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 16, Number 1, March 2005

Alcohol Researcher Draws upon both Eastern and Western Medicine to Identify Potential Interventions for Alcoholism

Researchers and clinicians seeking ways to help alcohol-dependent individuals face formidable challenges in unlocking the secrets of alcoholism, which the National Institute for Alcohol Abuse and Alcoholism describes as a chronic, currently incurable disease having both genetic and environmental determinants. Alcoholism is characterized by *craving*—an uncontrollable need to drink; *loss of control* over alcohol consumption; *physical dependence* reflected by the presence of symptoms such as nausea, tremors, and anxiety when alcoholics abstain from drinking; and *tolerance*, or the need for increasingly greater amounts of alcohol to feel the same effect. Dr. David Overstreet, Professor of Psychiatry and Bowles Center researcher has taken up the challenge of unraveling the complexities of this multifaceted disease and identifying means to help alcoholics. Overstreet researches multiple manifestations of alcoholism in animal models. His research initiatives include broad-ranging collaborations with other laboratories at UNC and around the country; he is a self-described advocate for interlaboratory interactivity and cooperation in advancing science. Currently, Overstreet's work focuses on two of the major manifestations of alcoholism: craving for alcohol and alcohol dependence as manifested by withdrawal symptoms.

Left to Right: George Breese, PhD, Robert Angel,Darin Knapp, PhD, Montserrat Thiele, PhD, David Overstreet, PhD, and Lara Marr

Measures or interventions that reduce the alcoholic's craving for alcohol may diminish the urge to drink and facilitate abstinence from drinking—an important aspect of controlling alcoholism. Overstreet's search for compounds that reduce the craving for alcohol led him to study components of herbal preparations that have been used for centuries in Eastern cultures to ameliorate drunkenness and reduce symptoms of hangover. Overstreet was attracted to herbal preparations because of the long-standing anecdotal evidence of their efficacy, the possibility that they would be associated with fewer side effects than conventional medicinal treatments for alcoholism, and the potential that herbal preparations would be more acceptable to some alcoholics than pills or injections. Overstreet and his collaborators made national headlines a few years ago with their discovery that a Chinese herbal medicine and its purified component extracts eliminated alcohol intake in rats bred to prefer to drink alcohol (P rats) and significantly reduced alcohol intake in alcohol-preferring African green monkeys. Overstreet continues this work today in collaboration with Dr. David Lee and other researchers at Harvard Medical School-affiliated McLean Hospital. Overstreet is principal investigator on a component of a large alcohol center grant awarded by the National Institute of Alcohol Abuse and Alcoholism and the Center for Complementary and Alternative Medicine to study the therapeutic potential of herbal medicines in alcoholism and drug abuse. He and his collaborators have recently identified a new herbal extract that potently reduces drinking in P rats but does not affect their food intake. This pattern of results suggests that the anti-drinking effects of the new herbal extract may be specific to alcohol—an important characteristic for a potential therapy for alcoholism. Possibly, the herbal remedies affect alcohol drinking by modifying the animal's craving for alcohol.

Alcoholic drinking is motivated not only by craving, but also by the need to avoid withdrawal symptoms, which can range from unpleasant to life-threatening. Working with Bowles Center for Alcohol Studies scientists Drs. George Breese and Darin Knapp, Overstreet seeks to identify drugs that can prevent withdrawal-motivated relapses to drinking. Their research centers on the withdrawal symptom of anxiety.

Overstreet studies withdrawal-asso-

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Better Safe Than Sorry: FAS Education Curriculum is Distributed Internationally

Maternal alcohol use is the leading known cause of preventable birth defects and developmental delays. The common use of alcohol by childbearing-age women, a high incidence of unplanned pregnancies, and the fact that alcohol can damage an embryo at a time when pregnancy frequently has not yet been recognized, are major factors accounting for the high incidence of alcohol-induced congenital disorders. Fetal alcohol syndrome (FAS) is at the severe end of the spectrum of alcohol-related birth defects. Fortunately, FAS and other prenatal alcohol-related disorders are 100% preventable if a woman does not drink alcohol while she is pregnant. Education and awareness about the effects of alcohol on the fetus are keys to prevention.

Drs. Marianne Meeker and Kathy Sulik

That message is now being disseminated far and wide by Kathy Sulik, Ph.D., and Marianne Meeker, Ph.D., of the UNC Bowles Center for Alcohol Studies. These scientists work diligently with educators to teach students about FAS and other alcohol-related birth defects. With support from the National Institute of Alcohol Abuse and Alcoholism (NIAAA), they were instrumental in developing *Better Safe Than Sorry: Preventing a Tragedy*, a science-based curriculum for middle and high school students. The goal of the curriculum is to educate young people about the science behind the consequences of maternal alcohol use, in the hope of encouraging students' healthy lifestyle choices. This classroom education kit includes such age-appropriate classroom activities as an information video, a simple hands-on science experiment, and an interactive game. The curriculum is provided free of charge through the Carolina Biological Supply Company (www.carolina.com) and is also available on the internet at *http://www.niaaa.nih.gov/publications/Science/curriculum.html*. To date, nearly 2,000 copies of *Better Safe Than Sorry* have been distributed to teachers in 39 of the 50 United States, as well as internationally to Argentina, Canada, Korea, Italy, India, Ukraine, South Africa, Nigeria, Poland, and APO Germany (for US military dependents overseas). Most recently, an additional NIAAA-supported initiative has focused on bringing the curriculum to rural schools in the Mississippi Delta states of Mississippi, Tennessee, and Louisiana.

