NIAAA: Advancing Alcohol Research for 40 Years

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The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has been the lead Federal agency responsible for scientific research on alcohol and its effects for 40 years. During that time, NIAAA has conducted and funded groundbreaking research, distilled and disseminated those research findings to a broad audience, and ultimately improved public health. Among NIAAA's many significant contributions are the National Epidemiologic Survey on Alcohol and Related Conditions, the largest survey ever conducted on alcohol and associated psychiatric and medical conditions; investment in research to identify the genes underlying vulnerability to alcoholism; creation of the Collaborative Studies on Genetics of Alcoholism, a study of the genetics of alcoholism in a human population; leadership in exploring the effects of alcohol on fetal development and on a variety of diseases and organ systems; fostering alcoholism treatment, including supporting a medications development program that has funded more than 30 Phase 2 trials and 15 human laboratory studies; international collaborations and work across the National Institutes of Health; influential research on preventing alcohol problems through community programs as well as policy changes; and the translation of research findings to everyday practice, including the production of award-winning clinician training materials. *KEY WORDS: Alcoholism; alcohol and other drug use, abuse, and dependence; National Institute on Alcohol Abuse and Alcoholism; National Epidemiologic Survey on Alcohol and Related Conditions; Collaborative Studies on Genetics of Alcoholism; research; health services research; treatment research; prevention research; research in practice*

In 1970, Congress passed and President Richard M. Nixon signed the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970. With the passage of that law, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) became the lead Federal agency to address the problems associated with alcohol abuse and alcoholism. Over time, NIAAA has continued to evolve. Today's research portfolio casts a net over a wide range of study—from epigenetics and neuroimaging to health disparities and personalized medicine. NIAAA continues to spark innovative approaches to research problems, to foster cooperation and collaboration with other agencies and programs, and to advance our understanding of alcohol and its effects.

For example, NIAAA took the lead in supporting research to explore alcohol's effects on fetal development in the 1970s, when many scientists and physicians doubted the existence of fetal alcohol spectrum disorder (FASD). NIAAA held the first international research conference on FASD in 1977 and issued the first government health advisory on FASD on June 1, 1977. (For an in-depth look at NIAAA's role in FASD research, see the article on p. 118 of this issue.)

In addition to FASD research, NIAAA has supported important work on other medical consequences as well as the potential benefits of alcohol use. Such research has provided a better understanding of alcohol's role in diseases such as cancer, diabetes, dementia, and obesity; how alcohol affects the liver, brain, and immune system; and co-occurring alcohol and mental health disorders. (For more information on the medical consequences and potential benefits of alcohol, see the section beginning on p. 76 of this issue.)

Alcoholism has long been recognized to run in families. NIAAA's efforts to explore the genetic component of alcoholism led to the establishment of the Collaborative Studies on Genetics of Alcoholism (COGA) to identify genes associated with vulnerability for alcohol dependence. This study has facilitated gene discovery, contributed to the development of medications for alcoholism, helped to identify those at risk for alcohol problems, and furthered research on the relationships between alcoholism and other disorders.

NIAAA's outreach has extended well beyond the research lab. NIAAA has collaborated with other Federal agencies and published numerous

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books, pamphlets, and brochures to bring awareness of alcohol-related issues to a variety of audiences. NIAAA's initiative on understanding and preventing underage drinking led to collaboration with the U.S. Surgeon General and the production of the Surgeon General's Report, *A Call to Action To Prevent and Reduce Underage Drinking*. This valuable report, published in 2007, turned the Nation's attention to the problem of underage drinking and highlighted promising strategies for prevention and intervention.

NIAAA's leadership in both the research and public health communities has ensured that what is learned through research is put into practice. For example, NIAAA supported the creation and evaluation of Project Northland, an ongoing community-wide alcohol use prevention research trial for sixth, seventh, and eighth graders. This and other evidence-based prevention programs provide valuable tools for communities, schools, and college campuses working to prevent alcohol use and related problems. On a broader scale, NIAAA research has been influential in preventing alcohol problems through public policies, including laws to raise the minimum legal drinking age, mandate server intervention, and enforce drinking and driving laws. (For more information on NIAAA's role in prevention research, see the article on p. 18 of this issue.)

NIAAA also has developed strategies to help prevent alcohol use disorders from escalating to serious problems. To aid in the early recognition and diagnosis of potential alcohol use disorders, NIAAA developed a training guide, *Helping Patients Who Drink Too Much: A Clinician's Guide*, offering evidence-based approaches on how to identify and intervene with patients who may be problem drinkers. That guide later was retooled into a full-length online training course, showing video cases of doctors interacting with patients in a variety of settings and circumstances.

In addition to working to improve diagnosis and prevention, NIAAA has further championed the successful

History of NIAAA

Forty years ago, on New Years Eve in 1970, President Nixon signed into law the bill that would create the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The President's signature represented the culmination of a long and difficult process that included much controversy and debate; moreover, it represented a fundamental shift in the way Americans perceive alcohol and alcoholism. Indeed, by founding NIAAA, the Federal Government took a stand against the popular belief that alcoholism resulted from moral failings or character flaws. When President Nixon signed the bill on New Years Eve, devoting government resources to understanding and addressing alcoholism, he acknowledged alcoholism as a serious, but curable, public health problem.

Historically, most Americans had viewed alcoholism as either a sign of weakness or flawed character, rather than an illness posing a serious public health problem. However, after the 18th Amendment was repealed in 1932, ending Prohibition, a movement developed characterizing alcoholism as a curable illness. In the 1930s, Bill Wilson and Bob Smith founded Alcoholics Anonymous (AA); the success of AA proved that alcoholics could recover from the disease. In 1930, the scholarly journal *Quarterly Journal of Studies on Alcohol* was founded as the fledgling field of alcohol research began to emerge, granting scientific legitimacy to the study of alcoholism. In the mid-1930s, Yale University founded its Research Council on the Problems of Alcohol.

