

# 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.*

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## Keys to Addiction Found in Brain Reward Systems

A fundamental aspect of human (and animal) nature is that we repeat those behaviors that accomplish a goal, or bring pleasure. The process by which certain actions become repetitive is called *positive reinforcement*. Simply defined, positive reinforcement is the ability of an environmental stimulus (i.e., a drug) to increase the likelihood of the behavior that produces the stimulus. The process of reinforcement most likely evolved to help maintain behaviors that are essential to the survival of the species, such as eating, drinking, and reproduction. Understanding how alcohol acts as a positive reinforcer may provide clues to the disease of alcoholism.

Clyde Hodge, Ph.D has conducted research to identify the neurobiological mechanisms that are responsible for alcohol self-administration (i.e., reinforcement). ***He has a hunch that alcohol induces craving by usurping the brain's normal reinforcement systems.*** In his initial research, Hodge demonstrated that specific neurotransmitter systems within the mesolimbic brain regions influence the *onset, maintenance, and termination* of alcohol self-administration. For example, different neurotransmitters and receptors in specific brain regions control the onset versus the termination of alcohol seeking behavior. Thus, using an animal model of positive reinforcement, Hodge and his collaborators have been able to characterize brain systems that “turn on” or “turn off” alcohol self-administration behavior.

Hodge's research has also provided clues about how alcohol influences brain systems that influence craving for food and feelings of satiety. For many years, scientists who study eating disorders have known that a brain region called the hypothalamus influences excessive food consumption, which leads to obesity. This prompted Hodge to wonder if alcohol might usurp the activity of the hypothalamus during the development of addiction. His initial research in this area demonstrated that the neurotransmitters norepinephrine and serotonin have opposing effects on alcohol

self-administration, just as they do in eating behavior. Then, by training rats to self-administer alcohol over a period of many months, he found that administering neuropeptide Y (NPY) into the paraventricular nucleus of the hypothalamus increased alcohol self-administration. This effect of NPY does not occur

in alcohol-naïve animals, suggesting that alcohol self-administration for long periods of time leads to brain adaptations that change the effect of NPY on alcohol reinforcement. Hodge also discovered that an NPY – Y1 receptor antagonist will block excessive intake induced by NPY. This seminal work has defined a novel role of NPY in the hypothalamus as a potential modulator of excessive alcohol

drinking. Hodge plans additional research to characterize the hypothalamus and its function in alcohol reinforcement using site-specific microinjections and genetic-mutant mice with “knockouts” of several different genes.

In addition to this research into the neurobiological mechanisms of alcohol addiction, a second major focus of Hodge's work is the development of medications to treat alcohol and drug abuse. Alcohol is the most widely abused drug in the country. Hodge points out that its cost to society is greater than that of all other drugs of abuse combined – the latest figure is some \$180 billion each year – yet biomedical science knows very little about how alcohol alters central nervous system activity or how to alleviate the condition. Hodge is pioneering a new approach to drug development based on increased knowledge of all mammalian genes known as “pharmacogenomics.” This approach focuses on the role of various genes on alcohol seeking behavior.

One interesting lead involves a gene that codes for the enzyme protein kinase C-epsilon (PKCε). In collaboration with Dr. Robert Messing at UCSF, Hodge found that mutant mice lacking the PKCε enzyme are supersensitive to alcohol and less likely to self-administer alcohol than mice with the enzyme. They further demonstrated that PKCε produces these effects by altering the activity of GABA<sub>A</sub> neurotransmitter receptors. The neurotransmitter GABA acts like a key that opens



**The Hodge Team.** LR: Clyde Hodge, PhD, Cheryl Hargraves, Vicky Lepoutre, Amanda Sharko. New post-doctoral fellows joining the team are Joyce Besheer and Jason Schroeder (shown at right).

the receptor, allowing signals of inhibition to flow into the central nervous system. Without the PKC $\epsilon$  enzyme, the receptor stays “open” longer and more inhibition is signaled. This heightened reaction of the GABA<sub>A</sub> receptor results in less alcohol self-administration and decreased rebound after alcohol deprivation.

