

# Center Line

Bowles Center for Alcohol Studies  
School of Medicine, University of North Carolina at Chapel Hill

Our mission is to conduct, coordinate, and promote basic and clinical research on the causes, prevention, and treatment of alcoholism and alcoholic disease.

Volume 20, Number 1, March 2009

## Bowles Center Hosts the Collaborative Initiative on Fetal Alcohol Spectrum Disorders

The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) is an NIAAA-funded consortium that is focused on informing and developing diagnostic measures, effective interventions and treatment approaches for prenatal alcohol exposure-induced defects. The structural and functional defects that result from maternal alcohol use comprise fetal alcohol spectrum disorders (FASD). At the severe end of the spectrum is Fetal Alcohol Syndrome (FAS), a condition characterized and diagnosed by facial dysmorphism, growth retardation and brain damage.

Clinical observation first recognized FAS in the 1970s, and currently, there is no doubt that prenatal alcohol exposure can cause FAS in humans and animals. While physical features of FAS identify the severely affected individuals, it is estimated by FAS epidemiology investigators that FAS represents only 25% of FASD, with the latter impacting 3-4 births per 1,000 in the USA. FASD is a problem not only in this country but worldwide. To move the field forward through scientific exchange, basic and clinical CIFASD investigators from across the US, the United Kingdom and South Africa, along with UNC scientists, met recently in Chapel Hill.

The CIFASD multidisciplinary research effort includes animal and human studies that focus on the neuroanatomical and behavioral manifestations of FASD. The collaborative endeavor fosters basic, clinical and translational research on FASD through common goals. Regular

The three days of stimulating scientific exchange began with presentations by two local guests: Drs. Al Johnson, a world leader in magnetic resonance imaging (MRI), and C.J. Malanga, a UNC pediatric neurologist who is initiating novel studies regarding the impact of prenatal alcohol on adult brain

reward systems and associated persistent behavioral changes. Dr. Johnson's talk about new imaging methodologies that allow improved structural and functional determinations in both small animal basic science experiments as well as in living humans generated considerable

excitement. Dr. Malanga's discovery of marked genetic determinants of prenatal alcohol-mediated disruption of adult reward systems also stimulated much discussion and interest.

Presentations by the CIFASD investigators started with Dr. Kathy Sulik. Her studies model early prenatal alcohol exposure in mice. Of particular importance for her work is the use of high resolution MRI, which allows identification of brain damage and concurrent facial dysmorphism (see Figure). This was followed by a presentation by Dr. Elizabeth Sowell (UCLA) whose work utilizes MRI to investigate characteristics of children following exposure to alcohol *in utero*,



**From Left to Right:** Sarah Mattson, Ph.D., Michael Charness, M.D., Kenneth Warren, Ph.D., Kathy Sulik, Ph.D., Ed Riley, Ph.D., and Fulton Crews, Ph.D.

meetings of the group not only facilitate exchanges of information but also allow rapid resolution of significance and identify specific areas for additional focus and implementation strategies. Drs. Ed Riley (CIFASD Program Director) and Michael Charness (CIFASD Scientific Director and Bowles External Advisory Board member) with CIFASD member Dr. Kathy Sulik (Bowles Faculty) organized the meeting of CIFASD investigators and invited guests. NIAAA leaders Drs. Kenneth Warren and Dan Hereld, as well as NIAAA Alumnus Dr. Faye Calhoun, contributed their expertise and leadership.

Continued on next page

allowing translational insights between the Sulik and Sowell MRI studies. Both reports highlighted new findings on brain regions that are affected in FASD. Dr. Ken Jones of the University of California, San Diego (UCSD), one of the physicians to originally describe FAS, continued with a presentation of new studies on morphological diagnostic factors that could be used to identify FASD. This was complimented by descriptions by Feng Zhou and Tatiana Foroud of Indiana University-Purdue University, Indianapolis (IUPUI) of the application of three-dimensional facial imaging to facilitate diagnosis. Tim Cudd (Texas A&M), utilizing a sheep model, is also exploring alcohol-induced facial dysmorphism and presented an update on this work.

Presentations by two guest scholars from England, Drs. Peter Hammond from University College, London, and Christian Klingenberg from the University of Manchester, highlighted the second day of the meeting. Both focused on state of the art systems for analysis of facial form and applicability for FASD diagnosis. The group discussed how these systems could be used in both human and animal studies.

Important insights were also provided by Dr. Hannah Kinney, a Boston Children's Hospital-based neuropathologist who is involved in sudden infant death (SIDS) research and is a member of the National Institute on Child Health and Human Development (NICHD) and NIAAA-funded Prenatal Alcohol and SIDS and Stillbirth (PASS) network. The large PASS patient population provides an additional potential study population for CIFASD. Large groups of humans need to be studied in order to understand the full impact of *in utero* alcohol exposure.