Perspectives on alcoholism were shifting, and many Americans, within and outside the scientific community, were beginning to see alcoholism as a problem that would yield to scientific solutions. By the 1950s, public health organizations such as the American Medical Association and the World Health Organization were addressing alcoholism in health care settings. By the 1960s, the American Psychiatric Association had declared alcoholism an illness. States began to develop treatment and support programs for alcoholics. However, these programs were often underfunded and underdeveloped. In order to make an impact, the Nation would have to address alcoholism on a Federal level, devoting national resources to the problem.

As perceptions on alcoholism changed, the Federal Government began to treat alcoholism as a public health problem. In the 1960s, the National Institute of Mental Health (NIMH) in the U.S. Public Health Service began a very small program of grants in the alcohol area. This led to the establishment in 1965 of the Center for the Prevention and Control of Alcohol Problems as a component of NIMH. However, under NIMH, the Center had limited authority and a limited budget. More resources were desperately needed for research. In a 1967 report, the Cooperative Commission on the Study of Alcoholism stated that "additional information about the nature and causes of problem drinking is urgently needed."

Researchers and policymakers felt that to comprehensively address the problem, a highly placed—and therefore highly visible—Federal

treatment of alcoholism. Forty years ago, the diagnosis of "alcoholic" carried a negative connotation. NIAAA and grassroots organizations such as Alcoholics Anonymous helped to change that perception, moving the public's view of alcoholism as a "moral failing" toward one that views alcoholism as a disease that, like diabetes or heart disease, can be treated. To accelerate medications development, NIAAA formed the Medications Development Working Group, which consists of members with multidisciplinary expertise, from molecular genetics and animal models to clinical trials and technology transfer.

Through these and other successful research and public health initiatives, NIAAA has provided important insights into nearly all aspects of alcohol use, abuse, and dependence, shedding light on questions that affect millions of Americans on a daily basis and improving public health. Based on findings from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), an estimated 65 percent of the U.S. population drink alcohol, with about 15 percent of drinkers consuming, on average, more than one drink per day for women and more than two drinks per day for men. Among current drinkers, an estimated 13 percent have either alcohol abuse or dependence (NIAAA 2006).

The following sections highlight a handful of research areas where NIAAA has made significant advances over the past 40 years. Additional information on the wide berth of research funded and supported by NIAAA is presented throughout this issue in articles written by some of today's most influential alcohol researchers.

Alcohol and Related Conditions: The Scope of the Problem

NESARC, the largest survey ever conducted on alcohol and associated psychiatric and medical conditions, was exceptional for its large sample

organization must be established to coordinate research and resources. However, to found such an organization, legislation was required. In 1968, a variety of individuals and organizations joined together to lobby for the establishment of such an organization.

In 1969, Senator Harold Hughes elected to take on the chairmanship of a newly formed Special Subcommittee on Alcoholism and Narcotics (SSAN) of the Senate Labor and Public Welfare Committee. Funds were not available for the committee's operations, but many volunteered to help with the work, and Senator Hughes donated his fees from speaking engagements to provide the necessary funding.

The first hearing of the SSAN was held in Washington, DC, on July 30, 1969. In 14 hearings held across the country during the summer of 1969, the Special Subcommittee received testimony from scientists, religious leaders, politicians, alcoholism treatment providers, and recovered alcoholics. Individuals from disparate backgrounds came together to tell the Nation that it was time to do something about the problems of alcohol abuse and alcoholism.

Based on these hearings, on May 14, 1970, Senator Hughes introduced into the Senate S. 3835, a bill that would provide a comprehensive Federal program to address the prevention and treatment of alcohol abuse and alcoholism. The bill was passed unanimously by the Senate on August 10, 1970. A version of S. 3835 passed the House on December 15; however, this version placed the proposed NIAAA within NIMH instead of granting it independent status. Senator Hughes accepted the House version in the interest of time.

S. 3835 now had only to be signed into law by President Nixon. However, according to the memoir of Thomas P. Pike, a wealthy businessman whose influence was instrumental in the bill's success, members of President Nixon's cabinet had advised him to veto the bill. Pike reports that he and other influential participants in the movement were able to persuade the President to sign the S. 3835 into law.

NIAAA did not achieve status as an independent institute until 4 years later, when the Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act Amendments passed in 1974. These amendments placed NIAAA, NIMH, and a new National Institute on Drug Abuse (NIDA) as equal partners under the Alcohol, Drug Abuse, and Mental Health Administration.

NIAAA's mission has evolved significantly since its creation 40 years ago. Changes have occurred in its leadership, its organizational home, and its primary program emphasis. However, NIAAA's commitment to discovering the best ways to prevent and treat alcohol abuse and alcoholism in America still embodies the strong hopes and dedication of those who fought for the Institute's creation. ■

SOURCE: Hewitt, B.G. The creation of the National Institute on Alcohol Abuse and Alcoholism: Responding to America's alcohol problem. *Alcohol Health & Research World* 19:13–16, 1995.

size, high response rates, and breadth of content. It comprised a large, nationally representative sample of U.S. adults originally interviewed in 2001–2002 and followed up approximately 3 years later in 2004–2005. The survey included respondents in Alaska and Hawaii and oversampling of Blacks, Hispanics, and 18- to 24-year-olds. The NESARC yielded estimates of current and lifetime substance use and mood, anxiety, and personality disorders (as defined by the *Diagnostic and Statistical Manual of Mental Disorders IV* [DSM–IV]), in addition to collecting extensive data on alcohol consumption, family history of alcoholism and other disorders, medical conditions, injuries and victimization, and health-related quality of life/disability. Wave 2 of the NESARC also collected data on acculturation and various types of discrimination.