For more information about the *Better Safe Than Sorry* curriculum, visit *http://www.med.unc.edu/alcohol/ed/fas* or contact Dr. Meeker at meeker@email.unc.edu.

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To become involved in our mission, call Angela Paige at (919) 843-6204 or email angela_paige@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

Center Line, Vol. 16 No. 1 *Published quarterly to bring greater understanding of alcoholism research and the Center's mission.*
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This document is supported by subscriptions and donations to the Bowles Center for Alcohol Studies.

ciated anxiety in rats by using a multiple withdrawal protocol that mimics many alcoholics' real-life patterns of drinking. Alcoholics typically do not drink continuously over the long term. Rather, they consume alcohol in binges separated by periods of abstinence. This binge pattern can lead to more severe withdrawal symptoms than does a single prolonged exposure followed by a single withdrawal. Overstreet and his colleagues have shown that withdrawal-associated anxiety is exacerbated by repeated cycles of alcohol exposure and abstinence relative to a single prolonged exposure followed by a single withdrawal. 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 than rats exposed to only one 5-day regimen of diet or 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 withdrawal-associated anxiety than was a single withdrawal. This effect was persistent: re-exposure of the rats to a single 5-day treatment and withdrawal cycle a week after the anxiety associated with multiple withdrawals had abated resulted in the same degree of anxiety as measured after multiple withdrawals. These findings suggest that repeated episodes of drinking and withdrawal sensitize the brain so that it becomes increasingly susceptible with each successive withdrawal to the deleterious effects of alcohol.

Overstreet and his colleagues found that stress can substitute for initial cycles of withdrawal in the multiple withdrawal protocol to sensitize withdrawal-induced anxiety. This intriguing finding raises the possibility that repeated withdrawals from chronic alcohol contribute to physical changes in the brain that both sensitize withdrawal-associated anxiety and allow stress to evoke anxiety-like symptoms during periods of abstinence. This finding could help to explain why abstinent alcoholics often relapse to drinking when they are stressed.

Overstreet and his coworkers found that the anxiety in the multiple withdrawal protocol could be reduced by certain drugs, such as corticotropin releasing factor (CRF) antagonists, administered during the final withdrawal. Remarkably, CRF antagonists also significantly reduced anxiety after the

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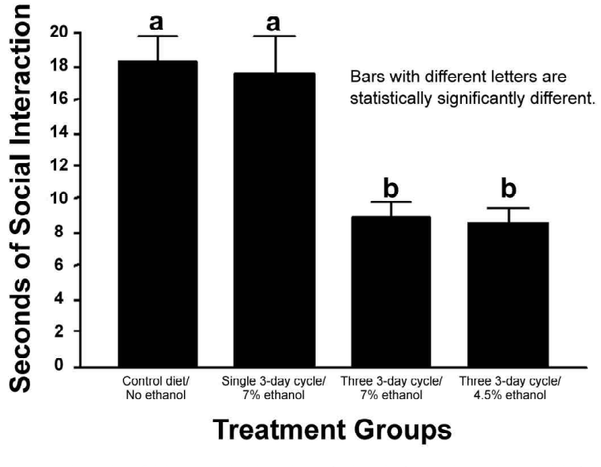

Three weekends of binge drinking in rats leads to reduced social interaction typical of anxiety.

David Overstreet, PhD

Professor, Bowles Center for Alcohol Studies and Department of Psychiatry, University of North Carolina at Chapel Hill (UNC); Adjunct Associate Professor, UNC Department of Psychology

Education

A.B., University of California (UC), Berkeley, Psychology; Graduate Student, Department of Psychology, UC Berkeley; Ph.D., UC Irvine, Psychobiology; NIMH Predoctoral Fellowship

Recent Publications

Overstreet DH, Knapp DJ, Breese GR. Modulation of multiple ethanol withdrawal-induced anxiety-like behavivor by CRF and CRF_1 receptors. Pharmacol Biochem Behav 2004; 77: 405-413.

Hensler JG, Hodge CW, Overstreet DH. Reduced 5-HT_3 receptor binding and lower baseline plus maze anxiety in the alcohol-preferring inbred Fawn-Hooded rat. Pharmacol Biochem Behav 2004; 77: 281-289.

Knapp DJ, Overstreet DH, Moy SS, Breese GR. SB242084, flumazenil and CRA1000 block ethanol withdrawal-induced anxiety in rats. Alcohol 2004; 32: 101-111.