One complication for understanding the full range of abnormality that results from *in utero* alcohol exposure is that it is common for women not to remember or not want to say that they drank during pregnancy. Biomarkers of alcohol exposure offer a potential solution to this problem. Drs. Charles Goodlett (IUPUI; CIFASD investigator) and Dan Savage, University of New Mexico (UNM) and CIFASD steering committee member, gave presentations regarding CIFASD tissue banks and efforts to discover and verify biomarkers of alcohol exposure in tissues such as hair, meconium and placenta.

Discussion of animal and human studies regarding the interaction of nutrition and prenatal alcohol exposure on FASD behaviors made for a lively afternoon. CIFASD Investigators Dr. Jennifer Thomas and Dr. Sarah Mattson (San Diego State University), along with Dr. Christina Chambers (UCSD), gave complementary presentations regarding detailed studies of

children exposed to alcohol and how diet during alcohol exposure can affect brain development. Interestingly, supplementation with choline, a key nutrient, is showing promising results in Dr. Thomas' animal studies. In the UNC Nutrition Department, Dr. Steve Zeisel has for many years studied the benefits of choline for brain development. His group has shown that when rat pups receive choline supplements *in utero* or during the second week of life, their brain function changes such that there is lifelong memory enhancement.

The focus of the final meeting day was on collection and analyses of data from national and international studies of human alcohol-exposed pregnancies and children. The international sites at which investigations are currently being conducted are in South Africa and Ukraine. Presenting site-specific progress, needs and goals were Dr. Claire Coles (Emory University), Phil May (UNM) and Dr. Colleen Adnams (University of Cape Town). This was followed by discussion of ways in which to best utilize resources and maximize uniformity in data collection and reporting, as well as intra-consortium access to data.

Overall, the meeting set the course for the coming year of studies. Additionally, it provided a wonderful opportunity for Bowles Center faculty to learn about and contribute to the CIFASD.

In mid-March, a number of the CIFASD members, including Bowles Center member Dr. Sulik, presented their findings in Victoria, BC, Canada, at the 3rd International Conference on Fetal Alcohol Spectrum Disorder: Integrated Research, Policy and Promising Practice Around the World: A Catalyst for Change (<http://www.interprofessional.ubc.ca/FASD09.htm>). The emphasis of this conference was the practical application of various forms of FASD research.

For more information on CIFASD and its news and upcoming events, please visit <http://www.cifasd.org>. ■

**Figure (Right):** 3-D reconstruction of high resolution magnetic resonance images allows detailed analyses of the faces and brains of fetal mice. As compared to a control fetus whose face is shown in (a) and whose brain is shown in (c; frontal view) and (e; dorsal view), a prenatally alcohol-exposed fetus (b, d, f) has defects involving both its face and brain. Most apparent in the face (b) is the small nose and abnormal upper lip. Both the frontal (d) and dorsal (f) views of the brain illustrate deficiencies primarily involving the forebrain (esp. cerebral hemispheres and olfactory bulbs). Similar examination of the spectrum of defects that results from ethanol exposure at specific developmental stages and comparison to human data, as is emerging from the consortium's efforts, promises to aid in identifying new FASD diagnostic criteria.





## The Director's Column

**Fulton T. Crews, Ph.D.**  
**Director,**  
**Bowles Center for**  
**Alcohol Studies**

The recent meeting was a great opportunity for UNC students and scientists to interact with the CIFASD faculty. The CIFASD is a model for translational research, bench to bedside and bedside to bench. The consortium is making remarkable advances in imaging, image analysis and computer diagnostics that are pushing the cutting edge in FASD research in new and novel directions. Parallel preclinical and human clinical studies are often difficult to compare due to different diagnosis and differences between animals and models and human disease.

With fetal alcohol exposure, the cause is maternal drinking, and that can be modeled, although not as easily as one might think. Diagnosis of human FASD includes facial morphological features and/or neurological dysfunction that are found in both humans and animals exposed *in utero* to alcohol (first trimester). We know that alcohol has different actions at different stages of development, mostly from animal studies. The ability of modern medical imaging to assess facial changes, brain structural

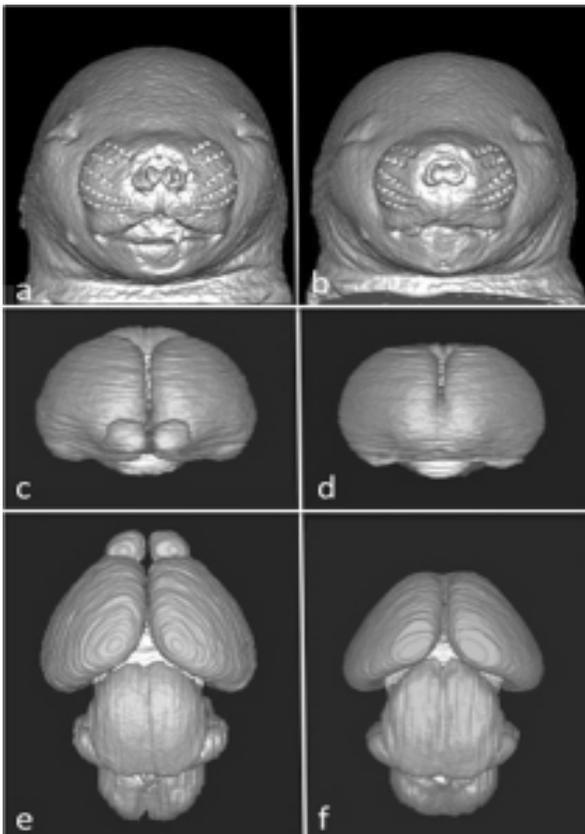
abnormalities and resulting alterations in performance, mood, cognition and many other measures of health is done in both controlled animal models and humans who are carefully assessed to best characterize exposure and abnormalities.

