Thank you!

Your generosity and willingness to share your resources with us has made a difference.

Bowles Club
(annual gifts of $1000 or more)

Mr. and Mrs. Ben Alston
Mr. and Mrs. Simon Addison
Ms. Elizabeth M. Amend
Anonymous
Anonymous
Mr. Hargrove Bowles, III
Mrs. Frances Neel Cline
Dr. Fulton T. Crews
Dover Foundation
Dr. John A. Ewing
Medical Foundation of NC, Inc.
Dr. A. Leslie Morrow
Philip L. Van Every Foundation
Ms. Ann Lewallen Spencer
Mrs. Beverley L. Stevens

Donors

The Honorable Martha B. Alexander
Mr. and Mrs. John F. Amend
Ms. Mary R. Amend
Mr. and Mrs. Michael R. Amend
Ms. Patricia Amend
& Mr. Steven Dean
Anonymous
Anonymous
Anonymous
Anonymous
Mr. and Mrs. Barry W. Arnett
Dr. Gavin E. Arteel
Mr. and Mrs. Michel P. Baudet
Mr. Baudet
Mr. and Mrs. John Bennett
Mr. and Mrs. Richard A. Bettis
Ms. Christine Beverly
Ms. Silvia Bison
Mr. and Mrs. Terry L. Blake
Mr. and Mrs. Robert J. Boening
Mr. Chris Braun
Ms. Donna Brewer
Ms. Linda Brezin
Mrs. Dorothy J. Bridgeman
Mr. Frank Bridger
Ms. Ada Jo Burke
Ms. Christine L. Cabot
Mr. Gordon Candle
Mr. Richard Cecil
Dr. and Mrs. James Chamblee
Ms. Elizabeth Chastain
Mr. Shao-yu Chen
Mrs. Marie Watson Cherry
Mr. Donald Conlin
Ms. Laura Conlin
Mr. and Mrs. Michael G. Conlin
Mr. Jim C. Copeland
Ms. DeSharie Covenington
Ms. Harriet M. Crisp
Mr. Phil Crisp
Ms. Phifer Crute
Mr. and Mrs. Johnny Dehart
Ms. Sue DeVinney
Dr. James R. Dineen
Ms. Wendy Dudka
Mr. William C. Dunty
Dr. Thomas R. Eckman
Mr. Pat Ellis
Mr. William Elstran
Ms. Josephine L. Erickson
Ms. Ina R. Evans
Dr. Amy D. Fairchild
Mr. and Mrs. Robert E. Farmer
Mr. Bruce Forrest
Dr. James C. Garbutt
Ms. Anne G. Gates
Mr. and Mrs. Erven Gladstein
Mr. Lee Glenn
Mr. and Mrs. Will Grossman
Mr. and Mrs. Kyle R. Hagen
Mrs. Annie Hager-Blunk
Ms. Sarah E. Holt
Ms. Jane E. Hughes
Ms. Jo Hughes
Ms. Beverly Huntington
Ms. Beth Ann Huskamp
Ms. Marsha W. Jackson
Dr. Jason A. Janet
Mr. and Mrs. Forrest B. Johnson
Mr. Chris Johnson
Mr. Marc Kaufman
Mrs. Maryane Kaufman
Ms. Kay H. Kaufman
Mr. Richard P. Kenney
Mr. Ed Kernick
Ms. Rachel Keyes
Dr. James N. Kimball
Mr. and Mrs. Norman J. Kimball
Mr. and Mrs. G. W. Kirichbaum, Jr.
Ms. Maureen Kurtz
Ms. Mary Kyles
Ms. Doris Lee
Ms. Casey Liston
Ms. Debbie Little
Ms. Raye Mann
Ms. Cynthia H. McCoy
Mr. Hal McKeel
Ms. Ashley Miller
Dr. Sheryl S. Moy
Mr. Robert A. Nicholas
Mr. John Nixon , III
Mr. and Mrs. John Nixon
Mr. and Mrs. C. D. Nottingham
Dr. and Mrs. David W. Ollia
Mr. Lester E. Pace
Ms. Shannon Penland
Mr. Roger Perry
Ms. Anna Boyce Phillips
Mr. Steve Pomeray
Ms. Renric Pope
Ms. Elaine Ratliff
Dr. Lance Reger
Mr. and Mrs. William F. Renn
Dr. Donita L. Robinson
Mr. Bryan Schuck
Mr. Albert F. Sloan
Ms. Barbara B. Smith
Mrs. Stephanie C. Stadler
Ms. Beth P. Storie
Mr. Jack M. Streb
Mr. Brent Thomas
Mr. and Mrs. Duke D. Thompson
Mr. and Mrs. Lane VanderHock
Mr. and Mrs. Joyce Vencint
Mr. Michael Walsh
Ms. Charlotte A. Weigel
Mr. Walker G. Weigel
Mr. and Mrs. T. W. Whisnant
Mr. and Mrs. C. Whitefield
Dr. and Mrs. Jack L. Wilhelm
Ms. Mary Beth Wilkie
Ms. Ann Wysong

