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National Institute on Alcohol Abuse and Alcoholism

INTRODUCTION

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the lead Federal agency responsible for research on the causes, consequences, prevention, treatment, and delivery of services for alcohol-related problems. NIAAA supports and conducts biomedical and behavioral research on the effects of alcohol on the mind and body, trials of the efficacy of prevention and treatment interventions, and studies on the epidemiology of alcoholism and other alcohol-related problems.

NIAAA's international objectives are carried out through the International Research and Training Program, in the Office of Collaborative Research. Through a variety of initiatives and mechanisms, NIAAA supports the research efforts of scientists throughout the world who are investigating questions about alcohol use that are relevant to the U.S. population.

The International Research and Training Program consists of international grants, medical education and research training, scientific exchange, and dissemination of research-based information. The Program is a designated World Health Organization (WHO) Collaborating Center for Research and Training on Alcohol Problems.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

International Measurement Standards

The Division of Biometry and Epidemiology, NIAAA, has been actively involved in the development of international standards for the measurement of alcohol consumption and consequences of alcohol use. Division staff edited a special edition of the *Journal of Substance Abuse* that was based on the proceedings of the Skarpö Conference on Measuring Alcohol Consumption and Social Harm, which was held in Skarpö, Sweden, in April 2000. This special edition includes an overview of conference recommendations developed in a lengthy consensus process, as well as methodological and substantive reports devoted to the design and aggregation of measures of alcohol consumption and alcohol-related harm.

Hungary

In fiscal year 2000 (FY 00), the Hungarian Ministry of Sport and Youth and the Hungarian Society of Addictology sponsored the highly successful course for family physicians—A Medical Education Model for the Prevention and Treatment of Alcohol Use Disorders. NIAAA and the Department of Family Medicine, University of Wisconsin, Madison, developed this course. A total of 40 faculty in family medicine and psychiatry from Hungarian medical schools, as well as alcohol treatment specialists, who are responsible for medical education on alcohol, participated in the course. Participants will be followed up at 6 months after the course to determine whether they are incorporating knowledge, skills, and methods taught in the course in their teaching of medical students, residents, and graduate physicians.

Russia

Russia has one of the fastest-growing populations with human immunodeficiency virus (HIV) in the world, and it is widely documented that alcohol consumption in Russia is extremely high. Researchers at Boston University Medical Center, Massachusetts, and Pavlov State Medical University, St. Petersburg, have begun an important study to determine the risk factors of heavy alcohol use in the spread of HIV and acquired immunodeficiency syndrome (AIDS). Based on work that was begun in the United States, this study will help (1) to determine the necessary elements of interventions to prevent HIV transmission in populations that abuse alcohol and (2) to develop treatment protocols for patients with alcoholism who are HIV positive or who have AIDS.

Investigators from the University of Minnesota School of Public Health, Minneapolis, are continuing to work with Russian prevention experts on implementing and testing an intervention to prevent alcohol abuse. This intervention is aimed at sixth-, seventh-, and eighth-grade students in Moscow. In FY 00, a peer-led intervention targeted to seventh graders was implemented in a sample of schools. This strategy uses students selected to lead their classmates in a series of activities that teach the real consequences of alcohol misuse and provides practice in strategies for delaying the use of alcohol until the legal drinking age. Students who took part in the intervention will have follow-up and will be compared with those who did not receive this intervention on a number of variables, including alcohol use.

South Africa

NIAAA supported a cooperative agreement with the University of New Mexico, Albuquerque, to hold the IXth Annual Meeting of the International Conference on the Treatment of Addictive Behaviors, entitled Addressing Addiction Through Health and Social Systems. This meeting was held in Cape Town, South Africa, on September 21–25, 2000. The Medical Research Council of South Africa was cosponsor and full partner in planning and implementing the conference, and NIAAA supported the attendance of 50 delegates from Africa. The keynote speaker was the National Minister of Health of South Africa. Throughout the world, the scope of alcohol and other drug problems far exceeds the reach of specialist treatment systems, even in nations where such systems are well developed. At the conference, presentations were made by leading researchers representing Brazil, England, Germany, Israel, the Netherlands, South

Africa, Sweden, Turkey, and the United States.

