Twice a year, dim light and classical music fill the Lipsett Amphitheatre at the National Institutes of Health (NIH) Clinical Center, as researchers and directors from NIH and institutions around the country gather for the NIAAA’s honorary lectures.

In the fall, the Mark Keller Honorary Lecture Series commemorates Mark Keller’s legacy as one of the guiding forces of very early alcohol research efforts. Keller Lecture honorees are recognized for significant contributions to our understanding of how alcohol affects the body and mind, how we can prevent and treat alcohol abuse and alcoholism, and how today’s scientific advancements can provide hope for tomorrow.

In the spring, the Jack Mendelson, M.D., Honorary Lecture Series pays tribute to Dr. Jack Mendelson’s clinical alcohol research legacy. The lecture also showcases a current outstanding alcohol investigator whose lifetime of clinical research is advancing our understanding of alcoholism susceptibility, alcohol’s effects on the brain and other organs, and prevention and treatment of alcohol use disorders.

Honorees present a talk that reflects their most significant research. Honorees of both lectures receive a plaque with a special personalized citation based on their research.

The intended audience for the lectures includes the NIH scientific community and researchers in the local community beyond NIH, including universities in Washington, DC; Baltimore, MD; and even Richmond, VA. Also invited are leaders at lay organizations that focus on prevention and treatment.

“The lectures are a good way to let the research community know that we are heavily invested in research, and it helps the lay organizations understand a more evidence-based bent,” explained Kenneth Warren, Ph.D., Acting Director of NIAAA.
Warren believes these lectures achieve two primary goals. One is to educate researchers outside NIAAA about the research that is going on in the field. The other goal is to educate nonresearchers about current research breakthroughs.

“We have seen a major shift in the treatment and prevention communities in terms of using research to inform their fields. They used to shy away from implementing the advances emerging from research into their own professional activities, but now they have a much better understanding of how NIAAA research is relevant to their mission,” he said.

Warren credits the Keller Lecture, which began in 1996, and the Mendelson Lecture, which began last spring, with helping develop these inroads. The most recent of these events was the Mendelson Lecture, which took place this past April.

Mendelson paved the way for the development of NIAAA as the Director of the National Center for the Prevention and Control of Alcohol Problems within the National Institute of Mental Health (NIMH), which was the precursor to today’s NIAAA.

“In many senses, Mendelson was the first director of the NIAAA because he worked for the Federal Government’s center on alcohol research within NIMH, which in 1970—through the Hughes’ Act—became NIAAA. After he passed away, NIAAA wanted to recognize his contributions, so this lecture series focuses on clinical research as a tribute to his long career,” said Warren.

Last year’s inaugural lecture featured Mark Schuckit, M.D., who discussed the genetic and environmental contributions to alcoholism. This year’s honoree was John H. Krystal, M.D.

Krystal, who is the Chair of the Department of Psychiatry at the Yale University School of Medicine, Chief of Psychiatry at Yale–New Haven Hospital, and Director of the NIAAA Center for the Translational Neuroscience of Alcoholism, is a pioneer of the translational neuroscience of alcoholism. Translational neuroscience applies the conceptual approaches used in animal and human laboratory experiments to clinical research trials.

Krystal’s talk discussed how this approach has helped reveal the connection between key neurotransmitters in the brain—glutamate and dopamine—and alcoholism.

Krystal also highlighted his personal connection to Mendelson. “When I was applying to psychiatric residency programs back in 1983, [Dr. Mendelson] very kindly offered me his advice on pursuing a career related to addictions. I am indebted to him for developing some of the ideas that I have used as a starting point. It makes this honor particularly meaningful for me,” said Krystal.

For more information on the NIAAA Honorary Lectures, please visit: http://www.niaaa.nih.gov/AboutNIAAA/Keller_and_Mendelson_Lectures

Traditional cellular assays have always provided a two-dimensional (2-D) environment in which scientists study the growth of cells. While these 2-D environments have proven invaluable to drug-development efforts, they do have limitations, notably that they do not always predict accurately how humans will respond to the drug being developed. Some scientists have begun using three-dimensional (3-D) assays that better mimic a real-world environment of cell growth, allowing researchers to draw more accurate conclusions about how the human body will react to a drug.

