see this mountain of information -- and only a small percentage of the children who are going to be enrolled have already been enrolled.

So I think that it would be possible to add another change to that study if it was important and it would I think save money to combine efforts.

DR. KIRSCH: Dr. Susser?

DR. SUSSER: I think it would be useful to include this in the National Children's Study, but it's going to be a long time and there already are studies of similar size and more in-depth information that exists in other countries, several other countries already, which could be used for these purpose.

There are two already, over 100,000 pregnancies with in-depth data on mother, father, child and following-up the children. One just started in Britain, another in Japan, and there are also national registries in probably at least 10 countries with huge numbers of people using current types of anesthetics as opposed to the ones that were in the readings that we have that could be used to study discordant siblings.

So there are many options at hand for investigating these questions, and then a future

option could be the National Children's Study. But it seems that we could just take advantage of what's already there.

DR. KIRSCH: Dr. Kon?

DR. KON: So I was thinking -- and I'm going to throw out an idea that I think is prohibitively expensive, but still worth just mentioning, which is when you look at our oncology colleagues, there is virtually no child with cancer in this country that isn't on protocol.

Yet, what we know is that in ICUs, both pediatric and neonatal, how we sedate children and to what extent we do so and with what medications and whether or not we use propofol and propofol washouts and dexmedetomidine varies not only by institution, but by practitioner within each institution.

It seems as though, while I think the animal studies are imperative to get some better ideas at the molecular levels, it would be great if, at some point, we could potentially roll out a system very similar to the COG, where we randomize children all

across our country to different sedative protocols and see what happens with that.

Now, I do understand that under the current economic times, that's probably not feasible right now, but I do think it's something that we should consider recommending for the future, if not now.

DR. KIRSCH: And I think that would be consistent with the comments that I've heard from others this morning.

Dr. Swedo?

DR. SWEDO: I would just add another potential way to do that, and that would be the physicians practice networks, where large groups such as we've heard about would just merge their data together, and it sounds like, quite quickly, you'd at least have the cross-sectional data that some have been asking for. And then following up, within that, some kind of case control design might be less expensive than some of the other options that are being explored.

DR. KIRSCH: I would comment -- now just as a member of the panel, I would be concerned

about making decisions about what's financially the best decision versus scientifically what's the best decision.

So personally, the suggestion that Dr. Kon made is something that I would favor rather than trying to go on the cheap -- and particularly now, as we're all paying our taxes. It's an important question and the study needs to be done right.

Dr. Newschaffer?

DR. NEWSCHAFFER: I think this is useful amplification and not redundancy, but you'll stop me if it crosses over into redundancy.

On the National Children's Study, I do think it's worth mentioning this. There has been a lot of discussion about medical records access in the NCS, and the idea is very much still alive about, for example, doing a sub-cohort where there would be medical abstraction on a representative sub-cohort, and then there could be follow-up on groups of interest, so it would facilitate -- so it's worth putting that in, because it's not a closed case, as has been mentioned.

On the registries, I'd just like to go a step further on Dr. Susser's comment and just mention that there have been successful initiatives in other areas to actually fund a consortium of registries, Swedish registry, Australian registry, Denmark registry around certain research questions, harmonize what they're doing. So I think there's some potential in that here, too.

Then my last comment was just the PANDA study is an exciting study. I guess it hasn't been launched yet, but I think there are opportunities to replicate a PANDA-like model, instead of a multisite design where there's heterogeneity of the study population within something like an HMO or some kind of a heath network, where you have a more homogenous population and you could do that same type of mixed design where you develop your study population and follow forward prospectively.

So I'd like to see planning for another -- even though PANDA has yet to get off the ground, I'd like to see us thinking about another study of that design, because I think it will be

extraordinarily helpful to have more than one.

DR. KIRSCH: Dr. Inder?

DR. INDER: It seems like one of the challenges we also have is taking the animal models data and the human clinical data, which are coming in very different modes, and building bridging tools that would actually allow us to have neurobiological relevance form what we've found in the animal model into the human clinical studies.

Imaging, I think, offers quite a lot now in this way, and there is new data that DTI markers are not just markers of development, but also markers of neuroapoptosis, both in inflammation and ischemia now. And if they were applied in the animal models that are being developed and the animal models can continue to inform those imaging markers, then they could be applied rapidly in phase II type trials and human clinical data to either show similar neurobiology or to refute that neurobiology with some degree of certainty.

It would not take away the need for those to be correlated with later outcomes, but that work is

being done in a lot of other types of developmental disorders, particularly for functional connectivity neural networks at risk and for DTI signals, and I think it could be a very helpful bridging tool.

DR. KIRSCH: Okay. I'm going to try to summarize our comments here, so far. Please suggest an outline of the research agenda I pediatric patients and complements the ongoing clinical and epidemiologic studies.

What I've heard the panel suggest is to use existing registries or form combinations of registries to try to -- and ask the registries to include variables that would be helpful to assess outcomes after children were subjected or provided with an anesthetic, either short-term anesthetic or a long-term sedative anesthetic in the ICU.

How to conduct research regarding the commonly used combinations of anesthesia sedative agents is a topic that has been largely ignored by our panel, maybe because it's a really hard question. I think the best I can come up with based on the comments is to -- coming back to the

comment that Dr. Kon made and I guess Dr. Inder made previously is to try to develop a registry and then define cohorts that are placed into certain individual anesthetic management techniques. And then at the end of the evaluation period, assess outcomes based on prospectively assigning patients to one or another anesthetic technique or sedative technique.

I'm going to pause there, because those are two important topics, and ask if I'm missing the boat again on these points. No? That's amazing.

Dr. Susser?