Impact

The strengths of the NESARC are reflected in the more than 300 peer-reviewed journal articles based on or citing the dataset, including almost 80 in the past year. The longitudinal design of the NESARC has permitted the first nationally representative estimates of the course of alcohol use and other mental disorders in the United States. One of the major research reports to come out of the NESARC estimated the 1-year incidence rates for alcohol and drug use disorders, mood disorders (including major depressive and bipolar I and II disorders), and anxiety disorders (including panic disorder, specific and social phobia, and generalized anxiety disorder) and importantly showed that although mood and anxiety disorders were independently associated with the incidence of substance use disorders, the converse was not true (Grant et al. 2009). What made this study unique was its ability to control for multiple comorbidities in assessing the prospective effect of one disorder on the odds of developing a second disorder, thus helping to identify common underlying (shared) versus disorder-specific risk factors for disease. The NESARC also has been used extensively to study comorbidity in a cross-sectional perspective (e.g., Grant et al. 2004*a*, *b, c*, 2005; Hasin et al. 2007; Stinson et al. 2005).

Studies of the course of alcohol dependence based on the NESARC have led researchers to question the perception of alcoholism as a chronic and remitting disorder for which the only solution is lifelong abstinence. Retrospective data from the Wave 1 NESARC revealed that half of all adults previously classified with alcohol dependence were in full remission in the year preceding the Wave 1 NESARC and that nearly one-quarter had returned to low-risk drinking (Dawson et al. 2005). However, data from Wave 2 showed that relapse rates among remitted alcoholics were higher among drinkers than abstainers, except among remitted alcoholics 18–24 years of age at Wave 1. For this latter group, relapse rates were high irrespective of type of remission, highlighting a particularly vulnerable group in need of new approaches for maintaining sobriety or abstinence (Dawson et al. 2007). Wave 2 NESARC data also revealed associations of transitions in and out of alcohol use disorders with changes in risk drinking and health-related quality of life (Dawson et al. 2008, 2009).

NESARC alcohol consumption data have played a key role in the Global Burden of Disease Project, which used NESARC measures of the prevalence of drinking, average volume of consumption, and frequency of heavy episodic drinking to develop alcohol-attributable fractions of disease for the United States (Rehm et al., in press). These fractions, which indicate the proportion of the prevalence of a specified disease that would not exist in the absence of alcohol consumption (i.e., the proportion that can be attributed to the effects of alcohol), are an important tool for assessing public health priorities in the United States and for international comparisons.

Future Directions

The unprecedented scope of information yielded by NESARC has been put to many additional uses, including assessment of the underlying factor structures and dimensionality of substance use and mental disorders. NESARC consumption data have been used to both inform and monitor progress toward achieving low-risk drinking guidelines. In addition, NESARC symptom item indicators have formed the empirical basis against which proposed revisions of the DSM have been evaluated. These diverse applications reflect the wide-reaching impact the NESARC has had and will continue to have in the fields of alcohol research and psychiatric epidemiology.

Analyses of survey data help define populations at risk for alcohol abuse and alcoholism. Research on the genetic component of alcoholism risk has helped to further explain why some individuals are more likely than others to experience alcohol-related problems. As described below, NIAAA adopted this research project as one of its primary missions for improving public health and was one of the first Institutes to take the lead in understanding the genetics underlying a complex disease.

Genetics of Alcoholism

A genetic predisposition for alcoholism has long been suspected because of the observation that alcoholism tends to "run in families." However, this in and of itself is not proof of a genetic vulnerability because a shared environment also could explain the pattern. It was not until the 1970s that this notion was scientifically tested in a systematic fashion. Adoption studies were the first to conclusively point to a sound involvement of genetic factors as playing a role in predisposition to alcoholism. Goodwin and colleagues (1973) studied the drinking history of 55 adopted-out sons of alcoholics and 78 adopted-out sons of nonalcoholics. All of the sons were adopted as infants, within the first 6 weeks of life. Importantly, the sons of alcoholics had no knowledge that their biological parents suffered from alcoholism. The results were striking. Biological sons of alcoholics who had been adopted by nonrelated foster families were four times as likely to become

alcoholics compared with biological sons of nonalcoholics. Subsequently, similar lines of research in twin and family studies have convincingly demonstrated that genetic factors account for between 50 and 60 percent of the vulnerability to alcoholism.

Genetic Mapping in Animal Models

These results spurred intense research that began in the last several decades of the 20th century to find the genes that underlie vulnerability to alcoholism. NIAAA's critical investment in COGA, which began in 1989, helped further the understanding of the genetics of alcoholism in a human population (see below). However, because of the complex nature of alcoholism and the substantial genetic heterogeneity known to underlie it in human populations, alternative and complementary approaches were sought to further advance the field. Genetic animal models, and in particular mouse genetic models, offer an alternative and complementary approach for identifying the genes underlying alcoholism. The principal reasons are that they provide a means of reducing genetic heterogeneity and allow for a tighter control of environmental variation.

In the late 1980s, genetic mapping in mouse models of alcoholism became a reality because of technological breakthroughs. A method called quantitative trait loci (QTL)[1] mapping began to be used in a host of mouse models to determine the chromosomal regions containing a genetic variant underlying alcohol-related behaviors ranging from voluntary consumption to withdrawal severity. QTL mapping involves identifying (i.e., genotyping) DNA markers distributed across the entire mouse genome in different mouse strains and correlating DNA marker genotypes with a specific phenotype or trait (e.g., alcohol consumption). The question is then asked: Do mice of one genotype score differently on the trait than mice of other genotypes? If the answer is yes, and the difference is statistically significant, then a QTL exists in the chromosomal region defined by the DNA markers. Importantly, the homologous region of the human genome is usually known, making it ideal for translational science. NIAAA saw this as a golden opportunity and made significant investments in QTL mapping efforts in animal models of alcoholism.

