

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.

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UNC Clinician Scientist Garbutt Translates Animal Research to Advances in Clinical Medicine

One in ten Americans grapples with alcoholism at some time during their life. Alcohol-dependent individuals face a challenge notoriously difficult to overcome, and more than 75% of alcoholics who seek treatment relapse to drinking within the first year. Dr. James C. Garbutt of the University of North Carolina's Department of Psychiatry, the Alcohol and Substance Abuse Program, and the Bowles Center for Alcohol Studies, is working to improve this statistic. Both a psychiatrist and a scientist, Garbutt is adept at identifying potential clinical applications of findings from animal models. Likewise, he is skilled in planning and implementing studies that translate concepts gleaned from basic research into clinical advances.

Garbutt's work with the drug baclofen illustrates his facility in these regards. Baclofen acts on the brain's GABAergic system, which is important in mediating alcohol intake and mood, among other functions. Garbutt was motivated to investigate the effects of baclofen on drinking in alcoholics by basic research showing that baclofen reduces alcohol intake in several animal models and attenuates the anxiety induced by repeated exposure to alcohol in alcohol-dependent animals. Based on these findings, Garbutt, in collaboration with Dr. Barbara Flannery of Research Triangle International, surmised that baclofen may be useful in reducing drinking and symptoms, such as anxiety,

that lead to drinking in human alcoholics. Garbutt and Flannery showed in a preliminary study that baclofen decreased alcohol drinking, craving for alcohol, and anxiety among 12 alcohol-dependent men and women and that baclofen appeared safe. Based on this pilot work, Garbutt and Flannery obtained funds from the NIAAA and

percentage of heavy drinking days. Because both groups demonstrated similar improvement, the efficacy of baclofen in reducing heavy drinking cannot be concluded on the basis of this investigation.

Garbutt is not discouraged by these results. He notes that placebo-treated patients often improve during the course of a clinical trial. This phenomenon, known as the "placebo effect," is thought to be related partly to the increased medical attention patients receive by virtue of their participation in a study. Garbutt cites as reason for continued optimism the recent demonstration by Addolorado's group in Italy that baclofen was more effective than placebo at enhancing abstinence from alcohol among alcoholics with



(Left to Right): Alexei Kampov-Polevoy, MD, PhD, Linda Kalka-Juhl, JC Garbutt, MD, Olivera Pluzarev, PhD, and Mark Tommerdahl, PhD, and Amy Ford (not pictured).

completed a randomized, double-blind, placebo-controlled, 12-week study that compared the effects of baclofen with those of placebo on drinking in 80 alcoholics. They found that patients treated with baclofen did indeed drink less while taking baclofen. However, the placebo-treated group also drank less while taking the inactive placebo pill. In fact, the baclofen-treated group and the placebo-treated group showed similar reductions in the percentage of heavy drinking days relative to the pretreatment baseline. To demonstrate efficacy of baclofen, the baclofen group would have needed to improve significantly more than the group given inactive placebo with respect to the

liver cirrhosis. In these severely ill patients, the placebo effect was not as marked as it is in patients who are less ill. "Considering the evidence in aggregate, we are seeing a signal that baclofen is working," says Garbutt. "We need to work to define the circumstances and patient types that might be most appropriate for baclofen treatment. It could be that there are subtypes of alcoholics who are particularly responsive to baclofen. For example, based on the animal work from the Breese laboratory, we predict that baclofen might be particularly effective in alcoholics who have anxiety as a prominent component of their illness.

Continued on next page



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Education and Training

Medical Staff Fellow, National Institute of Mental Health, Bethesda, MD, 1978-80; Psychiatry Residency, University of North Carolina at Chapel Hill, 1975-78; M.D., University of Illinois Medical Center, Chicago, 1975; B.A. in Biology, University of Illinois at Urbana, 1971.

Recent Publications

Bradford BU, Jackson JK, Powell LL, **Garbutt JC.** (2007) Rates of ethanol metabolism decrease in sons of alcoholics following a priming dose of ethanol. *Alcohol* 41:263-270.

O'Malley S, **Garbutt JC,** Gastfriend DR, Ounming D, Kranzler HR. (2007) Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent prior to treatment. *Journal of Clinical Psychopharmacology* 27:507-512.

Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BI, Loewy JW, Ehrich EW for the Vivitrex Study Group. (2005) Efficacy and tolerability of long-acting, injectable naltrexone for alcohol dependence: a randomized, controlled trial. *Journal of the American Medical Association* 293:1617-1625.

Kampov-Polevoy AB, **Garbutt JC,** Khalitov E. (2003) Family history of alcoholism and response to sweets. *Alcoholism: Clinical and Experimental Research* 27:1743-1749.

Website

www.med.unc.edu/alcohol/garbutt

We now want to examine whether baclofen is more effective for some subtypes of alcoholics than others.”