DR. SUSSER: Just one boat you missed, which is these in-depth, very large pregnancy cohorts that are now available already for study; so not just registries, but actual cohorts larger than 100,000 that have this kind of information already and could be used.

DR. KIRSCH: I'll accept that friendly addendum, the extent to which controlled comparative studies should be employed. And I think I'm hearing a strong sense from the panel

1 doing things in a controlled fashion with taking
2 advantage of the registries and the cohorts, like
3 the Cancer Network does, and identify -- pre-assign
4 individual patients to the type of sedative regime
5 that they're going to get would be the most
6 productive next step.
7 Dr. Zuppa?
8 DR. ZUPPA: Just to throw it out there. I
9 don't know how receptive a group of critical care
10 doctors are going to be to being told how to
11 administer sedative anesthetic agents to a group of
12 patients that they are at the bedside of who are
13 critically ill by a group of people that are
14 nowhere there.
15 DR. KIRSCH: I'm sure that when the
16 oncologists stepped over that line and agreed
17 nationally to having protocolized care for the
18 patients, I'm sure it wasn't easy either and I
19 know -- Dr. Kon?
20 DR. KON: Yes. I think that's a really good
21 point that you raise. There are some current
22 studies on a much smaller scale, multicenter

1 studies, where different centers have been
2 randomized to different regimens, one being
3 standard therapy, the other being nursing-driven.
4 And a lot of places have bought onto it, which I
5 think a lot of us were surprised that so many
6 people did. So I think that we may be able to make
7 it happen and I think it's worth trying.
8 DR. KIRSCH: I think one way of doing that
9 is to develop the communication tool from this
10 committee based on the information we've had to
11 inform practitioners that there's great concern as
12 to what the outcomes of the kids really are and how
13 they're affected by the anesthetic agents we're
14 giving them.
15 Dr. Paule, and then Dr. Rappaport.
16 Dr. Paule?
17 DR. PAULE: In considering the data that
18 we've looked at today in totality and over the past
19 few years, I as a parent would be most concerned
20 about my child in the neonatal intensive care unit
21 on chronic drips, with sedatives, anesthetics and
22 so forth, in the presence or absence of any

surgical intervention.

That seems to me to be the most susceptible population that's most likely to have problems. It's going to be impossible to tease that out in humans. You're going to have to go to reasonable animal models to work that out.

You can control the exposures very nicely. You can look at combinations of drugs. We already know some drugs can be protective. We can look at cocktails. We can try to come up with procedures that would ameliorate the known bad actors. We already know that xenon perhaps is a compound that doesn't cause problems. That's where I would put the effort and focus on the most likely population to suffer the most severe consequences.

DR. KIRSCH: Dr. Rappaport?

DR. RAPPAPORT: This is also in response to Dr. Zuppa's comment. And I really do think that that is the way to go with some type of a national or international organization to see these studies done properly and to find out what the risks and benefits of all of the different sedative and

anesthetic agents are.

It's not just important for here, but as many of you know and some of you are involved with, we're also just in the early stages of trying to develop a guidance document, with the community's help, for how to study sedative drugs.

The studies that we see come into the agency are so difficult to interpret, and I'm not sure that there's any good science to support the way the drugs are being used out there. It's probably mostly what you've all been taught by your mentors. And we really need to move into the age of evidence-based medicine rather than, as my friend Dr. Rogers says, imminence-based medicine.

Dr. Nelson also had a comment.

DR. KIRSCH: Dr. Nelson, then Dr. Zuppa.

DR. NELSON: Well, it's a comment, but it's as much a question, because I really don't know the answer. One of the questions in my mind would be if you've designed a clinical trial where you're randomizing between two different interventions, and there's really no difference between those

interventions in terms of the efficacy, but the only difference is the presumption that there may be less risk on one of those arms, it's unclear to me why, in the informed consent process, every parent would say that I would want the one that has the lower risk, if they're available as part of routine clinical practice, if they're not on that trial.

Absent any other risk information about the two interventions -- say, in the GAS trial, there are differential risks between general anesthesia and regional anesthesia. Absent some reason to necessarily say that there may be offsetting risks in the arm that reduces the risk of neurotoxicity, it's not clear to me why, after that informed consent process, everybody wouldn't say, "Well, of course, I would want xenon" or "of course, I would want" whatever other comparator there is.

I don't have the answer to that. I just think it might be a challenge going forward in some of this ideas.

DR. KIRSCH: So that's the second time in

the last five minutes that people have used the conclusion that xenon is somehow protective to the brain, and I think that's unfair. As I understand that data, it was primarily done by one laboratory that has a clear financial interest in the positive outcome of such a study. So I would caution understanding what the real effects of xenon are at this point.

Dr. Zuppa?

DR. ZUPPA: I just want to clarify, my comment was not to discourage those types of studies, but to kind of bring to light the need for education for a group of practitioners who have been -- it's almost generational, like their mentor taught them and so on and so on. So just to clarify.

DR. KIRSCH: And the last part of this question is an opinion as to whether studies should be conducted in all the typical settings in which anesthetic sedative agents are used, including general anesthesia, procedural sedation, and intensive care sedation.

Again, we've addressed this in the earlier question, and the answer was yes. However, the panel would like to focus on those areas where the largest number of patients would be impacted.

So with that, I'm going to go on to the next question. Again, there's a lot of overlap between these questions.

Given the risk associated with delay of surgical intervention or with the use of suboptimal anesthesia techniques, how does one incorporate the current knowledge base into the practice of pediatric anesthesia?

Dr. Jevtovic-Todorovic?

DR. JEVTOVIC-TODOROVIC: This is actually a question of interest to me. I am not a practicing pediatric anesthesiologist, but because I'm an anesthesiologist and I've been doing this kind of research, I get e-mails from parents actually quite often, and that's exactly the same, the question that they ask.