The image at left helps demonstrate how alcohols bind to sites of action in neural receptors. A better understanding of this process is an important step toward rational design of antagonist drugs that could inhibit or reverse the cognitive effects of alcohol. Current efforts in this field have leaned toward site-directed mutations and computational modeling of sites of alcohol action in receptors thought to be relevant to intoxication: glycine and GABAa receptors. A shortcoming of working with these receptors is that the 3-D structure is not yet resolved at high resolution and so the exact sites of alcohol binding are unknown.

(Continued on page 3.)
Feature

Two Meds Are Better Than One for Depressive Alcoholics

Unique study of co-occurring disorder treatment compares concurrent use of medications to treat depression and alcoholism to the use of placebos or medications administered singly.

Researchers from the Center for the Studies of Addiction at the University of Pennsylvania School of Medicine and the Philadelphia Veterans Affairs Medical Center have shown that more alcohol-dependent people who also suffer from depression were able to stop drinking when they received an antidepressant along with a medication that can help reduce cravings for alcohol than those who received only one drug or a placebo. These findings were reported online in March 2010, in advance of print publication in the American Journal of Psychiatry.

A number of medications are available to help treat alcoholism, including benzodiazepines (such as Valium and Xanax) that help treat acute alcohol withdrawal symptoms; disulfiram, which increases a toxic byproduct of alcohol metabolism within the body to produce various unpleasant symptoms including nausea and facial flushing; naltrexone, an opioid antagonist that reduces heavy drinking; and acamprosate, a medication that enhances abstinence from alcohol by targeting the glutamate receptor. Additionally, the medication topiramate, which targets the neurotransmitters GABA and glutamate, appears effective in reducing drinking in alcohol-dependent individuals. Ondansetron, a medication originally developed to prevent nausea and vomiting, may decrease drinking in patients who developed alcohol dependence early in life.

In the current study, researchers used the alcohol medication naltrexone and the antidepressant sertraline, a selective serotonin reuptake inhibitor, to treat a population with comorbid conditions. The researchers assigned 170 alcohol-dependent individuals with depression to different groups, with each group receiving one of the following: a combination of naltrexone and sertraline, sertraline alone, naltrexone alone, or placebo medications. Examining each medication alone, as well as in combination and in comparison to a placebo, made this study unique in comparison with previous studies that often investigated similar drugs alone or in combination, but did not study all four treatment groups at the same time.

When they analyzed their data, the researchers found that patients receiving the combination of sertraline and naltrexone were more likely to be abstinent and have a longer time before relapse to heavy drinking than those in the single-drug and placebo groups. Though the results only approached statistical significance, there was a clear trend in favor of the combination-drug regimen in reducing the symptoms of depression.

The researchers noted, “The co-occurrence of depression and alcohol dependence is highly prevalent and difficult to treat successfully. The present findings suggest that patients with both disorders would benefit from combination treatment with an antidepressant and medication for alcohol dependence.”

The article abstract can be found here: A Double-Blind, Placebo-Controlled Trial Combining Sertraline and Naltrexone for Treating Co-Occurring Depression and Alcohol Dependence. http://www.ncbi.nlm.nih.gov/pubmed/20231324

Photo Essay: Three-Dimensional Environments for Drug Development, continued

One group of researchers published a high-resolution X-ray structure of a fruit fly’s odorant receptor that had exact coordinates for the alcohol-binding site. A noteworthy feature of this structure was that alcohols were essential for stabilizing this receptor during crystallization, thus implying strong interactions between alcohol molecules and the receptor. The researchers who produced the image (see page 2) used this crystal structure in a review in which they emphasized how displacement of water molecules from a binding site could contribute to favorable binding-free energy of alcohols with their receptors. They used the coordinates of the crystal structure of LUSH (1) to prepare this model as an example of how specific amino acid side chains can contribute to sites of action for alcohols.