By 1991, QTL mapping in mouse models for alcoholism had provisionally mapped a number of chromosomal regions containing a gene or genes associated with alcohol phenotypes. Further research in the ensuing decade resulted in the definitive mapping of several of these QTL. High-resolution mapping efforts began in the late 1990s, using animals with identical genetic backgrounds that differ only in a relatively small segment of DNA (i.e., interval-specific congenic strains) to narrow relatively large QTL intervals to regions of less than 1 centiMorgan (cM) containing only a few genes. This was a significant advance for the field because the prospect of cloning a gene based on its position (i.e., positional cloning) was now in sight. In the early 2000s, researchers identified the first bona fide quantitative trait gene (QTG). This QTG was localized to mouse chromosome 4 and was found to contribute to genetic variability in alcohol withdrawal severity. This gene, named *Mpdz*, encodes the multiple PDZ domain protein (MPDZ) and had not been previously known to influence an alcohol phenotype, highlighting the sheer power of the QTL approach for identifying novel genes for a complex trait.

Advances in QTL mapping continued into the latter half of the 2000s with the identification of another potential QTG for an alcohol phenotype on mouse chromosome 1. QTL mapping studies in rat models of alcoholism also yielded promising candidate genes for alcohol consumption, including neuropeptide Y, α-synuclein, and the corticotrophin releasing factor receptor. At this time, new approaches for identifying candidate genes underlying QTLs also were developed. This was spawned by advances in microarray gene expression technology, which enabled investigators to examine changes in gene expression on a genome-wide scale. Using gene expression as a quantitative trait resulted in the identification of gene networks that underlie vulnerability to alcoholism, the so-called expression QTL (eQTL) approach.

The Collaborative Studies on Genetics of Alcoholism

Complementing NIAAA's research investment in genetic mapping in animal models, the Institute also has been on the forefront of research to identify genes associated with vulnerability for alcohol dependence in humans. Whereas earlier research using twin, family, and adoption studies pointed to a strong genetic component for alcoholism (Hesselbrock 1995), it also showed that the development of alcohol-related disorders varies widely and depends on a number of factors, from co-occurring medical and psychiatric disorders to social influences (Begleiter et al. 1995). Recognizing the need to tease apart these genetic and environmental factors, COGA investigators conceived a large-scale multidisciplinary research program to develop resources both to define the spectrum of alcohol use disorders and to provide a well-defined study population that could be studied over time with new and emerging technologies.

The COGA project was, and still is, a truly unique research endeavor and even at its conception was innovative in the field of the genetics of complex diseases. (The Human Genome Project was started a few years after COGA had begun.) One of COGA's major strengths lies in the rich sample of families with multiple alcohol-dependent members, where the initial participant and at least two first-degree relatives met stringent diagnostic criteria for alcoholism based on several diagnostic instruments. In addition, over the 20 years that COGA has been funded it has produced some very valuable resources that have made the project

[1] For a definiton of this and other technical terms, see the Glossary, pp 161–164.

itself successful and contributed to the advancement of science in general.

COGA organizers developed a robust sample from across the country through six core data collection sites. (As of 2010, there are 10 research sites where collection, analysis, and storage take place; see textbox.) Systematic recruitment of people receiving treatment identified individuals who met the stringent criteria of alcohol dependence, as described in the DSM–III–R (American Psychiatric Association 1987), and alcoholism, as described by Feighner and colleagues (1972). For the genetic studies, investigators initially focused on the families with a high prevalence of alcohol abuse and alcoholism. A second group of families was sampled from each community to act as a comparison group (Edenberg 2002). The study has grown to include more than 15,000 people from 1,900 families.

During the initial recruitment, researchers realized the importance of documenting the current status of a patient's alcohol abuse and their family pedigree, as well as the conditions that presaged that condition. To systematically gather this information, the COGA scientists developed the Semi-Structured Assessment for Genetics of Alcoholism (SSAGA), a tool for assessing and selecting individuals (Bucholz et al. 1994); this polydiagnostic instrument can make diagnoses using DSM–III–R, DSM–IV (American Psychiatric Association 1987, 1994), Feighner's (1972), and ICD–10 (World Health Organization [WHO] 1992) criteria. SSAGA, a direct-interview approach, enabled researchers to obtain both clinical detail and psychiatric histories of patients and family members. SSAGA has been translated into nine languages and now is widely used throughout the world, making comparisons across studies from different groups possible. Once identified using SSAGA, COGA family members were further characterized with extensive neurophysiological, behavioral, and psychiatric assessments. Blood and cell samples also were collected for genetic analysis. Because of COGA, more than 11,000 DNA and cell lines are now available to researchers.

COGA Sites

- Howard University
- Indiana University
- Rutgers University
- Southwest Foundation
- State University of New York, Downstate Medical Center
- University of California, San Diego
- University of Connecticut
- University of Iowa
- Virginia Commonwealth University
- Washington University, St. Louis

Researchers designed COGA to be reproducible and flexible in structure so that it could be quickly adapted to incorporate new findings and accommodate new approaches as the study progresses. The validity and effectiveness of this approach has been borne out by many smaller studies in countries around the world that have replicated and confirmed COGA's results.

