Center Line

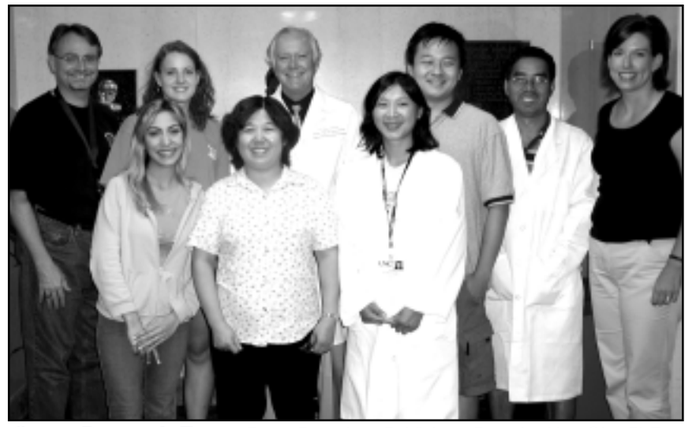
Bowles Center for Alcohol Studies
School of Medicine, University of North Carolina at Chapel Hill

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

ISSN 0738-6567 Volume 15, Number 2, September 2004

Crews Lab Discovers Ethanol Inhibition of Adult Neurogenesis

For decades neuroscientists believed that the number of neurons in the adult brain is fixed early in life and that adaptive processes such as learning, memory, and mood must be related to changes in synapses. It was thought that potentiation or inhibition of existing connections between neurons was the only mechanism by which the adult brain could modulate behavior to adapt to the environment. The recent discovery that adult brain contains neural stem cells and progenitor cells that give rise to new neurons throughout life has radically changed thinking about the mechanisms that regulate brain plasticity. Hundreds of thousands of new neurons are formed each month in adult brain. These new adult neurons have been implicated in mood, learning, and memory formation—particularly associative memories and memories involved in regulating mood and affective state. Examples of associative memories include those in which particular sensory experiences bring to mind other sensory experiences or evoke specific emotional or motivational states. For example, the smell of popcorn can evoke the sensory memories of popcorn's taste and appearance and can induce the motivational states of hunger and craving for food. Craving is a form of associative memory. Dr. Fulton Crews, alcohol researcher and Director of the University of North Carolina's Skipper Bowles Center for Alcohol Studies, points out that associative memories—particularly the motivational and emotional states that can be induced by various environmental and internal stimuli—are important in the development of alcoholism. He thinks it interesting that both adult neurogenesis—the formation of new neurons—and the risk of a drinker's becoming dependent on alcohol are influenced by both genetics and the environment. He hypothesizes that ethanol might disrupt adult neurogenesis in a manner that could contribute to alcoholism.



Crews Research Team: Front Row, L to R: Viviana Rosado, Liya Qin, PhD, Jun He, PhD; Back Row, L to R: Richard Hanes, Erin Potts, Fulton Crews, PhD, Daniel Kim, Jian Zou, MD, PhD, Kim Nixon, PhD

In a series of studies with postdoctoral fellow Dr. Kim Nixon, Crews found that both acute and chronic ethanol inhibited neurogenesis. In fact, multiple aspects of the process of neurogenesis were inhibited by ethanol (See figure on next page). Neurogenesis is a complicated, multistage process that includes cell proliferation, migration of new cells into appropriate brain regions, and differentiation into new neurons with cellular processes (i.e., dendrites and axons) that form connections with other neurons. An enriched environment (including the opportunity for social interaction, physical activity, learning) significantly increases neurogenesis and enhances performance on learning tests. Previous studies from the Crews lab show that binge drinking interferes with re-learning as well as neurogenesis. Similarly, stress has been found to reduce neurogenesis and to disrupt cognitive ability and is thought to contribute to the progression of alcohol abuse and alcoholism. Noting that one of the criteria for alcohol dependence is continued drinking in the face of negative consequences, Crews suggests that "maybe when people first start drinking, they drink small amounts of alcohol that do not markedly disrupt neurogenesis. The rewarding effects of alcohol and social positive feelings associated with drinking experiences create associative memories that result in positive associations with alcohol. The associative memories could be responsible for triggering a craving for an alcoholic drink when environmental cues such as bars or

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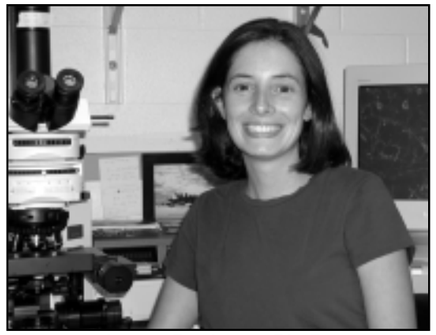
UNC Trainees Receive Prestigious RSA Awards

The Bowles Center for Alcohol Studies faculty, post-doctoral fellows, and graduate students turned out in high numbers to participate in the 2004 Research Society on Alcoholism's (RSA) Annual Scientific Meeting held in Vancouver, British Columbia, Canada. Members of our Center chaired, organized, and gave oral presentations at eleven symposia and paper sessions. They also presented over twenty posters during sessions throughout the four-day meeting. One former and one current member of the Center received two of the Society's most prestigious awards.