This work holds great promise for the development of drugs that can either disable the PKC $\epsilon$  enzyme, mimicking its absence, or mimic the enhanced GABA<sub>A</sub> receptor activity in the absence of the enzyme. Further, the effect of the PKC $\epsilon$  deficiency is similar to that of drugs used to treat anxiety and seizures. In an

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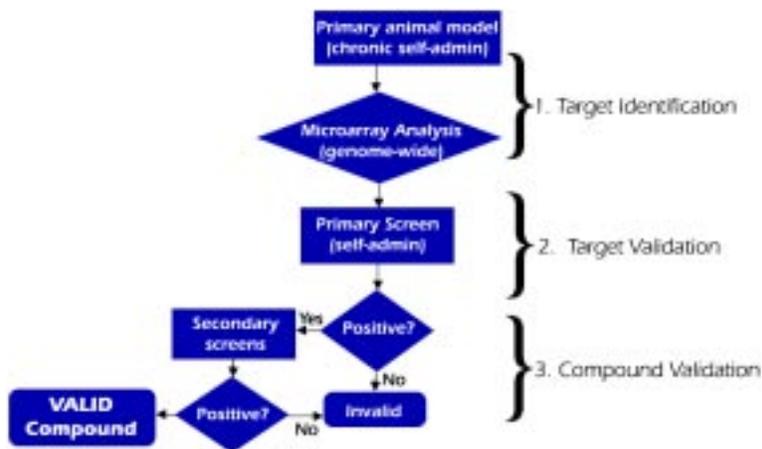
interview for *WebMD*, Hodge said, “This may turn out to be a novel way to target for the development of drugs to treat some of the reward aspects of alcoholism.... Lessons from the PKC $\epsilon$  knockout mice also support the concept emerging in alcohol research that increased sensitivity to alcohol lessens the likelihood that a person will become an alcoholic.”

To bring his goal of medications development to fruition, Hodge is using pharmacogenomic methods to **identify targets** and **validate compounds** that might be useful therapeutics for alcoholism. The principal strategy (shown in the figure below) is to identify potential drug targets by conducting microarray analyses of changes in neu-

ral gene expression. After target identification, selective compounds (i.e., receptor antagonists) will be tested for efficacy in the animal models used to identify the targets. Second, target validation is conducted by manipulating the gene or gene product to verify that it is functionally involved in the primary behavior. Target gene products can be manipulated by administering pharmacological agents, viral vectors, or altering the genes themselves. If a pharmacological agent alters the primary behavior in a desirable manner (i.e., reduces chronic self-administration or delays relapse), the target is validated. Other phar-

macological agents are administered to test for specificity.

Next, compound validation is accomplished by conducting additional behavioral screens to determine if the effects of the pharmacological agent occurred in a medically acceptable manner. For example, one might conduct studies to determine if the experimental agent is rewarding, which would infer addictive potential and rule out the compound for human use. Studies can be used to determine if the agent substitutes for alcohol. A particular compound that substitutes for alcohol in a medically appropriate manner, such as methadone for heroine, could be a valid therapeutic. Hodge feels that these types of experiments have the potential to translate functional genomic information into therapeutics for alcoholism.



**Pharmacogenomic Strategy for Novel Therapeutics.** The schematic shows the three-step Pharmacogenomics process toward developing rational therapeutic compounds for alcoholism. Once a compound passes secondary screens, it may be considered VALID in the sense that it passed preclinical screening.

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**Research funded by NIAAA.**

The pervasiveness of alcohol abuse and society’s resistance to the reality of its medical basis does not discourage Hodge. He says, “I look at it as an incredible puzzle - not an unsolvable problem.” He looks ahead and sees great possibilities: “I really do believe we can unravel the complexities of alcohol’s affects on the brain and use this to help people.” Early on, he chose preclinical research because he felt he could make the most contributions in basic science. Now, he feels the time is ripe for the development of medications to reduce alcohol craving and relapse.