So it is very important for us to come up with some kind of an answer that's ethically,

professionally acceptable, even if we don't have an answer as to whether that is necessarily detrimental or not.

Do we wait for an elective? And I get actually three or four e-mails from highly educated parents who not only read, but can act, and the question is usually, "What is a good time to do it and what kind of technique should I discuss with the anesthesiologist? What is the best for my child?" And they are totally healthy kids. Just as Randy said, they are totally healthy kids, and the parents are truly concerned that it's going to slow down their cognitive and behavioral development.

So this is a very important question for some of us who get these questions all the time.

Then the second one is -- and it's more for Sul. When you go and conduct your interview as a part of informed consent, how much of that do you discuss? What is the optimal technique to use with your child and should we even discuss that now. In my institution, we don't.

DR. KIRSCH: So I'm going to turn your question maybe and address one of the other panel members.

Dr. Clancy, whether you have an opinion from the developmental point of view, whether there is a right answer to this particular question.

Before you answer, I'd like to comment, we talked a little bit about the effects of regional anesthesia versus general anesthesia. There is emergent data out to suggest that the normal concentrations of local anesthetics actually are damaging to developing myelin cells. So I don't think the panacea is in regional versus general anesthesia. I think anesthetics -- as someone said previously, all drugs have toxicity and we just need to balance things.

Dr. Clancy, are you able to address that question?

DR. CLANCY: I wish I could address it more, I will say, thoroughly, but it's my understanding that the later in development, the less impact. And I think there have been some studies -- I don't

read all the anesthesiology studies, but I think there have been studies that indicate that; I think one by Dr. Anand's lab, where the impact was more profound earlier and not as profound later in development, and that's what I see from my research.

DR. KIRSCH: Dr. Swedo?

DR. SWEDO: I think in this case, it truly is apple blossoms and orange juice, because we don't -- maybe not even that. It's some kind of virtual apple blossom, because we don't know what the risks are for either of these conditions, actually. So suboptimal is an interesting word, but we've already heard that we don't actually have enough preclinical data to interpolate or extrapolate that to humans and we don't have the control to human data to answer the question. So given that we always, as we heard from dad or mom, you hear the risks and then that becomes your burden, whereas the benefits are things that you can either see or not.

So my answer would be to only speak to the

level of knowledge that you have, and at that point, we don't have much.

DR. KIRSCH: Dr. Kon?

DR. KON: I think that this comment was made earlier, but I think it's important to say particularly when we're talking about this very issue, which is that there does appear to be some data to suggest that multiple exposures to anesthetics can be detrimental.

I think we all know that there are many institutions that use general anesthetics for procedures that other institutions use merely swaddling and feeding. And I think one of the most powerful things that we could potentially do coming out of this meeting is to work on some sort of guideline for those types of procedures, be it MRIs or CTs or some of the more minor surgical interventions.

This I think becomes extremely important and a place that I think we can make a statement now that would really make a difference in a lot of kids' lives.

DR. KIRSCH: About 10 years ago, Dr. Yaster, who was one of my mentors, made a comment actually on 60 Minutes when he was interviewed about providing an anesthetic for children having their first haircut. Children are often screaming during their first haircut, and most of us wouldn't consider giving our child an anesthetic for that experience. I think your comment is well taken.

Dr. Mattison?

DR. MATTISON: This relates both to question 3 and question 4. I think they do suggest that there's a research agenda in risk communication that needs to be addressed in terms of communicating the complex and evolving information about risk, but also, and we've touched on it briefly, the issue of benefit, and both of those domains are evolving right now.

So I think working with risk communicators to better understand how to approach this would be useful.

DR. KIRSCH: Dr. Notterman?

DR. NOTTERMAN: This will be short, because

Dr. Kon actually just addressed this. I think it's important to make sure that whatever statement the FDA makes is also pertinent for pediatric intensivists, and it also encourages them to minimize, to the extent possible, the exposure to these agents in terms of number of agents, dosage, and duration.

DR. KIRSCH: Dr. Deshpande?

DR. DESHPANDE: A couple of points. First, the information that we've heard, a significant portion of it is focused on ketamine and isoflurane primarily. So all of a sudden, our discussions are generalized to anesthetics, and I'd like to keep that clean as we look at both suggesting studies and looking at protocols, because otherwise it does become a potential panic situation.

The second is my understanding of the information I've heard and read is that even with the human studies that we have, multiple exposures associated with neurodevelopmental problems not necessarily can be detrimental, and I think it's important to parse those words today.

1 From the standpoint of how do we incorporate
2 this into practice, from a practical standpoint, my
3 suggestion to parents has always been that if you
4 don't need to operate, have an operation on an
5 infant, at that age, it's better to delay because
6 there are other non-medication-related
7 complications that happen, including airway
8 problems, hemodynamic supports, thermoregulation,
9 et cetera.
10 So there are significant risks to taking a
11 child, infant to surgery or putting him under
12 anesthesia that are unrelated to the topic we're
13 talking about today. So postponing, where it's
14 appropriate, is a practical thing. And I think
15 that using medications that are necessary is the
16 other aspect. "It won't hurt" is something we
17 ought to take out of our jargon anyway for any
18 medication that we use, because all medications
19 have some effect that we don't want.
20 DR. KIRSCH: Dr. Flick?
21 DR. FLICK: Three quick comments. Your
22 clinical trials need to be guided by epidemiology.

If we're going to do clinical trials, which take a long time and are very expensive, they need to be focused. The epidemiology that we do and others do is sort of a blunt instrument, but it helps guide future studies, clinical trials.