Joyce Besheer, Ph.D.

Gavin E. Arteel, Ph.D. received the 2004 RSA Young Investigator Award. The award is given to an investigator to honor his/her outstanding contributions and potential for success. Arteel trained as a doctoral student and worked as a research associate at UNC with the late Dr. Ronald G. Thurman. In his acceptance speech Dr. Arteel mentioned that Dr. Thurman taught him to "do what you love and love what you do. That is science." Dr. Arteel is currently an Assistant Professor of Pharmacology and Toxicology at the University of Louisville Health Sciences Center.

Joyce Besheer, Ph.D., received the 2004 Gordis Award in the post-doctoral category for her poster, "Novel mechanism of ethanol discrimination: Interaction of mGluR5 and benzodiazepine-sensitive $GABA_A$ receptors." The esteemed award is presented to one post-doctoral fellow and graduate student each year to acknowledge their research accomplishments and professional integrity. Besheer is a research associate at the Center working under the mentorship of Dr. Clyde Hodge. The Bowles Center is proud of its successful trainees and their scientific accomplishments.

The Bowles Center for Alcohol Studies

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To become involved in our mission, call Melissa Mann at (919) 966-5678 or email melissa_mann@med.unc.edu.

For treatment information call UNC Health Care's Alcohol and Substance Abuse Program at (919) 402-1644.

www.med.unc.edu/alcohol

Thurman Lectureship Award

Many thanks to Mr. and Mrs. Glenn Thurman, parents of the late Ronald G. Thurman, for their generous gift in support of the Thurman Lectureship Award. The award was established to honor the scientific excellence of Dr. Thurman's research and teaching. It commemorates Ron's life for those of us who benefited from knowing and working with him and also for the students and scientists that will follow in his path. We thank everyone who contributed to make this award a reality.

Center Line, Vol. 15 No. 2 *Published quarterly to bring greater understanding of alcoholism research and the Center's mission.*
A. Leslie Morrow, Ph.D., Editor-in-Chief; Angela D. Farrior, Managing Editor; Jane Saiers, Science Writer

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This document is supported by subscriptions and donations to the Bowles Center for Alcohol Studies.

other drinking-associated stimuli are present. As alcohol drinking increases from moderate levels to abusive levels and eventually progresses to dependence, individuals drink more alcohol and inhibit neurogenesis such that negative events are not remembered as being associated with alcohol. It is as if the drinking has become disconnected from the consequences."

Crews' characterization of the alcoholic as drinking in the face of negative consequences is nowhere better illustrated than in alcoholic James Frey's 2003 memoir *A Million Little Pieces*. Having awakened in an airplane with a broken nose, a cut cheek, and soiled clothes—and with no memory of how he was hurt or knowledge of why he is on the plane—the 23-year-old Frey is met at the airport by his parents, who take him to the family's cabin to spend the night before he enters a residential treatment clinic the next day. At the clinic, Frey describes his drinking behavior to his new recovery counselor:

Counselor: When did you start using drugs and alcohol?
Frey: I started drinking at ten, doing drugs at twelve.
Counselor: And when did you start using heavily?
Frey: At fifteen I was drinking every day, at eighteen I was drinking and doing drugs every day. It has gotten much heavier since then.
Counselor: Do you black out?
Frey: Yes . . .[e]very day. . . . For [f]our years or five years.
Counselor: Do you get sick?
Frey: Every day.
Counselor: How often?
Frey: When I wake up, when I have my first drink, when I have my first meal and a few more times after that.
Counselor: How many times is a few?
Frey: Anywhere from three to seven.
Counselor: How long has this been happening?
Frey: Four or five years.

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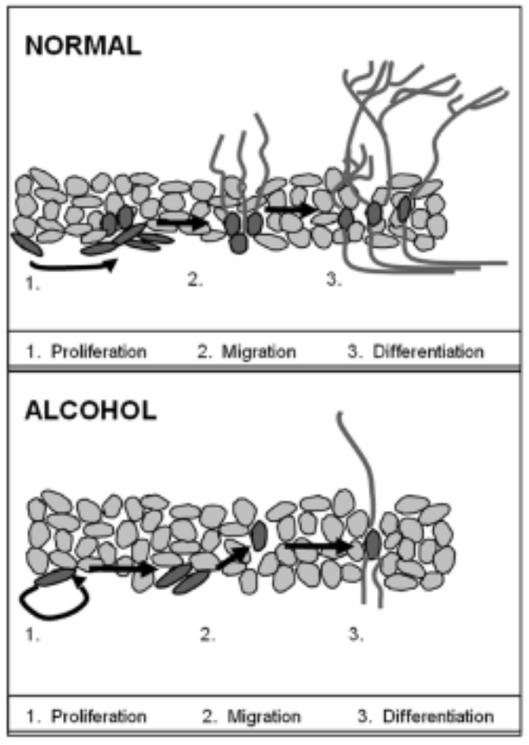
Fulton T. Crews, Ph.D.