Garbutt has also worked extensively with long-acting injectable naltrexone, a medication shown to reduce alcohol consumption when injected only once a month. Long-acting injectable naltrexone (Vivitrol®) was approved by the US Food and Drug Administration in April 2006 for the treatment of alcohol dependence and is now available in the United States. Like baclofen, naltrexone first became a candidate as an intervention for alcoholics after animal research showed that the drug could modify drinking in animal models. Naltrexone is thought to reduce craving for alcohol by binding to the brain’s opioid receptors—a mechanism different from that of baclofen, which acts on the GABAergic system. Garbutt was intimately involved in the research that led to approval of Vivitrol® and was lead author of the 2005 paper published in the *Journal of the American Medical Association* that described the results

of a large, Phase III clinical trial of the drug. Garbutt and his colleagues are now investigating the possibility that targeting two systems putatively

involved in alcoholism—the GABAergic system and the opioid system—might yield better efficacy than targeting these systems individually. In a 40-patient pilot study sponsored by the Bowles Center for Alcohol Studies, alcoholics are receiving one of four treatments: naltrexone+baclofen, baclofen alone, naltrexone alone, or placebo. Garbutt hypothesizes that baclofen may counteract the dysphoric/anxious component of alcoholism that is prominent in early recovery whereas naltrexone counteracts the rewarding response if alcohol is consumed and may also reduce craving for alcohol. Together, they may complement one another and lead to improved outcomes. The results of this study are expected to be

available next year.

In collaboration with Dr. Mark Tommerdahl of Bioengineering, Garbutt and colleagues are investigating a non-invasive sensory device that probes cortical glutamate and GABA function in real time. Early findings suggest that patients with alcohol dependence have deficits in their sensory responses that may indicate dysfunction in GABAergic/glutamatergic systems. Intriguingly, in some patients these deficits improve with time in recovery. Garbutt and Tommerdahl are extending this work in more patients and examining whether cerebral recovery can indeed be documented. If so, this method could provide a tool to provide patients with feedback to see progress as they recover. This method could also have relevance to predicting response to medications such as acamprosate that is thought to modulate glutamate hyperactivity.

In addition to drawing upon findings from animal models to identify drug candidates for the treatment of alcohol



ASAP Staff (Left to Right): Ben Lancaster, LPC, Bill Renn, LCSW, LCAS, Tom Watkins, LCAS, Arleta Brooks, CNA, Kathy Grace, LPC, J.C. Garbutt, MD.

dependence, Garbutt uses animal findings to point him to leads in the quest to discover the causes and consequences of excessive alcohol intake in humans. Recently, Garbutt was

motivated to investigate whether cytokine concentrations are abnormal in alcoholics’ blood. This study is based on findings from Dr. Fulton Crews’ laboratory at the Bowles Center that excessive alcohol drinking causes activation of cytokines and consequent brain damage in animal models. Cytokines are a diverse group of proteins that regulate immune responses, inflammation, and communication among cells in the brain. Although the action of pro-inflammatory cytokines is crucial for defending the body against infections and other challenges, excessive cytokine-mediated pro-inflammatory activity can cause cell damage. Garbutt and Crews are exploring the possibility that cytokines may be elevated in alcoholics and that they may contribute to



The Director's Column

Fulton T. Crews, Ph.D.
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This is an exciting time in alcohol research. This issue highlights translational efforts to move animal models of alcohol dependence and relapse to new therapies for those who have problems with alcohol. An interesting and sometimes frustrating aspect of translating animal models to humans is that people who are recruited must be treated with behavioral therapy as well as any investigational drug. Animal studies do not address the contribution of psychotherapy. Psychotherapy, usually motivational or cognitive behavioral therapy has helped many with alcohol problems. Psychotherapy helps those seeking help and most treatment clinics have patients who walk in needing help or who have been referred by the justice system. Often therapists run addiction clinics without a physician. Unfortunately, few physicians identify and refer patients for treatment. Pharmacotherapy requires physician supervision and most medication trials are run by physicians.

Multiple issues challenge the development of new medications. In many clinical trials, patients are recruited from radio, newspaper or other forms of advertisements. This process recruits motivated individuals who seek treatment. Interestingly, almost everyone who

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some of alcohol's detrimental effects in humans. Preliminary data from blood samples from patients enrolled in the baclofen study show a relationship between patients' baseline level of drinking during the period before the study and the blood concentrations of inflammatory cytokines.