The greatest benefit that we could probably have here is to have a population that's under continuous study that could be used as a resource for these kinds of questions. And as these questions evolve, new questions will arise and that population can be drawn upon to guide the clinical trials or prospective studies.

With regard to how do we advise parents, we don't know that we have a problem. We think we have a problem or we think we may have a problem, and we have to be careful about the unintended consequences that go along with changes in practice.

We cannot tell practitioners how to practice. We can raise some level of concern and communicate that concern so folks will change their practice because they share that concern and will

change their practice accordingly. But, again, we're not in any -- the data, as I see it, does not support a guideline or anything that compels people to change their practice.

DR. KIRSCH: Dr. Weinstein?

DR. WEINSTEIN: Again, not being an anesthesiologist, I just marvel at the discussion. As a neurologist, I take care of a large cadre of patients that are busy seizing. And I'm tinkering with the same chemical systems that you're tinkering with. You happen to do it a little deeper, for a heck of a lot shorter period of time rather than the years that I use these agents.

The same questions arise when parents say, "What are my options," and the option is either they have seizures or I give them a drug. What's the option in terms of an anesthetic? Either your child is awake and stressed and has all the potential problems or I give a drug. And my judgment is that this drug, whatever that drug is, is what seems to be the safest for your infant.

But again, this isn't just true for these

anesthetic gents. This is true for all these agents the psychiatrists use, the neurologists use for everything. We deal with these systems and we've gotten pretty good at it, I think.

DR. KIRSCH: Dr. Ikonodimou?

DR. IKONODIMOU: Well many of the things that I wanted to say have already been said, but I wanted to comment on the fact that I, myself, as a neurologist, also have to deal with young children and infants having seizers. And actually one thing I have found quite helpful in making decisions was the fact that we were able, with experimental work in a clinical setting, to actually test toxicity of the different medications that are available out there. And they do vary considerably in how neurotoxic they are in terms of causing apoptotic cell death.

Perhaps something similar could be done in the preclinical setting also for anesthetic medications. I found it very interesting actually, the results that Dr. Olney presented that certain anesthetics are more toxic at different times of

development. So maybe this is something that should be done.

I think, however, in my mind -- that was the statement I wanted to make, the preclinical work that is currently available, which replicates neurotoxicity of these agents, that occurs in a number of mammalian species, leaves no doubt in my mind that this is happening in humans also.

I think that the data we have so far do not provide evidence that a short anesthesia, lasting less than four hours, causes injury to the brain. I don't think that we have enough data to make recommendations concerning that.

I agree that we should recommend to avoid anesthesia where possible. And the other simple things to do would be to recommend to the medical practitioners to use as few agents as possible, as low doses as possible, and a short duration of treatment as possible. And this is something that I feel strongly had to be communicated in some way to the medical practitioners, because the way they practice varies considerably, and most of them are

not aware of the dangers, potential dangers these medications carry.

DR. KIRSCH: Dr. Rappaport?

DR. RAPPAPORT: I just want to focus some of your discussion a little bit. There are two issues here. One is how do you communicate to the medical community, and a lot of that is going to be within the medical community, so various anesthesia and pediatric organizations should be communicating to their constituencies. But some of it we could do possibly in the way we write our labels.

So I would like to hear if there's anything you think we should be changing in our labels in terms of making a comment in there, just as you were noting.

The other is what do you communicate and what should the anesthesiology, intensivist and ER communities be saying to the parents? I think you all know what to do when you have a patient who doesn't need the surgery. You'd say don't do it, put it off. Bu when you have to have the surgery, that's the question we're sort of getting at.

I'm a neurologist, too. I always told my patients that we know this drug causes birth defects and you run the risks, but you treat your seizures. But what would you have told that person if all we had was animal data, which is all we have?

DR. KIRSCH: I'm going to address that comment. So I'm for one not in favor of a boxed warning for anesthetic agents. I think that would be a mistake.

DR. RAPPAPORT: I don't think we're anywhere near that.

DR. KIRSCH: I just wanted to make that clear. That is one option. And I also don't believe that there is any one sentinel study that is definitively clear on the true impact of the anesthetic agents on patients. So another option would be just to provide data form a sentinel study or two in the label.

They're all very helpful, but I don't think there's one or two sentinel studies that adding that data to a package insert would be appropriate.

1 That's my comment. But we'll take others.
2 Dr. Tobin?
3 DR. TOBIN: I'd just like to comment to the
4 non-anesthesiologists that are a part of the panel
5 and in the room. Currently, pediatric anesthesia
6 has never been safer than it's been over the entire
7 five or six decades that we would consider the
8 modern era. We now have the shortest acting agents
9 we've ever had. And for those who don't do what we
10 do, we run the risk that we use paralyzing agents
11 on a daily basis. And part of the reason we do so
12 is to reduce the dose of the inhalation or the
13 intravenous anesthetic dose and still not have the
14 patient move.
15 In so doing, we run the risk that the
16 patient experiences pain without consciousness.
17 They may experience awareness with paralysis. And
18 we recognize those risks, but we still reduce the
19 dose to what we believe is the minimal dose
20 necessary to engage the patient in an amnestic and
21 a reduced autonomic state to responding to no
22 susceptive stimuli. And even if we realize it's

going to be for a non-painful state, such as MRI or CT scan, we use the lowest dose possible to try and achieve immobility to achieve getting the scan done.

Before the days of MRI, we did that do reduce the dose of radiation the child gets. We still worry about that. We worry about the complication of a child in an MRI who has an uncontrolled airway, who may have the opportunity to aspirate or obstruct or have another major catastrophic consequence.