Director, Bowles Center for Alcohol Studies; Professor of Pharmacology & Psychiatry

Education: Ph.D. in Pharmacology, Rackham Graduate School, University of Michigan, 1978; B.S., N.Y. State Regents Scholar, Syracuse University.

Web page:
http://www.med.unc.edu/alcohol/faculty/CrewsFT/Crews.htm

Research partially funded by NIAAA.



Ethanol Reduces Neuroprogenitor Cell Proliferation and Differentiation.

A. Adult neurogenesis includes several phases that regulate the formation of new neurons and glia. Shown is a representation of rat hippocampal dentate gyrus where approximately 9,000 progenitors are formed daily. Progenitors migrate from proliferative clusters and express doublecortin for several weeks as they differentiate into new functional dentate granule neurons with appropriate entorhinal dendritic inputs and axonal projections. Dividing progenitors develop into new neurons over approximately one month.

B. Alcohol (ethanol) decreases each phase of adult neurogenesis. The most pronounced effect of ethanol on adult neurogenesis is to reduce proliferation, the formation of new stem-progenitor cells. Neuroprogenitors continue to divide forming more stem cells and/or stop dividing and begin the process of migration into the neuronal cell layer and differentiation into neurons with complete dendritic and axonal processes. Ethanol also reduces the number of cells in the differentiation stage and the number of cells that ultimately become fully differentiated neurons.

Figure created by Melissa Mann.

The Director's Column

A. Leslie Morrow, Ph.D.
Associate Director,
Bowles Center for Alcohol Studies

I have the privilege of writing the Centerline Director's Column when it features our Director, Fulton T. Crews, Ph.D.. What an amazing man! Dr. Crews is an outstanding scientific leader, an outstanding and innovative administrative leader, an inspiring spokesperson for alcohol researchers and alcohol treatment providers, and an individual committed to the service of our community. His own research program boasts several important discoveries on mechanisms of alcohol dependence, neurotoxicity, and most recently on neurogenesis (the birth of new brain cells). The ability of ethanol to inhibit neurogenesis likely contributes to the negative consequences of abusive alcohol consumption. Crews is committed to finding the biological underpinnings of alcoholism.

Fulton's scientific leadership extends beyond his own lab. Under his leadership, the Bowles Center for Alcohol Studies at UNC is making great advances. Fulton has personally made this happen. He has brought us together to work on the mechanisms that mediate alcohol's pathological effects in all tissues. He has been a fantastic leader and there is a great feeling of admiration for him within the Center.

Fulton has strengthened the Center's outreach and service activities. He has initiated new outreach programs to serve and educate the people of North Carolina. He's organized education conferences for treatment providers. He serves on many boards dedicated to serving our State's and our nation's efforts to cure alcoholism. Finally, he co-sponsored the establishment of an alcohol and substance abuse treatment program with the Department of Psychiatry at UNC Hospitals. Although not a clinician himself, he was the person who led the effort to establish a clinical program at UNC! He is building a group of people who are working in the laboratory and the clinic to cure alcoholism.

Every month the Bowles Center principal investigators and our staff meet to review the function of our cores and discuss scientific progress. We share the fun and the challenge of new ideas, problems and progress in our science. We enjoy working together as a team and we've learned how being "Centered" makes us a better team. I tip my Bowles Center cap to Fulton Crews!

Continued from previous page

Frey derived no obvious reinforcement—not even a transient feeling of well-being—from drinking alcohol. Frey became sick enough to vomit as soon as he took a drink, experienced daily blackouts, suffered debilitating physical illness and injuries as the result of his alcohol abuse, damaged relationships with family and friends, and had frequent run-ins with the law. Crews and his laboratory seek to know why Frey and alcoholics like him continue to drink in the face of such consequences. Part of the answer, Crews believes, lies in the ability of ethanol to cause neurodegeneration (loss of brain cells) and to inhibit neurogenesis (the birth of brain cells).

If alcohol-induced neurotoxicity and inhibition of neurogenesis contribute to alcohol addiction, then cortical regrowth may be related to successful recovery from addiction. In fact, the Crews lab has demonstrated that neurogenesis increases during abstinence following alcohol dependence. Studies in human alcoholics find significant recovery of cortical volume in alcoholics after just a few months and improved performance on attentional, cognitive, and motor tests during abstinence. The degree of improvement in memory tests is directly related to the magnitude of increase in brain volume. Crews' finding of increased neurogenesis in abstinence could underlie aspects of successful association of negative events with drinking. This association could constitute an important component of recovery and sustained abstinence. His lab's recent finding that exercise can increase neurogenesis and reverse the inhibitory effects of ethanol drinking suggests the possibility that vigorous exercise might improve efforts at recovery from alcoholism. Other factors that can increase neurogenesis and thereby increase successful recovery are under investigation.

Bowles Center for Alcohol Studies
Second Annual Conference

"Fetal Alcohol Spectrum Disorders - Research to Practice"

September 11, 2004

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Chapel Hill, North Carolina

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