More information on this study can be found in:

http://www.spectrum.niaaa.nih.gov
Young adults are more likely than older adults to have had alcohol dependence in the past 12 months, but they are proportionately less likely to have received treatment or sought help from sources including health care professionals, rehabilitation programs, 12-step programs such as Alcoholics Anonymous, or the clergy. According to NIAAA’s nationwide survey of 43,000 adults, about one in nine people aged 18 to 24 have had alcohol dependence in the past year, more than double the proportion in the next most affected age group of 25 to 34-year-olds. Only 7 percent of the youngest adults with dependence received treatment or other help for the disorder, versus 10 to 20 percent of older adults.

Commonly known as alcoholism, alcohol dependence is a disorder marked by at least three of the following symptoms in the past 12 months: repeatedly drinking more or longer than intended, repeatedly trying to cut down or quit without success, showing signs of tolerance, showing signs of withdrawal, continuing to drink despite problems, spending more time drinking, and cutting down on other activities once considered important in favor of drinking. As the severity of dependence increases, mental health and emotional impairments rise steadily, limiting a person’s ability to function socially and to fulfill personal, work, or school obligations.

Regardless of age, why don’t most people with alcohol dependence receive treatment? The primary reason appears to be that the vast majority do not perceive a need for treatment. A recent statistical analysis found that insurance status and demographic variables such as gender and education do not predict whether people have a “perceived need” for treatment. Different disorder symptoms, however, were more—or less—related to perceived need. For example, having withdrawal symptoms and repeatedly trying to cut down or quit drinking without success were associated with a perceived need for treatment, whereas having tolerance symptoms and drinking more or longer than intended were not. The authors note that further research, initially through qualitative interviews, is needed to explore the reasons for a lack of perceived need for treatment.

To help promote awareness of alcohol disorder symptoms and treatment options, NIAAA has created families of products for health care professionals and the general public, including Helping Patients Who Drink Too Much: A Clinician’s Guide and Rethinking Drinking.

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(2) NIAAA. Unpublished data from the National Epidemiologic Survey on Alcohol and Related Conditions. May 3, 2010.
Diet Quality Worsens With Increased Alcohol Intake

According to new study, people who drink the largest quantities of alcohol have the poorest quality diets.

A recent study of more than 15,000 adults in the United States found that increased alcoholic beverage consumption was associated with decreased diet quality. As reported in the April 2010 issue of the Journal of the American Dietetic Association, researchers at NIAAA, the National Cancer Institute, and the U.S. Department of Agriculture (USDA) found that people who drink more are also likely to eat less fruit and consume more calories from a combination of alcoholic beverages and foods high in unhealthy fats and added sugars.

The researchers analyzed data collected from participants in the National Health and Nutrition Examination Survey, an ongoing survey of cross-sectional samples of the U.S. population conducted by the U.S. Department of Health and Human Services’ Centers for Disease Control and Prevention. Data included alcohol consumption information as well as Healthy Eating Index (HEI)-2005 scores. Created by USDA, the HEI-2005 measures how closely diets conform to the 2005 U.S. Dietary Guidelines for Americans.

“We found that as alcoholic beverage consumption increased, Healthy Eating Index scores decreased, an indication of poorer food choices,” said first author Rosalind A. Breslow, Ph.D., an epidemiologist in NIAAA’s Division of Epidemiology and Prevention Research. “It’s important to note that our study did not determine the cause of these associations.”

A previous study by Dr. Breslow and her colleagues showed that people who drink the largest quantities of alcohol have the poorest quality diets. In the present study, they were able to identify specific dietary components that worsened with increased alcohol intake. In addition to decreased fruit consumption and increased caloric intake among both men and women, the researchers found that increased alcoholic beverage consumption was associated with a decreased intake of whole grains and milk among men.