So I just want there to be a level of understanding that we currently make it one of our safety profiles to reduce the exposure of these drugs to the last dose possible, and that's because not just that we're worried about the neurotoxicologic effects, but because we recognizes the hemodynamic effects of these drugs, which are usually cardio-respiratory depressants, and we don't want to have that as another secondary physiologic variable which is going to contribute to potential neurotoxic effects.

1 So although there is variability, and I
2 can't say that propofol versus sevoflurane is the
3 best anesthetic to use for any specific surgery,
4 but I'll tell you we will still use the least dose
5 possible to accomplish the task at hand.
6 DR. KIRSCH: Dr. Tortella?
7 DR. TORTELLA: Just from an industry's
8 perspective, I think one of the interesting things
9 would be post-marketing commitments surrounding the
10 neurocognitive going forward. So that's something
11 that the industry could contribute as the new drugs
12 come forward.
13 DR. KIRSCH: Dr. Majumder?
14 DR. MAJUMDER: So just a disclaimer. I'm
15 not only not an anesthesiologist, I'm not a
16 clinician or a scientist or a clinician scientist.
17 So I really find it easy in this instance to speak
18 with a consumer voice and the patient voice.
19 But I wanted to go back to 2, and then
20 forward to 4, if that's okay. On 2, I noted in
21 Dr. Olney's talk the potential for synergistic
22 effects. I think he focused on caffeine.

I, again not having a scientific background, wonder if that should also be on the agenda for research in terms of whether there are agents that are routinely administered to populations that are vulnerable and whether there might be synergistic effects that should be examined.

On 4, this actually came up in my own experience as a patient. So I think the theme has been that there are different groups that require different responses in many ways, and I think the population of children who will need these procedures -- what you need to do is you need to have clinicians ready to say what Dr. Tobin said, we're doing everything we can to reduce the exposures, for a variety of reasons; so not unduly alarm parents, but also reassure them and have the confidence that indeed your practice is evidence-based.

This came up for me in the outpatient setting when my little boy was two and a half years old and went to a sleep clinic, and spent about 45 minutes with a fellow who mentioned, in passing,

some of the diagnostic studies that might be done and some of them would involve sedation, and would the risks really be -- should we absorb those risks in our case, because it wasn't clear that there was a serious problem; then raised it in our five minutes with the attending who said, "If it were my child, I would do it." And that was the extent of the response.

So I went back, Google'd it and actually found the minutes from the 2007 meeting, and just for myself said when we get to the ENT, if this comes up, I'm going to ask for more information.

So I'm not sure it should be raised with parents, especially in that setting, because I found what I read reassuring. If he had actually needed those procedures, which he didn't, I think the data that exists is somewhat reassuring for a very short duration and so on, although it probably would have been more elective in his case.

But I think the clinicians in that setting need to have some information to have a discussion with parents when this has been raised either

because they're out Google'ing it on their own in advance or because somebody said something to them, that those clinicians need to have some sort of reference that they can consult that will equip them with the information that they can then use to have a discussion with parents in that context.

DR. KIRSCH: Thank you. Dr. Martin?

DR. MARTIN: I wanted to call out and thank the FDA for their support with the research that's been collected and their efforts at helping us study this potential problem.

I think one of the issues for many clinicians, health care providers, is lack of awareness about this potential topic. As an anesthesiologist, particularly a pediatric anesthesiologist, you're reading every study that comes out. But I can promise you my surgical colleagues don't have much of an idea about this, and I think you could point to just about any specialty and say the same thing.

So I wonder, in my mind, if there isn't some potential benefit of some kind of summary,

publication that's disseminated widely to many medical specialties that potentially are referring kids for -- or giving kids sedative or anesthetic agents.

DR. KIRSCH: Dr. Rappaport, I have not had a chance to look at the New England Journal article, but maybe you can make a comment about that article.

DR. RAPPAPORT: It just was published last night online. It will be in the April issue of the New England Journal, an article that we wrote that summarizes this problem and basically calls for the same thing, for additional research and appropriate communications.

DR. KIRSCH: You had a request and it's taken care of. How do you like that?

So I'm going to try to summarize this. So given the risk associated with delay of surgical intervention or with the use of suboptimal anesthesia techniques, how does one incorporate the current knowledge base into the practice of pediatric anesthesia?

I think what I'm hearing from the committee is having well informed clinicians who practice in the operating room and the ICUs, in the emergency departments, and probably for general pediatricians who have a common understanding of the state-of-the-art in this area, which is hopefully informed by knowledgeable sources. And I'm expecting that this New England Journal article will be helpful in that regard. And for those individuals to express the current state. And as Dr. Tobin commented, to try to reassure parents that although there's lots of new knowledge to be gained on these agents, there is also a lot of knowledge, and that the people who are administering these drug will do their best to minimize the exposure, duration and concentration.

Did I miss something? Dr. Rappaport? Dr. Flick? I'm sorry. Dr. Kon?

DR. KON: So I appreciate that anesthesiologists in general try very hard to minimize exposure of these medications. But I do find that not infrequently there are procedures

performed under anesthesia, albeit the minimum dose necessary, that in fact don't need anesthesia at all. However, it's performed under anesthesia because it is much more convenient for the radiologist or the intensivist or the anesthesiologist.

So I think one of the things that I would really love to see is a statement not only that we need more research and that we need good communication, but that we need to prioritize children's long-term cognitive outcome over the convenience of the health care providers.

DR. KIRSCH: And as I said, there's lots of overlap between these questions, and that's a comment that's been made each of the previous three questions.

Dr. Soriano?

DR. SORIANO: Well, the question I have for Dr. Kon is should those patients be in play. The issue is these preclinical data clearly show it's a dose and duration phenomena rather than just a single dose, small dose. And that's the way most

pediatric practitioners use these drugs, ketamine, propofol, give them 2 or 3 ccs of this just to provide a brief amount of sedation.