Results

COGA's early strategy of using densely affected families has facilitated gene discovery and has provided a clearer picture of the genetics underlying alcoholism. A successful approach used by COGA has been to use quantitative neurophysiological traits (brain oscillations) to identify susceptibility genes that may be difficult to detect with clinical diagnosis alone. In the mid-1990s, researchers published the first reports of chromosomal regions linked to a variety of alcohol-related traits (i.e., phenotypes) in the COGA sample. Candidate genes within the critical linked chromosomal regions were prioritized to determine which genes contained variation that could contribute to the phenotypes under study. Genes encoding both specific receptor molecules for the neurotransmitter γ-aminobutyric acid (GABA) and alcohol-metabolizing enzymes floated to the top of the list for associations with alcohol-related phenotypes. Other less obvious genes also were discovered, such as a gene for a receptor for acetylcholine (*CHRM2*), a glutamate receptor gene (*GRM8*), and genes encoding the protein α-synuclein and the transcription factor, nuclear factor B. Recent studies using a DNA sequence variation occurring when a single DNA subunit (i.e., nucleotide) in the genome differs between individuals (i.e., single-nucleotide polymorphisms) and approaches using a set of DNA variations inherited together (i.e., haplotyping) have further refined efforts to identify and locate genes in the sample population of alcohol-dependent patients. COGA researchers also have confirmed alcohol genetic spectrum conditions, including drug dependence and some forms of anxiety and mood disorders. An important finding has been the identification of conduct disorder as a precursor to alcohol problems, related through a $GABA_A$ receptor gene (Dick et al. 2006). Most recently, COGA has implemented a genome-wide association study on a case–control sample derived from COGA. To date, the list of genes associated with alcoholism in the COGA sample has grown to more than 20, highlighting a tremendous payoff from NIAAA's investment in this project.

Future Directions

Going forward, COGA scientists have launched a prospective longitudinal study of high-risk youth ages 12–21 from families with a history of alcohol abuse as well as from comparison families. This ongoing study, with followups every 2 years, is designed to provide more detailed information on the interaction of genes and the environment. The data and samples accumulated by COGA may allow researchers to identify the mechanisms that underlie the onset of alcohol use

disorders and to understand how these mechanisms influence risk.

Scientists continue to identify and confirm other genes and gene variants that affect the risk for alcoholism and related phenotypes and to characterize the expression of those genes at the molecular and cellular level. Researchers also are testing the role of changes not caused by changes in DNA (i.e., epigenetic modifications) that might alter gene expression and affect the long-term alcoholism risk for study participants and their offspring.

Ultimately, the findings from COGA will help scientists to develop new approaches for preventing and treating alcohol use disorders, identifying the precursors for risk of alcohol problems, developing effective measures to prevent early onset of alcohol abuse, and understanding how alcohol abuse and alcoholism are related to other comorbid disorders, such as substance abuse, anxiety, mood, and spectrum disorders. (For more information on studies of the genetics of alcoholism, see the article on p. 64 of this issue.)

Advances in Medications Development

Over the past 40 years, researchers have made significant advances in developing medications to treat patients with alcohol use disorders. In 1992, Volpicelli and colleagues (1992) and O'Malley and colleagues (1992) reported naltrexone to be effective in reducing drinking in alcohol-dependent patients. These two NIAAA-supported studies were used to obtain Food and Drug Administration (FDA) approval for naltrexone, the first medication approved for alcohol dependence in more than 40 years. These studies also changed the landscape of the NIAAA medications development program. Before the Volpicelli and O'Malley studies, NIAAA was funding approximately six projects on human medication studies. After the naltrexone findings, 10 new pharmacotherapy studies were funded within a year, and today's medications development program has expanded to fund more than 30 Phase 2 trials and 15 human laboratory studies. This increased research activity also led to heightened interest from pharmaceutical companies, resulting in the FDA approval of acamprosate (Campral®) in 2004 and a long-acting injectable form of naltrexone (Vivitrol®) in 2006.

Alcohol researchers currently are exploring new molecular targets and testing new medications, including about 20 medications being evaluated in NIAAA-supported human studies. The most promising medications at this time are topiramate and ondansetron (Johnson 2009; Johnson et al. 2006). Studies also are ongoing to evaluate medication efficacy in various undertreated populations, including people with comorbid psychiatric, substance abuse, and/or medical conditions; adolescents; and young adults. Because no current alcohol medication is effective for everyone, new efforts are underway to predict the patients who are likely to respond positively and those who are likely to experience adverse events. This progress toward personalized medicine is exemplified by the findings that the A118G allele on the opioid receptor gene is associated with a positive response to naltrexone (Oslin et al. 2003) and that the L versus S allele of the serotonin transporter gene appears to influence alcohol craving and response to ondansetron (Ait-Daoud et al. 2009; Johnson 2009). (For more information on how neuroscience is helping to inform new approaches to treatment for alcoholism, see the article on p. 144 of this issue.)

This progress notwithstanding, many exciting research challenges remain, including the following:

1. Identifying new molecular sites to target with promising compounds. This requires studying the complex systems of genes, proteins, cells, and neurocircuits involved in alcohol use disorders. In particular, it is important to identify the specific neurocircuits that drive such aspects of addiction as reward and motivation; negative affect; cue conditioning and craving; disinhibition, impulsivity, compulsivity, and habituation; memory; and executive and cognitive function. It is equally crucial to understand the interactions and integration of these neurocircuits (a process that will require sophisticated mathematical modeling) to eventually target specific key sites with appropriate medications.

2. Developing and testing new medications to provide additional choices for clinicians and patients. As noted, because of the heterogeneity of alcohol use disorders, no current treatment is effective for all patients. The search continues for new compounds to address one or more aspects of alcohol use disorders.

3. Exploring combinations of targets. Most complex disorders (e.g., high blood pressure, diabetes, cancer, and acquired immune deficiency syndrome [AIDS]) are treated with medications that address multiple targets. This is accomplished either by combining medications or by developing a medication with multiple sites of action. The challenge for alcohol medications development is to identify the molecular sites that will produce optimal effects without simultaneously increasing risk for patient side effects.

4. Advancing personalized medicine. Progress is being made in brain imaging, mathematical modeling of multiple human characteristics, and understanding how the actions of and reactions to drugs vary with a patient's genes. Future research will integrate combinations of biochemical, physiological, and behavioral variables to produce multiple informative personalized treatment algorithms.