“Our findings underscore the importance of moderation for individuals who choose to consume alcoholic beverages, and the need for a greater awareness of healthy food choices among such individuals,” noted Dr. Breslow.


Light to Moderate Drinking Linked to Lower Risk for Cardiovascular Death

Research confirms that heavy alcohol consumption negates the cardiac benefits of light to moderate drinking.

Light and moderate alcohol consumption is associated with a reduced risk of death from cardiovascular disease, but consumption above recommended limits is not, according to a NIAAA-supported analysis published in the March 2010 issue of the Journal of the American College of Cardiology.

Researchers led by Kenneth J. Mukamal, M.D., M.P.H., M.A., of Harvard University’s Beth Israel Deaconess Medical Center in Boston, MA, analyzed data from nine administrations of the National Health Interview Survey (NHIS). Conducted annually by the U.S. Centers for Disease Control and Prevention, the NHIS surveys a nationally representative sample of U.S. adults. The study by Dr. Mukamal and his colleagues used NHIS data collected between 1987 and 2000 on more than 245,000 individuals.

Since the NHIS includes detailed questions on alcohol consumption, the researchers were able to categorize study subjects into alcohol consumption categories.
ranging from those who have never drank alcohol, through those who drink light to moderately, to those who are heavy drinkers. Light drinking was defined as not more than three drinks per week for both men and women. Moderate drinking was defined as 3 to 7 drinks per week for women, and 3 to 14 drinks per week for men, while heavy drinkers were women who consumed more than 7 drinks per week and men who consumed more than 14 drinks per week. Current U.S. dietary guidelines define moderate drinking as no more than one drink on any day for women and no more than two drinks on any day for men.

The researchers then linked the NHIS data with a nationwide database of death certificate information to determine the association of alcohol consumption and death from cardiovascular disease among individuals who had died during the study period. Analyses showed that a total of 10,670 cardiovascular deaths had occurred among study subjects. Compared with lifelong nondrinkers, light and moderate drinking was associated with a lower risk for cardiovascular mortality whereas heavy drinking was not. They found little difference in risk among lifelong nondrinkers, lifelong rare drinkers, and former drinkers.

Dr. Mukamal and his colleagues note that their data “bolster previous epidemiological studies that have found lower rates of incident cardiovascular disease among moderate drinkers but also provide cautionary evidence that drinking above recommended limits eliminates this risk reduction.”

They add that while “randomized trials to evaluate these relationships might yet be conducted to test these issues definitively, clinicians and patients at this time must continue to make informed, individualized, and collaborative decisions about the safety of alcohol consumption.”

The article abstract can be found here:

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**NEWS FROM THE FIELD**

**OLDER BUT NOT WISER: AT-RISK DRINKING IN OLDER ADULTS**

*More than a third of older adults who drink may be at risk of alcohol-related health complications, including higher mortality.*

We usually think of golfing, traveling, and visiting the grandkids as popular pastimes for adults in their “golden years.” We might not put drinking at the top of that list, but about one-half of men and about one-third of women over the age of 60 in the United States are drinkers. A new study shows that many of these older drinkers are putting themselves at risk.

Researchers at the David Geffen School of Medicine at the University of California, Los Angeles analyzed the drinking habits of more than 3,300 current drinkers ages 60 and older in Santa Barbara, CA. According to the study, published in the April 2010 online edition of the Journal of General Internal Medicine, about 35 percent of this group drank enough to be considered “at-risk” on the basis of the Comorbidity Alcohol Risk Evaluation Tool (CARET).

The CARET screening tool identifies older adults at risk for harm from alcohol consumption on the basis of three categories: (1) alcohol behavior; (2) alcohol use and select comorbidities, or additional medical conditions; and (3) alcohol use combined with certain medications.

The study defined at-risk drinking levels as drinking twice a day most days, drinking once or twice a day most days and having certain comorbidities, or drinking once a day most days and taking certain medications. About 21 to 22 percent of the group analyzed fell into one of these risk categories. About 56 percent fell into at least two of these categories, and about 31 percent fell into all three categories.