Psychologist Probes the Genetic Secrets of Uncontrollable Drinking

There are many factors that may cause an individual to progress from a moderate or social drinker to an alcoholic. In addition to environmental influences, there is growing evidence that genetic factors contribute to alcohol abuse. With a complex disease like alcoholism, it's not likely that the risk is associated with any single gene, but rather with multiple genes interacting with the environment.

Dr. Todd Thiele, Department of Psychology, UNC-CH, uses genetically altered animal models to focus on genes associated with an inherited propensity to develop uncontrollable drinking. Thiele, a new member of the Center for Alcohol Studies, takes aim at the complex genetic factors that control voluntary alcohol consumption, a key component in the development of an uncontrollable urge to drink more and more alcohol. Using knockout mice (created when a gene is "knocked out" of the code, resulting in animals that lack the protein expressed by that gene) and transgenic mice (created by adding or replacing a gene), he is revealing the ways in which certain genes affect alcohol drinking.

One line of Thiele's research has focused on a protein called neuropeptide Y (NPY), which is distributed throughout the nervous system and is believed to modulate neurons involved in feeding behavior, anxiety, and depression. In an article in Nature in 1998, he published his findings on the role of NPY in voluntary alcohol drinking behavior. Compared to their wild-type kin, the knockout mice consume more alcohol, and the transgenic mice consume less. In addition, knockout mice show less intoxication than wild-type mice following alcohol administration, and transgenic mice show more. These results provide evidence that alcohol consumption and resistance to its intoxicating effects are inversely related to NPY levels. Currently, Thiele is exploring the mechanisms by which NPY influences drinking, narrowing in on the NPY *receptors* that are responsible for this effect. Again using knockout and transgenic techniques, he found that the NPY Y1 and Y2 receptors appear to mediate voluntary consumption of alcohol, and that the Y5 receptor may be involved with regulating alcohol's intoxicating effects.

Todd E. Thiele, Ph.D.

A second line of research has focused on the intracellular second messenger, cAMP-dependent protein kinase (PKA). Many neurotransmitters, including NPY and dopamine, transduce their signal into neurons via PKA activation. Early research indicates that alcohol influences PKA function. With PKA knockout mice, Thiele showed that PKA signaling also modulates voluntary alcohol drinking and some of its intoxicating effects. Together, this research promises to bring us one step closer to mapping out the genetic patterns associated with alcoholism.

The Bowles Center for Alcohol Studies
Tel. (919) 966-5678
Fax. (919) 966-5679

To become involved in our mission, call Elizabeth Amend at (919) 843-6204 or email amend@unc.edu.

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

www.med.unc.edu/alcohol

Center Line, Vol. 13 No. 1 *Published quarterly to bring greater understanding of alcoholism research and the Center's mission.*
A. Leslie Morrow, Editor-in-Chief; Casey Liston, Managing Editor; Jane Saiers, Writer

UNC Bowles Center for Alcohol Studies
CB# 7178, Thurston-Bowles Building
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599-7178

Non-Profit Organization
US Postage
PAID
Permit No. 216
Chapel Hill, NC 27599-1800

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

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.

Volume 13, Number 1, 2002

When Abstinence Can Be Harmful: The Dangers of Repeated Withdrawals from Alcohol

Like many aspects of the life of Edgar Allan Poe, the legendary American writer and father of the detective story, his mysterious death at age 40 has not been satisfactorily explained. Many, citing evidence that Poe died of delirium tremens, attribute his death to abuse of alcohol. Others, citing only sporadic drinking by Poe, contend that alcohol is an unlikely explanation:

> *[The alcohol theory] is the theory most people think of when they are asked about Poe's death. That Poe engaged in bouts of drinking . . . is well established, but how exactly he may have died of alcoholism has never really been explained. Clearly . . . his drinking seems to have been neither so consistent nor so intense as to cause sclerosis of the liver. It has been suggested that poor nutrition and a weakened condition brought on by other illnesses could have allowed delirium tremens to occur with fewer and less intense episodes of drinking than would normally be required, but none of these offerings completely explain his condition . . .*
> *—The Edgar Allan Poe Society of Baltimore, 1999 (available at www.eapoe.org)*