5. Improving tools for drug development. This activity will include

validating animal and human laboratory paradigms as screening models to predict clinical performance. Research also is needed to improve the methodology for conducting alcohol clinical trials by addressing optimal design, placebo effect, and treatment end points. Discovery and development of biomarkers and alcohol-sensing devices will be instrumental in this effort. For example, biomarkers can help identify population phenotypes, screen for excessive drinking, identify placebo responders in clinical trials, and serve as independent, objective end point measures for alcohol studies.

6. Identifying and removing barriers to medications use in real-world settings. Multiple barriers to incorporating medications into alcohol treatment exist at both the structural and individual levels. Strategies are needed for diffusion of this innovation to longstanding treatment models.

7. Establishing collaborative networks and partnerships among government, academia, pharmaceutical industry, health care organizations, and advocacy groups. Medications development is too large a task for any single government agency or private company. Establishing strategic alliances should enable a comprehensive effort to discover and efficiently develop safe, effective medications and facilitate their application.

Results of these initiatives during the next decade should lead to improved treatment outcomes, thereby sparing affected individuals and their families costly alcoholism-associated medical, psychological, social, economic, and personal problems. (For more information on the use of medications and other treatment methods for alcohol use disorders, see the article on pp. 55 of this issue.)

Collaborating Across the National Institutes of Health and Beyond

To achieve the research and public health successes described here and to meet the current and future challenges that lie ahead, NIAAA recognizes the importance of working with scientists and administrators outside its own agency and has strived to establish connections and collaborations across the National Institutes of Health (NIH) and around the world.

NIAAA and Global Health

NIAAA has had a strong global presence throughout much of its 40-year history. Because the problems that arise from harmful use of alcohol pose considerable challenges for societies throughout the world, the international alcohol research community has recognized the need for scientific collaboration to accelerate knowledge building in this area to improve public health. NIAAA develops and supports collaborations with foreign scientists that range from molecular and cellular studies of alcohol's impact on liver and brain function to studies of effective identification and treatment of children with FASD. And NIAAA's role in international scientific collaborations is increasing in importance: alcohol misuse has recently been identified as a significant global health priority by the health community at large (*Lancet*, Vol. 373, June 27, 2009), and the WHO is scheduled to put a substantial focus on this health issue with the adoption of its "Global Strategy to Reduce Harmful Use of Alcohol" at the May 2010 World Health Assembly.

Historically, support for international alcohol scientific projects has comprised 1 to 2 percent of NIAAA's annual extramural research budget. But this small investment has led to important scientific findings. For example, collaboration between investigators in Canada and the Indiana University Alcohol Research Center revealed that rats selectively bred to like alcohol display a higher preference for nicotine, providing a basis to study genetic influences in human patterns of alcohol and nicotine addiction (Le et al. 2006). In another collaborative study, scientists at SCRIPPS Alcohol Research Center and investigators in Trinidad found an important interaction between genetic and environmental risk factors that influences the development of alcohol dependence and alcohol-related liver disease in Afro-Trinidadians that also influences alcohol use in African Americans who have the same gene sequence (Ehlers et al. 2007).

Understanding the role of alcohol abuse and dependence in the development of human immunodeficiency virus (HIV)/AIDS has increased tremendously as a result of international collaboration between NIAAA-funded scientists in the United States and investigators in Africa, India, and Russia. International alcohol research groups have had significant involvement in NIAAA cross disciplinary initiatives, such as the French Institut National de la Santé et de la Recherche Médicale (INSERM)-supported laboratory that participates in the Integrative Neuroscience Initiative on Alcoholism (INIA), and the contributions of investigators from South Africa, Finland, Italy, Ukraine, Australia, Northern Ireland, and Russia to the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD).

The NIAAA intramural program also has strategically invested in international collaborative research on alcohol through the training of hundreds of foreign research fellows over the years who not only contribute to research in NIAAA's intramural research programs while in the United States but who continue to collaborate with U.S. colleagues on scientific projects upon return to their home countries. In addition, NIAAA intramural research scientists conduct important studies overseas. For example, a current effort led by NIAAA's Biometry and Epidemiology Branch is looking at alcohol use in hospital emergency department patients at several sites in China, Taiwan, Korea, and Japan in a collaborative effort to determine the association between alcohol use and injury as a first step toward developing effective prevention interventions.

Trans-NIH Collaborations

Other research partnerships have transpired closer to home. NIAAA has participated in several trans-NIH initiatives including the following:

- The NIH Obesity Research Task Force, to accelerate progress in obesity research and education across NIH.
- The NIH Blueprint for Neuroscience Research, a cooperative effort that pools resources and expertise to support the development of new tools, training opportunities, and other resources to assist neuroscientists in both basic and clinical research. (For more information on NIAAA's role in neuroscience research, see the article on p. 127 of this issue.)
- The NIH Pain Consortium, which promotes collaboration among researchers studying sensory and basic mechanisms of pain as well as the emotional and biobehavioral aspects of pain.
- The NIH Public Trust Initiative (PTI), which is working to promote public understanding and confidence in the research that NIH conducts and supports across the country and throughout the world.

NIAAA and the NIH Common Fund. The NIH Common Fund is a collection of far-reaching initiatives designed to transform the Nation's medical research capabilities and improve the translation of research into practice. NIAAA is actively participating in the Metabolomics Technology Development Initiative; the Genes, Environment, and Health Initiative to understand the interaction between genes and the environment and the impact on health and disease; and the Roadmap Epigenomics Program, all of which emerged from NIH Common Fund initiatives.