Now, should these parents be told that their kid may be at risk for neurodevelopmental problems. Just judging from the preclinical data, I say no.

DR. KIRSCH: I would have to interject here. Like my colleague with the haircut, I think it would be disingenuous to parents for some procedures to say that the only way it could be done is under sedation or an anesthetic. I think as clinicians, we need to provide patients with the breadth of information that we have, and clearly there are some places that can do procedures like an MRI without sedative agents on board.

Dr. Swedo?

DR. SWEDO: Just to follow-on to that, if you can find a different -- I agree completely with Dr. Kon's statement about convenience, but I would not want to see that extended to sedation for all non-surgical procedures, as swaddling and administration of sugar solutions is great if the

child is 6 months or younger. It's not as helpful in a 12 to 24-month old, and at least the preclinical data were impacting on those individuals as well.

DR. KIRSCH: Dr. Flick?

DR. FLICK: As we talk about writing something or informing the public with a guideline or something, I wonder -- the devil is always in the details. So what age are we going to inform them of? What drugs are involved in this? What duration are we going to warn them against?

The details here, we don't know the answers to those. So I don't know how we can inform parents or develop guidelines when we don't have -- there is no clarity, in our minds, as to what the age, what the dose, what the drugs, what the duration is.

So we're left saying that we have concerns about this class or these classes of drugs in children and it appears that younger children are at greatest risk, but the information to go beyond that is really lacking.

DR. KIRSCH: Dr. Weinstein?

DR. WEINSTEIN: The question I suppose for me is how do you explain relative risk. What is the risk of having anesthesia in a skilled practitioner's hands with nursing and everybody around monitoring everything versus running down First Avenue carrying my 6-month-old baby, talking on the cell phone and trying to cross the street?

We talk about these risks being so great, but I'm not sure what the risks really are, and I think a priority for me would somehow, with Dr. Flick's data or somebody else's data, try to come up with a notion and then compare it to real world risk and let parents decide, because once you say something, that's what they pick up on. The question is how real is it, how big is the risk, and what do they do with it.

DR. KIRSCH: Dr. Susser?

DR. SUSSER: I think people already said the things I was going to say.

DR. KIRSCH: Dr. Notterman?

DR. NOTTERMAN: I think that any statement

should refrain from addressing specific procedures or clinical contexts, because I think it's clear that we don't really know. I'm mindful of Dr. Flick's comment we don't really know what the risks are. We have a foreboding sense that there are risks associated with these drugs that have not heretofore been delineated and we're trying to do it.

But I do think we have an obligation to remind our colleagues of the essentials of good medical practice. We should, in all contexts, try to consider alternative methods of calming children and of distracting them, and if we decide to use these drugs, we should use the minimum dosage for the minimum amount of time. And I believe that's what we can say based on what we know now.

DR. KIRSCH: Thank you. Dr. Inder?

DR. INDER: So there are going to be a group of families who are going to require multiple procedures in the first year or so of life. So it would be upon us I think to not ignore the neuroprotective approaches and data that is

suggestive, at least from hypothermia and from xenon, which are now in two randomized clinical trials in the newborn in the U.K. So those treatments are being used in the newborn now. And so it would be great to have some research focus and also to provide some hope to families that are not able to avoid prolonged or repeated procedures if there is concern until that data is available.

DR. KIRSCH: I would add that for children who have had to have that exposure, I would assume that there will be ongoing research to determine how to identify those individuals and give them the other support that they need in order to be successful and meet their full potential.

Dr. Deshpande?

DR. DESHPANDE: For me, incorporating the precautions that I've heard are logical clinical practice that have nothing to do with the neurocognitive impact of the drugs we are talking about. Using the last amount for the shortest period of time, at the time you need it, minimizes the immediate risks of airway, cardiovascular, and

1 overall collapse of the infant under the care of
2 any anesthesiologist or intensivist. So if you
3 don't need the drug -- you don't need too much of
4 the drug and you don't need it for too long, don't
5 use it because it's unsafe for the immediate
6 problems that you may get into.
7 The same thing has been shown in intensive
8 care practice, that prolonged sedation at high
9 doses for long periods of time is bad for patients
10 on ventilators. It's bad for patients who have
11 additional support that's needed in the ICU. It
12 has nothing to do with the neurocognitive aspects
13 that we're talking about today.
14 So I think what we're talking about is
15 reinforcing good precautions that we should talk
16 about not related to the impact that we were
17 discussing today on neurocognition.
18 So I'd like to separate those two, because a
19 statement saying those things is generally
20 important as a reminder, but I don't necessarily
21 want to mix it with the neurocognition issue we're
22 talking about today, because of what Dr. Flick

said, which is I'm not sure that we have a problem yet.

DR. KIRSCH: Okay. Last question, another easy one. Please suggest how to best communicate these concerns to both prescribers and patients at this time -- parents, I'm sorry. Prescribers and parents at this time. Comments? Come on, this group can't be quiet.

Dr. Swisher?

DR. SWISHER: I think that there are different populations of patients, as we talked, the short procedure, the long procedure, the prolonged sedation, and then there's also the repeated sedation, like my daughter had general anesthesia for radiation, 33 treatments of general anesthesia. And how that affects her long-term cognitive ability, having a brain tumor and radiation, being premature, I'm not sure that you can sort out.

But 11 years later, I can tell you, we have neurocognitive issues. And when I listen to this and the concerns, I think about the radiation

oncology signing the consent for whole brain and spine radiation. Let me tell you, it's clear, it damages 5-year-old kids' brains, and parents do it all the time because they want to save their kids.