A highly productive, collaborative research program on fetal alcohol syndrome (FAS) continues in the Western Cape province of South Africa. This work involves leading scientists from the United States and South Africa. The overall goals are as follows:

1. to build a multidisciplinary and multicultural team of investigators and clinicians from both countries;

2. to work with the South African government and nongovernmental agencies in South Africa to develop capabilities and methods that address the high incidence of FAS in populations in the Western Cape region and to provide support for the development of a nationwide prevention effort;

3. to develop methods and procedures for research to advance the state of the art in diagnosing FAS, determining its prevalence, and finding reasons for differential vulnerability of some populations and some individuals; and

4. to apply these results to the study of populations in the United States by using a team approach.

Significant progress has been made in establishing the prevalence of FAS among students in one city in the Western Cape. Epidemiologic findings from a study published in the *American Journal of Public Health* (December 2000) reported FAS in 40.5–46.4 per 1,000 children aged 5–9 years, and age-specific community rates for children aged 6–7 years were 39.2–42.9 per 1,000. This study documents the highest FAS rate to date in an overall community population.

Diagnosis of FAS involves interviews with mothers, neurobehavioral testing, and examination of children by a clinician trained in dysmorphology. The methods used and tests selected in this work were developed by collaboration between U.S. experts in assessment in Native American children and South African specialists in child development. The refinement of these screening tools will form the standard for active case ascertainment studies in the United States and throughout the world. Pilot studies of metabolism and genetics are also under way to determine why some women who drink similar amounts of alcohol have affected children and some have normal children.

A high-resolution videocassette recorder is now being used in concert with ultrasonography equipment donated by General Electric Medical Systems, Milwaukee, Wisconsin. This project will make it possible to maintain a video library of pregnancies with alcohol-related high risk that are being monitored in the Western Cape studies. The sonograms from ultrasonography are providing information to assist in prenatal diagnosis of alcohol-related fetal heart problems, which may lead to early interventions.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Australia

Queensland Institute of Medical Research, Brisbane, collaborated with the University of Missouri, Columbia, on a project that uses data from the Australian twin registry. The scientists investigated genetic and social factors and their covariation and interaction in the development and natural history of patterns of alcohol use, abuse, and dependence. In this study, lifetime prevalences of alcoholism, major depression, conduct disorder, and panic disorder were higher among both males and females who also reported childhood sexual abuse than among those who did not report such abuse. Among females, social phobia was also associated with report of childhood sexual abuse.

Another aspect of this study measured platelet monoamine oxidase (MAO) in Australian twins who had provided information on alcohol use and dependence, smoking, and other psychological problems. The investigators found that reduced activity of platelet MAO was associated with current smoking and that this reduction had a dose–response effect. However, history of alcohol use and lifetime alcohol dependence, measured according to the *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSM-III-R),* was not associated with MAO activity. The investigators concluded that platelet MAO activity was not a direct genetic marker of vulnerability to alcohol dependence.

Canada

In rats, chronic alcohol use during pregnancy induces an exaggerated response to stress. This finding suggests that the ability of the endocrine system to regulate the hormones involved in stress responsiveness is altered and that the animal's ability to adapt to stressful situations is impaired. Researchers at the University of British Columbia, Vancouver, investigated whether an early environmental manipulation (postnatal handling) could attenuate the impact of prenatal alcohol on hormonal responses to stressors. Although handling by itself during the preweaning stage of development reduced the hormonal response to stress; this treatment had no effect on the deficits in stress responsiveness exhibited by animals that were exposed to alcohol in utero.