Outreach and Dissemination of Research Findings

Research findings about the best ways to prevent and treat alcohol problems can have a significant impact on public health but only if those findings are adequately reported and translated to the relevant audiences. An important part of NIAAA's mission, therefore, is "translating and disseminating research findings to health care providers, researchers, policymakers, and the public." NIAAA's pioneering work in public outreach, communications, and clinician training aims to stimulate new areas of research and foster growth in the field; to improve prevention efforts and treatment outcomes; and to educate the general public about alcohol and alcoholism. Through its award-winning publications, Web sites, e-learning tools, and public service announcements, NIAAA targets a variety of audiences.

Figure 1 Materials developed by NIAAA to educate the public.

Materials and Audiences

NIAAA produces a variety of materials tailored to meet the needs of people interested in alcohol research. NIAAA's scientific journal, *Alcohol Research & Health*, is a fully peer-reviewed journal targeting scientists in the alcohol research field. Each issue of *Alcohol Research & Health* takes an in-depth look at one topic in alcohol research. Recent and upcoming issues examine findings on systems biology and alcohol, the latest findings in FASD, and the role that alcohol plays in HIV/AIDS.

In addition to the journal, NIAAA produces publications targeting other professionals with an interest in alcohol research. The six-page bulletin *Alcohol Alert*, sister publication to *Alcohol Research & Health*, is geared specifically to treatment professionals, and the *Alert* often focuses on the same topic as the current journal. The *Project COMBINE* and *Project MATCH* manuals offer evidence-based guidelines for therapists, clinicians, and counselors for treating alcohol use disorders. NIAAA also produces publications especially for its grantees and other researchers in the alcohol field. Additionally, NIAAA's triannual Webzine, *Spectrum*, offers accessible and relevant information for anyone interested in the alcohol research field. Each issue includes feature-length stories, news updates from the field, informative "charticles" showing important data in an easy-to-read format, photo essays, and an interview with an NIAAA staff member or researcher from the field.

To reach clinicians, educators, and other professionals, as well as members of the general public, NIAAA attends and exhibits at a variety of conferences. NIAAA will attend 20 conferences in 2010, including those given by the American Psychiatric Association, the American Academy of Family Physicians, and the Community Anti-Drug Coalitions of America, as well as the annual meetings of the Latino Behavioral Health Institute, the National Middle School Administration, and the Science Festival on the Washington, DC, Mall. NIAAA representatives at these conferences answer questions, distribute literature, and discuss current initiatives and research.

NIAAA's public education materials provide the general public with evidence-based, easy-to-read information about alcohol. *Rethinking Drinking* debunks myths about alcohol use and abuse and provides strategies for people who want to curtail their drinking. *Alcohol: A Woman's Health Issue* addresses alcohol problems common among women. *A Family History of Alcoholism: Are You At Risk?* describes genetic and environmental factors that may contribute to the development of alcoholism and the special risks that those with a family history of alcoholism may face. *Harmful Interactions: Mixing Alcohol With Medicines* discusses the potential dangers

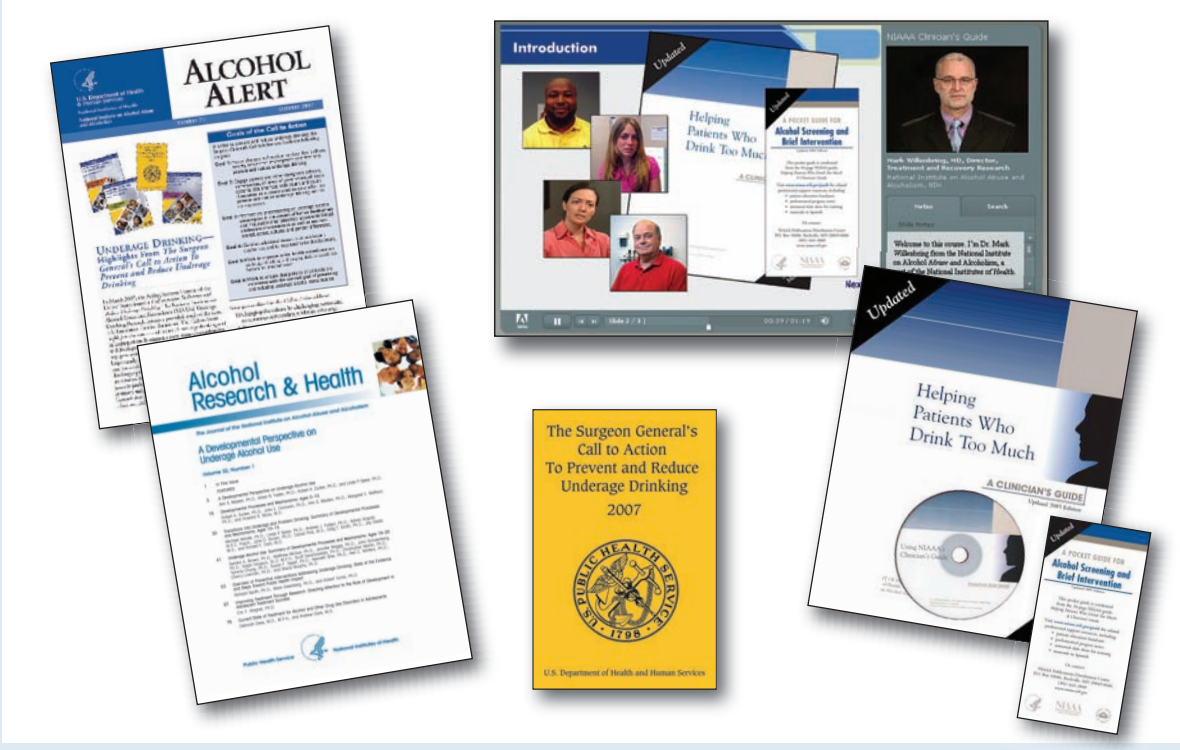

Figure 2 Materials developed by NIAAA to support professionals in the alcohol research field.

of drinking while taking common prescription and over-the-counter medications. A revised version of this publication has been adapted for an older audience—the population most likely to be taking prescription medications.