So there are ways to talk to parents to know that there's problems coming out and that you're going to have to be aware potentially to address it. Some kids don't have that many effects, other kids have a lot. But I'll tell you, the best long-term effect that I like to talk about is she's still here with me 10 years later. And there are the fine points. We don't want to do harm to kids, but I don't want to throw the baby out with the bathwater, that you want to do the right thing for kids so they're not scared, that they're not in pain, and we treat their disease as quickly as possible.

Now, for the parents, parents can be crazy both ways. I am on listservs that the parents write doctors all the time about different things. There's other parents that are information blunters, and getting this information just makes

them nervous and crazy.

So from the parent perspective, I think you have to address the information for the parents in the way they need. Early on, they may -- if you have somebody who is having chronic medical issues, they may not want to know about the long-term need for IEPs and special education and the potential of that. They're just trying to get through today.

So I don't think that there's one answer either for the patients or the parents.

DR. KIRSCH: And how best to communicate these concerns, I think someone commented previously to encourage the national societies that we all belong to make sure that the symposia that are at these different meetings inform the prescribers, us, as to whether the state of the current research is so that we can best be able to communicate with parents and patients.

How best to get to the parents other than through the clinician is a bit more tricky, and I'd like to -- if anyone has a thought on that particular topic.

Dr. Zuppa?

DR. ZUPPA: I want to answer your question with a question I guess to the group. So I'm just trying to put myself in a clinical setting where I'm in the ICU. There's a patient that comes in. Again, I keep going back to respiratory failure. I go to the parent and I say, "We need to put a breathing tube in. We need to sedate your child for this."

At that moment in time, are we suggesting that I say to that mother, "I just want you to know that the sedation that we're going to use to intubate your child may have long-term potential neurologic implications?"

I'm just trying to understand what we are saying we are going to say to a parent.

DR. KIRSCH: I'll answer the question. I think you have to, as a seasoned clinician, do what's right for the parent at that time, and I think that you have to be able to address.

There's a lot of savvy people out there, so I would not personally say "I'm going to put a

breathing tube in your child and these are all the other awful things that could happen." But if a parent then came and said, "Well, doctor, I understand the reason you're going to put the breathing tube in, but you're also going to give these medications." If they ask specifically, "Can you tell me, are these medication safe," then I think you're obligated to say what the issues are, what the potential issues are.

Dr. Kon?

DR. KON: I personally would not say that at that moment, because I don't -- first of all, there's an awful lot of data that shows that parents don't hear what you're saying anyway. So I'm not sure that that would be a moment that you would actually be imparting much information.

But I do think that part of any good critical care practice is once a patient is a bit more stable or stably on the ventilator, et cetera, et cetera, as stable as you can be in an ICU, that we sit down with parents and we talk about not just what's going on now, but what's going to happen in

the future. I mean, we knowledge that kids that survive their ICU stay have long-term issues, not just neurocognitive, but other as well. And in general we sit down at some point when the parents are ready to start talking about that and talk about that.

I don't think it's unreasonable. And I would agree, I don't think -- one of the comments that was made earlier as we've seen in association, I don't think an of us feel that there's certainly any data that would say that this is causing problems.

But I think we have a worry, and I think sharing that worry with parents when they're ready to hear it I do think is important, and I think it's particularly important as a way to build trust, because I fear that if clinicians aren't up front about it and honest about it and forthcoming, if parents then later hear about it and hear, "Well, the FDA held meetings about this back in 2007 and why did I never hear about this," I think that's a problem for a lot of parents. So being

very honest I think could be very helpful.

DR. KIRSCH: Dr. Rappaport, you had a comment to make. I also have a question for you. You had your hand up. Before you ask the question, I have a question for you.

The FDA has a very effective partnership with -- I don't know if it's advertising, but informing in the public venue about a whole variety of different issues, like locking your cabinet with the narcotics and so forth.

Is there opportunity with regards to the anesthetic agents to partner with -- getting the message out into parents' magazines and so forth ? Is that within the realm of possibilities or would that be too alarming, do you believe, to the public?

DR. RAPPAPORT: I think that the problem here, the one that we're all addressing, is that we don't know what this means for children, and because of that, for us to come out with a public statement for parents, it would be I think saying that we know more than we do. We generally don't

do public communications of that level until we really have some clear signal that there's a problem in patients.

Now, on the other hand, I do think that that could come from other organizations and not us. And I think a lot of the discussion here is very useful about how the medical community should be communicating to parents. But for us, really, I was surprised that there was sort of a surge of angst when we announced all of this and people were worried that we're going to be limiting the use of the products or putting a box warning in or something like that, which is not really what this was all intended for. It was really more just to air publicly what we do know and make sure that we have a good understanding of what we need to do from here on.

There is one area where we haven't changed the label and are trying to decide what to do about that, and that's in the animal data section, and whether to include any of this information in there. Up to now, we have chosen not to, because,

again, we just weren't sure what the implications were.

If anybody has opinions on that, I'd be interested in hearing them, although ultimately it's a decision we'll make internally.

DR. KIRSCH: Dr. Anand, would you come up to the microphone?

DR. ANAND: Here's my two cents as a country doc. I would not tell that mother that these drugs have any effects on brain development. I would say, "I'm going to sedate your child, she will not be in pain, she will not feel any stress. These drugs can drop her blood pressure, can keep her from breathing, et cetera, and we'll give her the least possible for the smallest duration of time. That's it.

Like Jay said, I would not bring this up at all, because it has, really from my point of view, no implications in the clinical arena at this point.

DR. KIRSCH: Dr. Markman?