Hodge came to the Bowles Center for Alcohol Studies at UNC-Chapel Hill a year ago from the Gallo Research Center in San Francisco. What brought Hodge across the country to Chapel Hill? It was not a dramatic decision, but more the natural progression of his career. The multidisciplinary Bowles Center is one of only 14 National Institute

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## The Director's Column

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

This issue of the Centerline includes aspects of our continuing efforts to translate discoveries to therapies. Dr. Clyde Hodge, our newest faculty recruit, is focused on discovering the neurobiological mechanisms of addiction and converting these discoveries into new pharmacotherapies for addiction. His genomic approach to understanding the neurobiology of alcoholism creates opportunities for discoveries beyond the factors that control the responses to alcohol. We know that genetics plays an important role in addiction and we know that there are several genes involved. We also know that alcoholics are not all the same and therefore the genes may be different for different alcoholics. The genes involved in addiction are complex, but understanding which genes regulate drinking can lead to therapeutic targets. These genes may be different than the genes that increase the risk of alcoholism, yet still modify drinking behavior in medically appropriate ways. Dr. Hodge is targeting agents that will help clinicians prevent relapse, reduce craving, diminish or eliminate the withdrawal syndrome. He has already made key discoveries in this area.

Dr. Garbutt is doing clinical trials with agents that are hoped to improve recovery in our patients being treated for addiction. Naltrexone has been found to reduce relapse to heavy drinking, although not robustly. Some clinicians feel a subset of patients do much better than others. I have heard patients claim that naltrexone was the only way they could stay dry, whereas, the overall data of all patients shows modest improvements over behavioral therapy alone. Many patients do not like to take naltrexone and compliance is a problem. The new formulation Vivetrex® will address compliance and may provide enhanced efficacy.

New medications are being developed at UNC and our goal is to develop robust, effective treatments as well as finding biomarkers of addiction. There is a need to help distinguish subtypes of alcoholism and use this to provide improved treatment guidelines. We would like to have Center faculty that discover the basic mechanisms of alcoholic pathology and Center faculty that translate them to therapies that improve peoples lives. We hope to be able to convert basic science to clinical practice by formulating best practice plans and teaching them to the medical professionals across North Carolina and eventually the world. Skipper Bowles said in one of his speeches: "The people of North Carolina should be proud that something is happening right here in North Carolina that will change the course of the entire world....change it in a tremendous and significant way to the benefit of all mankind today, tomorrow and for all of the tomorrow's to come." This motivating and positive speech says it all. We are making progress!

[Continued from previous page](#)

on Alcohol Abuse and Alcoholism research centers in the country. Hodge describes the research program as "world class" and notes it even includes a clinical program for testing novel pharmacologies. After a moment of reflection, he explains his move to Chapel Hill, "UNC is poised to understand alcohol's addictive properties at the basic science level and to translate this information into new medications. Since these are precisely my goals, I can't think of a better place to be."

## CAS Faculty News

Dr. Fulton T. Crews, Director of the Center, organized and chaired two symposia at the joint meeting of the Research Society on Alcoholism (RSA) and International Society for Biomedical Research on Alcoholism (ISBRA) in San Francisco, June 28 - July 3, 2002. "Alcohol and the Liver: A Memorial for Ron Thurman" focussed on new advances in the field a hepatobiology relevant to alcoholic liver disease. Dr. Thurman was a leader in this area of research and played a major role in founding the ISBRA organization. In addition, Dr. Crews organized a symposium, "Neuronal Stem Cells and Alcohol," that included Dr. Kim Nixon, a post-doctoral fellow at the Center, as a speaker.