How could Poe, who by all accounts was an intermittent drinker, have died of alcohol withdrawal syndrome? New research conducted by Assistant Professor of Psychiatry Darin Knapp and his colleagues at the University of North Carolina's Bowles Center for Alcohol Studies has shed light on why many alcohol abusers—including Poe, perhaps—seem under certain conditions to be surprisingly susceptible to the adverse effects of alcohol. Knapp uses animal models to study the behavioral and physiological effects of the alcohol withdrawal syndrome. Alcohol withdrawal syndrome can culminate in a return to drinking in order to alleviate withdrawal-associated neurological and motor symptoms such as anxiety, hallucinations, and muscle tremors. Untreated, it can also culminate in death. By studying the physiology and behavioral aspects of the alcohol withdrawal syndrome in animals, Knapp hopes to elucidate strategies that will contribute to the management of human alcohol withdrawal syndrome so that withdrawal-motivated relapses to drinking can be prevented.

Knapp is particularly interested in the symptom of withdrawal-associated anxiety because of the key role of anxiety in perpetuating chronic drinking. "Anxiety is a potent negative reinforcer of drinking behavior," says Knapp. "Alcoholics experiencing anxiety as part of the alcohol withdrawal syndrome or because of stressful life events are incredibly strongly motivated to relieve that anxiety. The best way they know to relieve the anxiety is to drink. Our research centers on identifying the brain centers that mediate the anxiety experienced by the alcoholic and on identifying pharmacotherapies that could reduce the anxiety and, therefore, reduce the alcoholic's need to drink excessively."

Center investigators George Breese, Darin Knapp and David Overstreet (left to right) have established a productive collaboration to investigate the mechanisms of alcohol withdrawal syndrome, with the goal of preventing relapse due to withdrawal-induced anxiety.

In experiments conducted with colleagues David Overstreet, George Breese, Sheryl Moy, and Gary Duncan, Knapp found that rats withdrawn from 17 days of a nutritionally complete diet containing intoxicating amounts of alcohol showed increased levels of anxiety compared with control rats that had been given 17 days of the same nutritionally complete diet that did not contain alcohol. In these experiments, anxiety was measured via several standard behavioral tests including the social interaction test and the elevated plus maze test, as well as with a novel ultrasonic vocalization test that Knapp brought to the Bowles Center from Rutgers University, his graduate-school alma mater. This test is especially well-suited for measuring anxiety during alcohol withdrawal because it is not painful or invasive and provides an easily quantifiable measure of anxiety: the number and duration of ultrasonic vocalizations, quantified using a special detector, are directly proportional to the animal's level of anxiety. In one experiment, for instance,

rats in withdrawal from a diet of chronic alcohol vocalized five times as much as control rats not undergoing withdrawal. Knapp and his colleagues subsequently found that certain drugs such as the corticotropin releasing factor antagonist CRA1000, the benzodiazepine receptor antagonist flumazenil, and the 5HT2C receptor antagonist SB242084 mitigated withdrawal-associated anxiety in these types of anxiety tests whereas withdrawal anxiety was not affected by the type 1 benzodiazepine receptor agonist zolpidem, the NMDA receptor antagonist ifenprodil, or the receptor 5HT3 antagonist MDL 72222. These data show that anxiety associated with ethanol withdrawal is amenable to specific pharmacological treatments.

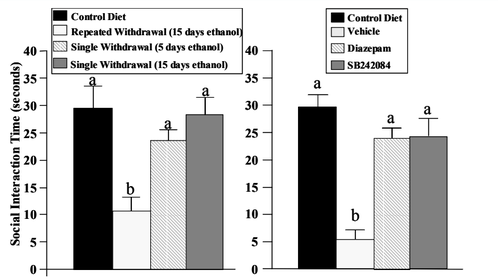
Using neurobiological markers of brain cell activation, Knapp and his colleagues extended these finding by showing that some brain areas but not others were activated by ethanol withdrawal. The proteins cyclooxygenase-2 (COX-2) and Fos-LI both robustly increased in areas of the limbic cortex during ethanol withdrawal at a time when anxiety, as measured by ultrasonic vocalizations, was high. These limbic areas and other brain regions activated during alcohol withdrawal generally overlapped with areas that Knapp and others had previously implicated as being important in mediating anxiety. These results suggest that certain limbic and other brain areas are important in mediating certain aspects of alcohol withdrawal—specifically, the symptom of anxiety.