DR. MARKMAN: I'd just go back to

Dr. Nelson's lecture about professional responsibility. I think one take-home from today's discussion is that there's a spectrum from a high degree of certainty to a high degree of uncertainty. And we're relatively I think very certain about the tradeoffs acutely with regard to physiologic stability of children who are undergoing surgery or other procedures. We know that there are very certain tradeoffs in the acute window, and we are very uncertain about the long-term effects. And I think it's important to contrast the level of certainty with the tradeoffs in the acute period for parents, with a high degree of uncertainty for the long-term consequences.

DR. KIRSCH: Dr. Flick?

DR. FLICK: If the question is should we as a committee formulate some communication to the public, I think the answer is clearly no. And the reason for that is we cannot get out ahead of our colleagues and communicate something to the public that our colleagues are unprepared to deal with and there is no clear alternative to.

If we're going to communicate something, we have to communicate, in my view, through our professional organizations to develop from within the specialties affected an organized, thoughtful response to this and, in some sense, that we can communicate that effectively to our parents on a one-on-one individual basis.

DR. KIRSCH: We'll take a few more comments, but I'm going to log Dr. Flick's comments as the official summary, because that's what I've hear over and over again as we've discussed this topic.

But with that said, I'll take some additional questions. Dr. Susser?

DR. SUSSER: I’m going to disagree with that, because I've seen this so many times with social movements, you can't control them. They have a dynamic of their own. You see it with autism, you see it with Gulf War illness; if you just look at medical history over the last 20 years.

I totally support the FDA, what it's doing at this moment, which is like putting it out there

that there's concern. We have no evidence yet, or may never. We don't know that these agents cause neurodevelopmental damage. The question has arisen. If you don't acknowledge that question -- it's already out there; it's in the New England Journal already.

This is going to be picked up by everybody and you can guarantee that there will be like Internet groups, parent groups and so forth. You're going to have to -- if you don't take it on at the start and say we take it seriously, and just say honestly where things are; there is no evidence at this point that anesthetic damage long-term neurodevelopment, but some concerns have been raised and we're doing everything we can, that will make a huge difference.

To say nothing is disastrous, I think, because that's happened in Gulf War, that's what happened in autism vaccines. You could go through so many examples. So I would preempt that.

DR. KIRSCH: So I'll add my commentary. What Dr. Flick said was I think a reasonable

summary of the consensus of opinion of the committee. Everyone should be aware that every single word that we're saying is part of the public record. It's all being transcribed and is recoverable; just Google it on the Internet.

So any public group that wants to know the debate that we've had can easily pick it up by looking at the Internet.

Dr. Deshpande?

DR. DESHPANDE: As we talk about communicating with parents and the questions that Dr. Zuppa addressed, I took the liberty of looking up the package insert for ketamine, and I think about the commercials on television for a variety of medications., about three-quarters of which is this long list of various things that can and may happen. And those are real, documented probably proven; I didn't go through each medication that's advertised. Therefore, listed on the insert as a concern, one would hope, from the most common to the last common.

As w talk about communicating with parents

and not wanting to hide any information, I also don't want to provide false or inaccurate information that we know that this impacts children, that we know that this causes neurocognitive problems, and, therefore, we should tell you.

I don't know that. I didn't hear that today that there's an overwhelming sense of the committee or overwhelming sense of the data that there is a problem. It is a possible problem and that's the reason for the research questions that were posed to us. And therefore, I don't think that bringing up at the time you're intubating or providing care is necessary, because we're not there yet.

DR. KIRSCH: Dr. Schreiner?

DR. SCHREINER: Right now, my full-time job is to serve as an IRB chair. And so I'm kind of thinking about what we're saying today in analogy to what would happen if this were before a research ethics committee. First of all, I'm going to assume that, as many people have said, that we're going to use these agents based on the risk-benefit

for each individual at that moment.

One of the major problems for oncology research is that in listing everything that might happen, people are less informed; that it's important in those individual discussions to highlight whether the real risks are.

Right now, the new chair of Children's Oncology Group is at my institution, and I have discussed with him the possibility of changing the oncology consent forms to say while you're in this research, you might die, you might get a major infection, you might have bleeding.

What happens instead is we have five or six pages of possible side effects for which is lost the major impact that you might die, that you might have bleeding. So I think that requiring a discussion or even anticipating a discussion without the parent offering a question is not to inform somebody, but it's to rather misinform them.

Then the other analogy I thought was that what to do with reporting of research results. Right now we have a tremendous problem of doing all

this genetic research, but what is the meaning of those results. And the answer is that you have to report all clinically significant results.

Well, what does that mean? Well, first of all, it has to be actionable. And what are the choices in most situations here? There is no action to be taken. And there's certainly a considerable literature on what happens when you report results to people for which there is no action, and, in general, the results are quite negative. To tell somebody that they have Huntington's disease when they're 10 is to decrease the quality of their life for the next 30 years, because there's nothing to be done about it.

So I think that before we report things voluntarily to individuals who don't ask a question about this issue is I think a grave error and that we should restrain from doing it.

DR. KIRSCH: Okay. The last comment I'm going to have is from Dr. Thurm.

DR. THURM: I was going to say something a little bit similar as a clinical researcher. But

as a clinician now, and all I do is actually assess language and neurocognitive deficits in children, from actually children who are pretty typical to children with autism and Rett disorder, very severe, I would just say that if comments are going to be made about risk, it should be put into context, because we have children who are speaking at 19 months instead of 18 months and parents are asking was it the laptop I used when I was pregnant, was it the Motrin, was it the sugar I gave my child; so just making sure that it be put into context with a lot of the other things that are going out there that people are asking about.

Adjournment

DR. KIRSCH: Thank you. And thank you for the committee's attention. It was an important question and there were lots of helpful comments.

Thank you. We're done.

(Whereupon, at 3:00 p.m., the meeting was adjourned.)