Dr. A. Leslie Morrow, Associate Director of the Center, was recently appointed as chairperson of an NIH Biomedical Research Study Section (NIAAA - AA-1) that reviews alcohol-related applications. In addition, she received an new NIAAA Research Grant Award to investigate "Neurosteroid Adaptations in Genetic Models of Alcoholism." This project is part of an NIAAA "Integrative Neuroscience Initiative on Alcoholism" project that integrates research across institutions to facilitate new advances using shared animal models.

Dr. David H. Overstreet, chaired a symposia at RSA/ISBRA titled "Herbal Remeddia for Alcoholism: Promises and Pitfalls."

Dr. Kathleen K. Sulik participated as an invited speaker in a satellite syposium on June 27, 2002. The symposium was entitled Experimental Therapeutics for Fetal Alcohol Syndrome and was sponsored by NIAAA. Also, on June 29<sup>th</sup> she participated in a symposium entitled "Modulators of alcohol's effects on the fetus".

Bill Dunty, a graduate student working with Dr. Sulik, was a finalist for the Gordis Scholarship Award.

Dr. John J. Lemasters recently organized a Keystone Conference on "Mitochondria and Pathogenesis," that was held April 6-11 in Copper Mountain, Colorado. He also coordinated an American Association for the Study of Liver Diseases Basic Research Single Topic Conference on "Human Liver Cells in Biomedical Research" that was held June 7-9 in Airlie, VA.

# CAS Researchers Conduct a Clinical Trial of Extended Release Naltrexone

Pharmacotherapy is becoming a more widely accepted adjunct to behavioral treatment for alcohol dependence. Daily oral naltrexone has been shown to reduce the likelihood of relapse to heavy drinking in alcohol-dependent patients and decrease the number of drinks consumed when relapse does occur. However, in a clinical trial comparing oral naltrexone to placebo, greater than 40% of patients treated with naltrexone were noncompliant with the daily oral regimen. Furthermore, the positive effects of naltrexone in reducing relapse and enhancing abstinence were limited to those individuals who were compliant with medication – compliance is critical for successful outcome.

UNC researchers J. C. Garbutt, M.D., and William Renn, M.S.W., faculty members of the Center for Alcohol Studies and the UNC Alcohol and Substance Abuse Program, and their colleagues are currently conducting a clinical trial of Medisorb® naltrexone (Vivitrex®), an injectable extended-

release formulation of naltrexone that is administered once a month. The study will test the effectiveness of the long-acting Vivitrex® to assess whether this method enhances compliance and improves outcomes in alcoholic patients. Dr. Garbutt explains “We want to know if Vivitrex® will be an effective regimen by reducing relapse and increasing the percentage of patients that stay in psychotherapy”.

The study is underway at the General Clinical Research Center at UNC Hospitals. Subjects will receive one of two intramuscular doses of Vivitrex® or placebo every four weeks for 24 weeks as well as biopsychosocial support therapy throughout the trial. Subjects must be actively drinking to be eligible for the study. The UNC team will study up to 25 subjects. The UNC trial is part of a national multi-center effort funded by Alkermes, the manufacturer of Vivitrex. To obtain more information or participate in the study, contact Meghan Cody by phone at (919) 966-5770 or e-mail at [meghan\\_cody@med.unc.edu](mailto:meghan_cody@med.unc.edu).



J.C. Garbutt, M.D.  
Principal Investigator



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

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

Post-doctoral fellowships are now available. For more information, please visit <http://www.med.unc.edu/alcohol/postdoc>.

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

## The Ronald G. Thurman Lectureship Award

The Ronald G. Thurman Lectureship Award was established to honor the scientific excellence of Dr. Thurman's research and teaching contributions. This endowed Award will support an honorarium and travel for a distinguished researcher contributing to our knowledge of alcohol and liver function. Your gift will make this Award a reality. Please send your contributions c/o Elizabeth Amend to the Bowles Center for Alcohol Studies.



Dr. Ronald G. Thurman  
1941-2001

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