The study also examined the demographic characteristics of at-risk older drinkers. Women were about half as likely as men to be at-risk drinkers. Participants without high school degrees were about two and a half times more likely to be at-risk drinkers than those with a graduate school degree.

The study brings to light the prevalence of at-risk drinking in older adults. As doctors better understand how common these behaviors are, they can offer patients more effective advice and treatment recommendations.

The article abstract can be found here: Prevalence and Correlates of At-Risk Drinking Among Older Adults: The Project SHARE Study. http://www.ncbi.nlm.nih.gov/pubmed/20396975
Scientists Find Genes That Influence Brain Wave Patterns

NIAA scientists have identified new genes and pathways that influence an individual’s typical pattern of brain electrical activity, a trait that may serve as a useful surrogate marker for more genetically complex traits and diseases. One of the genes, for example, was found to be associated with alcoholism. The report appears in the May 2010 issue of the Proceedings of the National Academy of Sciences.

The researchers used genome-wide association studies (GWAS)—techniques that involve scanning the complete set of DNA of many individuals—to search for genetic variants related to electroencephalogram (EEG), or brain wave, patterns in a sample of more than 300 Native American individuals. EEG patterns are highly heritable and have been associated with alcoholism and other psychiatric disorders. The researchers identified multiple genes that were associated with the amplitude, or height, of two of the four characteristic electrical frequencies that make up the wave patterns found in EEG recordings.

One of the genes identified in the study was found to account for nearly 9 percent of the EEG theta wave variability seen in the Native American sample. Theta waves are relatively low-frequency brain waves; previous studies have shown that their amplitude is altered among alcoholics. The researchers then showed that the same gene accounted for about 4 percent of theta wave variability in a sample of North American whites. In the same study, researchers showed that genetic variation in one of the genes identified for theta wave variability was also associated with an altered risk for alcoholism.

“While our main findings are for genes that influence EEG wave patterns, this study represents an important step towards the use of EEG as a surrogate marker for alcoholism,” notes David Goldman, M.D., chief of the NIAAA Laboratory of Neurogenetics and an author on the paper. “It also reveals new molecular pathways involved in addiction processes.”

The article abstract can be found here: Genome-wide Association Identifies Candidate Genes That Influence the Human Electroencephalogram. http://www.ncbi.nlm.nih.gov/pubmed/20421487

5 Questions With...

ROBERT HUEBNER, PH.D.
Deputy Director, Division of Treatment and Recovery Research

1. Recently, NIAAA has talked about looking at alcohol abuse and alcoholism in a new and different way. What does that mean?

Overall, we’re learning more and more about when, and how, alcohol use can become a problem and how we diagnose and treat those with alcohol use disorders.

Research advances, particularly in recent years, have helped us develop a more sophisticated understanding of the causes of alcohol use disorders, how alcohol affects body and mind, and how alcohol is used and abused by Americans. These advances in knowledge are helping us take a fresh look at everything—from the age that alcohol use disorders typically begin, to variations in their severity and course, and even to the variable paths to recovery that are possible for different individuals. Ultimately, this new research-based perspective on alcohol use disorders will lead to better diagnostic practices and better treatment options.

2. Can you give us any specific examples of this more nuanced understanding of alcohol use disorders?

We now understand that problems with alcohol use can be arrayed along a continuum of severity, replacing the long-held notion that alcohol use disorders are an “all or nothing” phenomenon—a person is an alcoholic or not. People with alcohol use disorders have mild, moderate, and severe forms of the disorder, with the majority of people experiencing problems in the mild-to-moderate range. This finding has major implications for our treatment system because the focus traditionally has been on people with disorders at the most severe end of the continuum. While providing quality care for people with severe alcohol
problems needs to be a priority, we need to refocus our efforts on the larger population with mild-to-moderate disorders, where the potential for a positive impact on public health is greatest. The research findings that have given us a more sophisticated perspective on alcohol use disorders have changed our way of thinking about how our treatment system should be configured.