In recent years, NIAAA has focused on better understanding and preventing underage drinking. NIAAA was instrumental in producing the Surgeon General's Report, *A Call to Action To Prevent and Reduce Underage Drinking*. NIAAA's underage drinking prevention products also include a poster that presents alternatives to drinking, designed especially for children in sixth through eighth grades; public service announcements and Web sites targeting children and their parents; and the popular booklet, *Make a Difference: Talk to Your Child About Alcohol*. "The Cool Spot" (www.thecoolspot.gov), NIAAA's Web site for middle-school students, was created for children who may be facing pressure to drink. This Web site provides accurate information about alcohol, as well as strategies for resisting peer pressure, in a dynamic, interactive, and engaging online environment.

Another important initiative for NIAAA focuses on preventing drinking specifically among college students. NIAAA's Task Force on College Drinking features materials aimed at college presidents, college students and their parents, high-school administrators, and high-school parents and students, with information on prevention relevant to each population. These materials are available online at www.collegedrinkingprevention.gov. (For more information on NIAAA's work in the areas of underage and college drinking, see the article on p. 45 of this issue.)

NIAAA has collaborated with other organizations and NIH Institutes to reach an even wider audience. In collaboration with the National Center on Minority Health and Health Disparities/NIH, NIAAA produced a public education campaign focusing on reducing fetal alcohol syndrome among populations at risk. In another collaborative effort, this time with the National Institute on Drug Abuse and HBO, NIAAA helped to produce HBO's *The Addiction Project*. The *Project* included a 14-part documentary that aired on HBO main service, multiplex channels, HBO-On-Demand, podcasts, Web streams, and DVD.

In recent years, NIAAA has embraced new technology to further its mission. NIAAA has produced an "e-learning" educational program for health care professionals based on the *Clinician's Guide*. This interactive, Web-based course offers four 10-minute video cases based on scenarios clinicians might face in everyday practice and provides evidence-based clinical strategies for dealing with patients at different levels of severity and readiness to change. Physicians and nurses who complete the course can earn continuing medical education (CME) or continuing education (CE) credits through Medscape®; in the first 3 weeks the program was offered, 3,600 participants earned credit.

Figure 3 Awards garnered by NIAAA materials in recent years.

Evidence of Success

NIAAA is succeeding in fulfilling its mandate to bring information to researchers, clinicians, and the general public. NIAAA's publications are widely distributed, and its work often is publicized extensively in the news media. Outreach efforts also have won multiple awards, and clinicians and professional and government organizations are adopting NIAAA's evidence-based practices.

The *Clinician's Guide* has been included in the clinical practice guidelines of several HMOs. Since its launch, NIAAA's College Drinking Task Force Web site has had more than 114 million visitors. In addition, statistics from the Task Force materials are commonly cited in both research papers and public policy to describe the extent of the problem. *The Addiction Project* was featured in the Associated Press; *The New Republic*; CNN television programming; CNN, NPR, and CBS Radio; *The New York Times*; and other news outlets.

Many of NIAAA's outreach efforts have garnered awards for excellence. The *Clinician's Guide* earned awards

from the Society for Technical Communication Awards for Excellence (2005), the Distinguished Technical Communication (2003, 2005), and the NIH Plain Language Awards (2003, 2005). HBO's *The Addiction Project* received the American Academy of Television Arts and Sciences' highest honor, the Board of Governors Award (Emmy), and a PRISM award. The video associated with the booklet *Alcohol: A Woman's Health Issue* won several awards, including the New York Festival's (2002) Bronze "WorldMedal" award. Other publications have won the NIH Plain Language Award, National Association of Government Communicators Blue Pencil Awards, a Gold Screen Award, a World Wide Web Health Award, NIH Director's Awards, and others. The e-learning program associated with the *Clinician's Guide* recently received five awards, including first place from the National Association of Government Communicators Gold Screen Awards (2009), Platinum and Gold awards from the Association of Marketing and Communication Professionals Hermes Awards (2009), and two Bronze awards from Horizon Interactive Awards (2009).

Future Directions

Looking to the future, NIAAA has selected *Alcohol Research & Health* and *Alert* topics that will focus on the latest findings from the alcohol research field, striking a unique balance between biomedical and psychosocial topics. Upcoming publications will address, in particular, the problem of health disparities and will target populations who are especially at risk for alcohol-related problems. (For more information on NIAAA's role in health disparities and alcohol research, see the article on p. 152 of this issue.) NIAAA will translate more publications, including *Rethinking Drinking*, into Spanish. Additionally, NIAAA currently is developing a curriculum for undergraduate nursing faculty with topics such as the neurobiology of addictions; screening, treatment, and prevention issues; and management of intoxication and withdrawal that will help educate a new generation of nurses on issues related to alcohol research.

Looking Forward

As NIAAA moves into its 40th year as the Nation's lead agency on alcohol abuse and alcoholism research, it looks back on a rich and productive investment in research on a wide range of areas, including genetics, neuroscience, epidemiology, health risks and benefits of alcohol consumption, prevention, and treatment. As technological advances continue, such as novel high-throughput technology and complete annotation of the mouse genome, the field is set to move into a new era of discovery for alcohol research. In the area of treatment for alcoholism, the emerging field of personalized medicine promises to apply information about a patient's protein, gene, or metabolite profile to tailor treatment to that individual's needs. NIAAA also is pursuing the challenge of preventing and treating alcohol problems among special populations to decrease health disparities and further improve public health. To attain success in these and other endeavors, NIAAA will continue to rely on its partnerships with individuals and agencies within NIH and around the world. ■

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