Besides exploring consequences of and treatments for alcohol dependence, Garbutt is interested in identifying predictors of alcohol dependence. If risk factors that predict a tendency to consume excessive alcohol can be identified, then alcoholism could potentially be prevented through behavior modification among individuals having the risk factor. With UNC Psychiatry Department researchers Drs. Alexei Kampov-Polevoy and David Janowsky, Garbutt showed in research conducted more than a decade ago that alcoholics express a preference for much stronger sweet solutions than do nonalcoholics. Additional studies demonstrated that preference for stronger sweet solutions appears to be associated with heightened genetic risk for alcoholism. This research, like Garbutt's work on pharmacotherapies for alcohol dependence and the cytokine work, was stimulated by earlier animal research indicating that rats genetically bred for high alcohol intake had a much greater preference for highly concentrated sweet solutions than did their

is treated by minimally supportive or other more intense psychotherapy in a clinical trial has some degree of recovery. This makes pharmacotherapy trials such as those being done by Dr. Garbutt particularly difficult. Placebo controls have a very high response rate, making it difficult to determine if pharmacotherapy helps, e.g. it is hard to show a difference in response rates when 70-80% of all groups respond. Experience among therapists practicing in the community suggests that 80-90% recovery rates are uncommon, but appear unique to clinical trial patients. The common practice of exclusion of subjects with co-morbid mental disease, low motivation, and/or other complicating factors creates a group of motivated individuals, most of whom respond to whatever therapy is provided. Further, trials are often short, following patients for a few months, whereas life is much longer. Cancer researchers use five years of recovery as an end point. This standard would benefit the alcoholism field as well.

More studies are needed in high risk individuals and heavy drinkers who do not seek treatment. There are drugs that help maintain abstinence and reduce heavy drinking days, and most of these were first found to reduce animal drinking. New approaches to clinical trials with varied end points are needed to better translate efficacy from animal models to humans. In addition, physicians need to be engaged to identify and treat risk for dependence, e.g. heavy drinking. Science and medicine can reduce alcoholic pathology, but greater innovation and efforts to involve the majority of individuals with alcohol problems is needed to translate discoveries to improved health. ■

non-alcohol-preferring counterparts. Garbutt has recently extended the work on sweet preference to show, in a preliminary human study, that the sweet-liking phenotype interacts with high novelty-seeking interact to greatly increase risk for alcohol-related problems. The two risk factors appear to synergize such that the risk of excessive alcohol consumption is much higher when both are present than when one is present alone. In a study of individuals who at study entry did not meet diagnostic criteria for alcoholism, problems with alcohol were two times more likely to develop in high novelty-seekers (identified using a personality questionnaire) than in low novelty-seekers and three times more likely to develop in sweet-likers than in sweet-dislikers. In individuals who were both high novelty-seekers and sweet-likers, the risk of alcohol problems was markedly elevated: those with both characteristics were 17 times more likely to develop alcohol problems than individuals who were both low novelty-seekers and sweet-dislikers.

"Every day the basic research findings give us a new lead to follow." Garbutt remarks. "Our research initiatives show how animal research has pointed the way to some significant clinical advances that can make a difference in patients' lives." ■

Bowles CAS Trains Future Leaders

The Bowles Center for Alcohol Studies (CAS) is pleased to announce the second renewal of its 5-year training grant from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) that has been funded for over 10 years. The \$1.2 million funding will help the Center to build on its well-established research training program, focusing on the molecular and cellular approaches to alcoholism.

Since 1997, Center faculty members have trained nearly 200 students in order to develop the next generation of addiction medicine researchers. Training for our research scientists includes programs in basic laboratory science, addiction biology, neuropharmacology, alcoholic liver disease, alcohol-related birth defects, clinical research, and substance abuse treatment therapy.

CAS Director Fulton Crews, Ph.D., believes the program's success is based largely on a philosophy that includes the selection of top-quality students, as well as faculty members who share a common goal of providing the best training and experience. "Our multidisciplinary and collaborative faculty provides training in state-of-the-art techniques and an

understanding of pathophysiology and molecular mechanisms of disease," said Crews. "Our diverse, coordinated approaches to the study of alcohol and alcoholism attract some of the brightest and motivated candidates from around the world.

"Annual tours of treatment facilities across North Carolina provide our students with a better understanding of the human aspects of addiction. This experience motivates and challenges their intellect in dissecting the causes of alcoholism and finding new targets for treatment and prevention."

Trainees are strongly encouraged to apply for individual sources of career development funding after one to two years of support on the training grant. Our pre- and post-docs have been very successful in receiving National Research Service (F31 or F32) awards as well as Career Development (K) awards from the NIH. Many of our trainees have also been honored by the Research Society on Alcoholism with the Student Research award, RSA Enoch Gordis Research Recognition award, or the prestigious Young Investigator award.

CAS trainees have gone on to study, teach and develop independent research programs at major colleges and universities across the world. Others are successful professionals in the private sector or in government management of research funding. From the first day in the lab, through every discovery, manuscript and grant application, we work with our trainees to hone their critical thinking skills and develop into competitive scientists who love their work.

"The present era is marked by opportunities to apply unprecedented recent advances in molecular and cellular biology and immunology to alcoholism research and toxicity of alcohol," said Crews. "We are going to continue to expand our training program and provide our trainees with opportunities to make valuable contributions to addiction medicine." ■



The Bowles Center for Alcohol Studies

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To become involved in our mission, call Elizabeth Thomas at (919) 966-4977 or email 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

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