Overstreet DH, Keeney A, Hogg S. Antidepressant effects of citalopram and CRF receptor antagonist CP-154,526 in a rat model of depression. Eur J Pharmacol 2004; 492: 195-201.

Overstreet DH, Knapp DJ, Breese GR. Similar anxiety-like responses in male and female rats exposed to repeated withdrawals from ethanol. Pharmacol Biochem Behav 2004; 78:459-464.

Breese GR, Overstreet DH, Knapp DJ. Conceptual framework for the etiology of alcoholism: a "kindling"/stress hypothesis. Psychopharmacology 2004 Oct 23; (Epub ahead of print) PMID: 15517196.

Website

http://www.med.unc.edu/alcohol/faculty/OverstreetDH/DHO.htm

Research partially funded by NIAAA.

The Director's Column

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

The development of medications to supplement treatment of alcoholic diseases has many hurdles to overcome. These hurdles include cost, acceptance by the treatment community, and the need to tailor medication therapy to a heterogeneous group of individuals who suffer from alcohol use disorder. I like to think that the advances in medication treatment that have occurred with cancer in the twentieth century will be followed by similar advances in medication for alcoholism in the twenty-first century.

At the beginning of the twentieth century cancer was a poorly understood disease with few therapies. There was a stigma associated with cancer and little physicians could do for patients. Now each patient's cancer is specifically assessed with multiple diagnostic procedures that determine the precise nature of the cancer, often including genetic and cellular phenotyping obtained by biopsy. Health professionals promote early identification and treatment as being among the most important components of effective therapy. Therapy often involves multiple medications given in specific sequences that have been shown through extensive clinical trials to best treat specific cancers. Patients are followed for many years after initial diagnosis, with effective treatment defined by 5 years of cancer remission. I believe this is the future of alcoholism treatment.

We will encourage early identification of problems and initiation of treatments well before patients hit bottom. Each individual will be assessed for various specific subtypes of alcohol use disorder. Each patient's treatment, including both behavioral and medication therapies will be specific to the individual and may include multiple medications in an appropriate sequence to help reduce key elements of alcoholic disease including craving, anxiety, and other elements that may be specifically important to that patient's successful treatment. Assessments of success will be extended to 5 years or more as is appropriate for a chronic recurring disease such as alcoholism. Insurance will cover medications, clinician time and follow up costs, reducing barriers to implementing medications and extended treatment. Treatment will be more effective and will better serve the needs of patients.

The studies that Dr. Overstreet is doing to define various medications focused on craving or withdrawal anxiety will help define which medications are most useful for patients with varying degrees of craving and/or anxiety. Dr. Overstreet's studies have included components of genetics and environmental stress that contribute to alcohol problems and show which medications are best used to address each individual component. Ultimately, these studies will form the foundation of new therapeutics specifically designed to help each patient individually. In the future, I am confident we will see dramatic improvements in the use of medical diagnostic tools and treatments for alcoholism. I am confident it will happen, the only question is how fast will it happen. Dr. Overstreet is helping to make it happen soon.

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third withdrawal when the drugs were administered only during two prior withdrawals. This finding demonstrates that pharmacological reduction of anxiety during early withdrawals can mitigate the worsening of withdrawal-associated anxiety that occurs over repeated cycles of intoxication and withdrawal. "CRF antagonists affects some of the brain circuitry that mediates responses to stress," says Overstreet. "Prophylactic administration of drugs such as CRF antagonists may help to counteract the progressively worsening anxiety and the increasing stress-induced negative affect that occur during periods of abstinence. If we can get these drugs on board before the alcoholic begins to experience withdrawal-associated anxiety, the drugs could eventually prove useful in preventing relapse to drinking."

Overstreet plans to extend the use of the multiple withdrawal protocol to studies of adolescent animals. He notes that the prototypical pattern of drinking among college students, who may drink excessively on the weekends and abstain from alcohol during the week, resembles that of the multiple withdrawal protocol. In a modified version of the multiple withdrawal protocol that he calls the "college binge protocol," Overstreet found that withdrawal-associated anxiety can be produced in adolescent animals with an abbreviated pattern of exposure of 3 cycles of 3 days on alcohol plus 4 days off alcohol. He will next examine the extent to which the withdrawal-associated anxiety in adolescent animals is modifiable by drugs.

"We've got to attack the problem from multiple angles," says Overstreet. "Because alcoholism is a multifaceted and multiply determined disease, combinations of interventions, including polypharmacotherapy, will probably be essential. For example, a CRF antagonist may be useful for addressing withdrawal-associated anxiety whereas another drug or intervention may be necessary to reduce motor symptoms of withdrawal. We're working on several promising leads for interventions that may one day prove useful for alcoholics."

Post-Doctoral Fellowships Now Available!

Our Center is offering post-doctoral fellowships in a multidisciplinary training program funded by NIAAA. Research is focused on molecular and cellular studies on alcohol actions. Applicants must have an M.D. or Ph.D., U.S. citizenship or permanent residency, and an interest in alcohol research.

For more information, visit www.med.unc.edu/alcohol/postdoc.htm