Rarely or perhaps never before has a group directly compared controlled animal studies and descriptive human studies using sophisticated analytic techniques. Similar imaging methodologies allow comparisons of human dysmorphology and dysfunction with animal models of varied dose, exposure, genetics, diet and all the other factors that may contribute to these alcohol-related pathologies. These are exciting studies prompting back and forth comparisons, looking for insights.

The workshop was mostly, but not all, work. A few guests, including Michael Charness (Bowles Center Executive Committee member) and Dan Savage watched the UNC basketball team play the College of Charleston at the Dean Smith Center. Both the UNC hosts and CIFASD scientists felt this was a win-win exchange of science and knowledge. We hope they come back.

As spring arrives, the Bowles Center welcomes Dr. Thomas Kash to our faculty with high hopes that he will reach his potential and make significant contributions at UNC. We look forward to integrating him with our research, teaching and service programs, collaborations, and fostering his growth as a scientist and upcoming star in the alcoholism research field. ■

Figure



## CONGRATULATIONS

**Dr. Linda P. Spear**  
**on Receiving**  
**the 2009**  
**Bowles Lectureship**  
**Award**

This annual award honors distinguished researchers that have made significant contributions to our understanding of the causes, prevention and/or treatment of alcoholism and alcohol abuse.

# Thomas Kash Joins CAS

The UNC Bowles Center for Alcohol Studies (BCAS) welcomes Tom Kash, Ph.D., to our faculty. Kash, assistant professor in the Department of Pharmacology and the BCAS, brings exciting research achievements and potential.

Kash joins the BCAS from the Department of Molecular Physiology and Biophysics at Vanderbilt University in Nashville. He spent the last several years focusing on the electrophysiological alterations in brain slices associated with alcohol withdrawal. "I will continue to use a combination of slice electrophysiology, biochemistry, behavioral manipulations and genetic animal models to better understand alcohol abuse," said Kash.

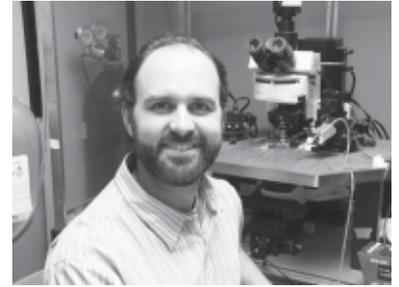
"It has long been assumed that dopaminergic neurons in the ventral tegmental area are the major source of dopamine that influences the motivation to use alcohol and drugs," said Kash. "However, recent reports have challenged this dogma, demonstrating that a previously uncharacterized population of dopaminergic neurons originating in the periaqueductal gray

(PAG) are involved in the acute rewarding properties of abused drugs, as well as negative states associated with chronic drug use."

Several reports have shown that the PAG is a major source of dopamine to both the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala, two regions involved in the negative affect associated with alcohol abuse. Further, *in vivo* ethanol increases the levels of dopamine in the BNST, and antagonism of dopamine receptors within the BNST can alter alcohol seeking behavior. "The neurons in the PAG have been shown to have altered electrophysiological responses during ethanol withdrawal," said Kash.

Kash hypothesizes that dopaminergic cells in the PAG are critical for both acute and chronic aspects of alcohol abuse. He is also interested in studies of brain function in the BNST, because this area regulates the stress response and anxiety-like behavior. Kash's post-doctoral research examined the interactions of acute and chronic ethanol with excitatory transmission in the BNST. "In continuing my research, I will focus on inhibitory transmission in the BNST," he said. "I plan on utilizing a multi-disciplinary approach to evaluate these hypotheses, building on the extensive experience obtained in slice electrophysiology during my post-doctoral training."

His work is partially funded by a R00 Pathway to Independence Award from the NIAAA. ■



**Thomas Kash, Ph.D.**



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To become involved in our mission, call Elizabeth Thomas at (919) 966-4977 or email [ethomas@med.unc.edu](mailto:ethomas@med.unc.edu).

For treatment information call UNC Health Care's Alcohol and Substance Abuse Program at (919) 966-6039 or (888) 457-7457.

[www.med.unc.edu/alcohol](http://www.med.unc.edu/alcohol)

**Center Line, Vol. 20, No. 1** Published quarterly to bring readers a greater understanding of alcoholism research and the Center's mission.  
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