Additionally, recent research has shown that people with alcohol use disorders can be categorized into multiple subtypes based on family history, age, drinking pattern, age of onset of problems with alcohol, number of diagnostic criteria endorsed, and problems in other areas of their lives (e.g., mental health or other drug abuse). One important research study identified five “subtypes”: a young adult, functional, intermediate familial, young antisocial, and chronic severe. Research-based classification approaches such as this offer enormous potential in helping us tailor our treatment approaches and maximize the chances for successful patient outcomes.

3. What are we learning about treatment and recovery in particular?

First of all, it is important to emphasize that the full spectrum of evidence-based treatments—both pharmacological and behavioral—are effective. Several studies that have systematically “summed up” what we know about treatments for alcohol use disorders have concluded that these treatments produce results that are similar to or better than those for other chronic health disorders. In general, of the people who receive treatment for alcohol use disorders, about one-third are in full remission, one-third show significant improvement (partial remission), and about one-third show no improvement. The fact that about two-thirds of patients improve is important to keep in mind in light of the skeptical view about treatment effectiveness that occasionally emerges in the popular press.

Another major finding from the alcohol treatment literature is that screening and brief interventions (SBIs) delivered in primary care settings are effective in treating nondependent at-risk drinkers. Not only is SBI effective, but it has been shown to be cost-effective. This line of research supports a longstanding NIAAA initiative that promotes the integration of alcohol treatment in primary care and general mental health settings. We now have a strong research base for SBI, and we have the tools (i.e., the NIAAA Clinician’s Guide). Primary care doctors and psychiatrists now can be reimbursed for delivering SBI services. The adoption of SBI in primary care and general mental health settings means many more people will receive needed treatment for alcohol problems than otherwise would be the case.

We also have learned that there are multiple pathways to recovery from alcohol use disorders. For example, there is strong evidence that a substantial proportion of people who have had an episode of alcohol dependence recover without the benefit of professionally facilitated treatment. In addition, active participation mutual-help groups can play a major role in sustaining post-treatment recovery.

Finally, we are benefitting greatly from advances in genetics research. The field of pharmacogenetics—the study of how genetic variation affects a person’s response to a medication—is an important part of NIAAA’s treatment research effort. We know that genetic variation can influence the effectiveness of several U.S. Food and Drug Administration-approved and experimental medications for alcohol use disorders: naltrexone, acamprosate, ondansetron, and olanzapine. Pharmacogenetics research also can help in identifying which medications are not appropriate for certain kinds of patients. This area of research is in its early stages, but it holds great promise for the treatment of alcohol use disorders. Clinicians will be able to move away from a “trial and error” approach to prescribing medications to a “matching” strategy based upon genetic information.

4. How will health care reform affect alcohol treatment?

There are a number of provisions in the Patient Protection and Affordable Care Act of 2010 that will have major implications for the treatment for alcohol use disorders. First and foremost, insurance coverage for alcohol, other drug, and mental health (AOD/MH) problems will be considered an “essential benefit” in future health insurance benefit packages. This will be true for individual and group health plans. Coverage for AOD/MH services will be treated like coverage for emergency room visits or medical/surgical procedures. Second, all plans need to adhere to the Wellstone/Domenici Parity Act, which requires that AOD/MH benefits are provided at the same level as medical and surgical benefits. Finally, health care coverage for Medicaid enrollees will now include AOD/MH services. Other provisions in the Act also are relevant to alcohol services: an emphasis on prevention and an initiative to strengthen the AOD/MH workforce. This landmark legislation is likely to present great opportunities—and more than a few challenges—to our existing system of AOD/MH services. These are truly exciting times!

5. As an avid skier, what are your favorite places to ski?

My favorite ski resort is Whistler-Blackcomb in British Columbia. It affords the opportunity to ski on backcountry glaciers, and the scenery is spectacular. I also enjoy my family’s annual spring vacation trip to Steamboat Springs, CO. It’s a great family ski area, and the town of Steamboat Springs is very welcoming.