Knapp was concerned that these experiments, involving a single, prolonged episode of exposure to alcohol, are not representative of the experience of the typical alcoholic. Most alcoholics, like Poe, undergo periods of alcohol bingeing separated by periods of abstinence, and they experience repeated episodes of alcohol withdrawal. Would the severity of alcohol withdrawal and its amenability to pharmacologic treatment differ in an animal that had undergone one withdrawal episode compared with an animal undergoing repeated withdrawal episodes? To answer this question, Knapp and collaborator David Overstreet turned their attention to the effects of repeated bouts of alcohol exposure and withdrawal on the withdrawal symptom of anxiety. They found that rats exposed to three 5-day regimens of alcohol-containing diet with 2 days of withdrawal between each regimen (the equivalent of three bouts of moderately heavy alcohol drinking separated by periods of abstinence) showed significantly more anxiety in two behavioral tests than did (1) rats exposed to only one 5-day regimen of diet; or (2) rats continuously exposed to ethanol continuously over 15 days with no periods of abstinence. Thus, repeated bouts of drinking punctuated by repeated withdrawal episodes were associated with more severe anxiety than was a single withdrawal.

Repeated episodes of drinking and withdrawal appear to sensitize the brain so that it is more susceptible ... to alcohol's deleterious effects.

This effect was also persistent: after the anxiety associated with multiple withdrawals had abated, re-exposure of the rats to a single 5-day treatment and withdrawal cycle a week later resulted in the same degree of anxiety as measured after multiple withdrawals. Like the anxiety associated with a single, prolonged exposure to alcohol followed by a single withdrawal, the anxiety associated with repeated bouts of alcohol exposure and

continued on next page



Animals on a control diet (no alcohol) exhibit normally high levels of social interaction behavior (i.e, low anxiety) while animals experiencing repeated withdrawals from three 5-day cycles of a 4.5% alcohol-containing diet show very little social interaction (i.e., high anxiety). In contrast, animals experiencing withdrawal after a single 5-day or 15-day alcohol exposure do not exhibit reduced social interaction behavior. In the right graph, the benzodiazepine drug diazepam (valium) and the compound SB242084 (a serotonin receptor antagonist) but not the drug vehicle prevented the reduction in social interaction caused by repeated withdrawals. Bars in each graph that do not share common letters are significantly different from each other.

Darin J. Knapp, Ph.D.

Assistant Professor, Dept. of Psychiatry; Bowles Center for Alcohol Studies, University of North Carolina at Chapel Hill.

Ph.D., 1992, Rutgers University.

Recent Publications:

Ming Z, Knapp DJ, Mueller RA, Breese GR, Criswell HE (2001) Differential modulation of GABA- and NMDA-gated currents by ethanol and isoflurane in cultured rat cerebral cortical neurons. Brain Res 920:117-24.

Knapp DJ, Braun CJ, Duncan GE, Qian Y, Fernandes A, Crews FT, Breese GR (2001) Regional specificity of ethanol and NMDA action in brain revealed with FOS-like immunohistochemistry and differential routes of drug administration. Alcohol Clin Exp Res 25:1662-72.

Crews FT, Braun CJ, Ali R, Knapp DJ (2001) Interaction of nutrition and binge ethanol treatment on brain damage and withdrawal. J Biomed Sci 8:134-42.

Knapp DJ, Sim-Selley LJ, Breese GR, Overstreet DH (2000) Selective breeding of 5-HT(1A) receptor-mediated responses: application to emotion and receptor action. Pharmacol Biochem Behav 67:701-8. Review.

Moy SS, Knapp DJ, Duncan GE, Breese GR (2000) Enhanced ultrasonic vocalization and Fos protein expression following ethanol withdrawal: effects of flumazenil. Psychopharmacology 152:208-15.

Research supported by NIAAA.

Webpage:

http://www.med.unc.edu/alcohol/research/Breese/knapp.htm

The Director's Column

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

Alcohol withdrawal is a clinical syndrome that can affect people accustomed to regular alcohol intake when drinking is decreased or stopped completely. Alcohol has the most severe physical withdrawal syndrome of all the drugs of addiction, more severe than heroin and other opiates and, in some cases, resulting in death.

Every year more than one and a half million people in the U.S. either enter an alcoholism treatment program or are admitted to a hospital due to the consequences of alcohol dependence. These individuals, as well as a substantial number of other people who stop drinking without professional help, experience alcohol withdrawal. In some alcoholics, withdrawal symptoms can occur at blood alcohol levels that are intoxicating for non-dependent individuals.

The most common symptoms of alcohol withdrawal are insomnia, tremors, craving for alcohol, vivid dreams, anxiety, agitation, irritability, loss of appetite, nausea, vomiting, headache and sweating. Some symptoms resolve in hours, but others may last for days and weeks. The severity of symptoms that individuals experience varies; some experience only mild symptoms, while others suffer severe symptoms, which include hallucinosis, seizures and delirium tremens (DTs). DTs can last for several days, and about 5% of patients who experience DTs die from metabolic or cardiovascular complications and/or trauma. In addition, alcohol withdrawal is one of the most common causes of status epilepticus—continuous, unrelenting, life-threatening seizures.

Clinical and preclinical studies have clearly shown that seizures associated with alcohol withdrawal increase in severity after multiple withdrawals, a fact that is very important in the management of alcohol detoxification. Darin Knapp's findings, that anxiety significantly increases with multiple withdrawals, will be an important factor in designing successful new treatment protocols, since anxiety and craving are closely linked to each other and to relapse. The evidence that residual anxiety can last for long periods prompts further studies to determine the contribution of this pathology in relapse. In addition, the finding that after one month of abstinence a short drinking episode will reinstate withdrawal anxiety to high levels is consistent with the common notion that alcoholics in recovery who drink again will rapidly return to dependent drinking. Understanding the processes that underlie withdrawal-induced anxiety and it's relation to relapse can radically improve treatment, and may lead to the development of non-addictive medications to reduce that anxiety.

April is Alcohol Awareness Month and April 11th is National Alcohol Screening Day. Screening Day provides information about the signs, symptoms and treatment of alcohol problems and includes a screening test and the opportunity to discuss the results with a health professional. Knapp's studies on the long-term changes in the brain that result from repeated withdrawals would seem appropriate information to share.

"Alcohol causes the most severe physical withdrawal syndrome of all the drugs of addiction."

April 11th is National Alcohol Screening Day

See www.med.unc.edu for details on alcohol screening at UNC.

continued from previous page

withdrawals was significantly attenuated by certain drugs administered during the final withdrawal. Remarkably, these drugs also significantly reduced anxiety after the third withdrawal when the drugs were administered only during the first two withdrawals. This encouraging finding shows that pharmacological treatment of early withdrawals can mitigate the worsening of withdrawal that occurs over repeated cycles of intoxication and withdrawal (see figure).

This research provides a potential explanation for the surprising susceptibility of Poe and other long-time intermittent drinkers to the toxic effects of alcohol. Repeated episodes of drinking and withdrawal appear to sensitize the brain so that it is more susceptible with each successive withdrawal to alcohol's deleterious effects. In Poe's case, it appears that years of intermittent binge drinking separated by periods of abstinence possibly led to a withdrawal syndrome severe enough to result in death. "Whereas continuous heavy drinking may be more toxic than intermittent heavy drinking to organs such as the liver, the brain may be unique," says Knapp. "With repeated bouts of drinking and withdrawal, we have an unusual situation in which abstinence from alcohol may actually be more harmful to the brain than continuous drinking." McCown and Breese showed several years ago that seizures, a motor symptom of alcohol withdrawal, are exacerbated by repeated cycles of alcohol exposure and abstinence. "Our research extends these findings to the withdrawal symptom of anxiety. Our research also shows that, in animals, sensitization of withdrawal caused by repeated episodes can be mitigated by certain drugs, so there is considerable reason for hope with respect to developing intervention strategies for human alcoholics."

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

Yes, I would like to join the effort to cure alcoholism in our lifetime.

❑ $50 ❑ $150 ❑ $250 ❑ $500 ❑ other _____

❑ $1000 *(Bowles Club level)* ❑ $2000 *(Chancellor's Club level)*

❑ Check enclosed, payable to the Bowles Center for Alcohol Studies

❑ I would like to transfer stock, please send information

❑ My company matches gifts. The form is attached.

❑ I would prefer to remain anonymous.

NAME _____ E-MAIL ADDRESS _____

ADDRESS _____ CITY _____

STATE AND COUNTRY _____ ZIP/POSTAL CODE _____

CREDIT CARD NUMBER _____ EXPIRATION DATE _____ ❑ Visa ❑ Mastercard

SIGNATURE (if using credit card) _____

The Bowles Center for Alcohol Studies
CB#7178, UNC-CH
Chapel Hill, NC 27599-7178

For more information about our research and treatment programs, or to discuss alternate ways of giving, please contact
Elizabeth Amend
(919) 843-6204
amend@unc.edu,
or visit our website,
www.med.unc.edu/alcohol