Chronic ethanol intake during pregnancy in rats has been shown to retard fetal skeletal growth and adversely affect the skeletal system of pregnant females. These effects of alcohol may have significant implications for the development of osteoporosis at a later stage. Because calcium plays a major role in the growth, development, and metabolism of bones, scientists at the University of British Columbia, in a second study, are investigating the effects of chronic alcohol use on calcium regulation and bone during pregnancy in both dam and fetus. The specific aims of this project are to determine the mechanisms by which alcohol impairs calcium regulation in pregnant rats and to ascertain whether adverse effects of alcohol on fetal growth and skeletal development result from the inability of dams to regulate calcium levels. Findings to date are demonstrating that ethanol-fed rats have greater decreases in blood calcium levels than controls.

Researchers at the Center for Addiction and Mental Health, Toronto, Ontario, are receiving NIAAA support for a study of the role of 5-HT1b receptors in ethanol reinforcement. This work tests the hypothesis that 5-HT1b receptors modify ethanol's reinforcing efficacy. The researchers examined the effects of the 5-HT1b antagonist RU24969 on ethanol self-administration by rats. Higher doses of RU24969 reduced ethanol self-administration when solutions of higher concentration were available. Low doses of RU24969 reduced ethanol's reinforcing effects when the ethanol dose was manipulated by changing the volume of a reward of 12% ethanol solution. Administering RU24969 over a 13-day period significantly reduced ethanol self-administration during the entire interval. Alcohol self-

administration returned to baseline levels once RU24969 administration was stopped, and there was no evidence of rebound or carryover effects. This work confirmed that 5-HT1b receptors are involved in ethanol reinforcement. Further work will reveal specific aspects of ethanol reinforcement affected by 5-HT1b systems and their anatomic locus.

NIAAA is supporting a study by investigators at the University of Alberta, Edmonton. This research on the replicability of drug and genetic effects on behavior is designed to identify and develop optimal procedures for phenotyping mice that have genetic differences in motor coordination and ataxia, as well as memory and learning. In the course of testing, the investigators identified factors limiting the reliability of certain standard tests for some genetic strains. For example, the Y-maze, spontaneous-alternation test does not yield significant differences among strains of mice, and the low activity of the 129s3 strain renders tasks requiring spontaneous activity nearly useless. During FY 01, unreliable tests will be culled, and test reliability will be examined after ethanol administration. This project has practical importance in developing reliable tests of mouse behavior on the basis of empirical criteria rather than convention.

Researchers at the University of Guelph, Ontario, are studying alcohol-induced liver damage in situ by using functional magnetic resonance imaging, a unique, noninvasive technique. The technique measures oxygenation changes in the sinusoids of the liver of rats exposed to long-term ethanol treatment alone or simultaneously subjected to acute ethanol or hypoxic challenge. Oxygen changes in the liver are evaluated to determine whether ethanol treatment leads to hypoxia, which plays an important role in the etiology of early ethanol-induced liver injury. Results of this project may help in the development of a simple, noninvasive, clinical diagnostic test for early prediction of liver disease due to alcohol abuse.

NIAAA provided support to the Canadian Center on Substance Abuse, to help in underwriting the costs of the 3rd International Symposium on the Economic and Social Costs of Substance Abuse. This meeting was held in Banff, Alberta, on May 31–June 3, 2000. The International Guidelines for Estimating the Economic Costs of Substance Abuse, which were developed through earlier symposia in this series, are being revised and updated on the basis of discussions and presentations at the Banff meeting.

Finland

Investigators at the University of Indiana, Indianapolis, are conducting a large-scale study of Finnish twin pairs. In an age-standardized, population-based sample of more than 5,700 Finnish twins, the investigators showed that abstinence from alcohol to age 16 years is significantly associated with practices in the family and is largely due to nongenetic differences. Socioregional variation, reciprocal sibling interactions, and parental drinking patterns influence abstinence rates for children. Influences from siblings and parents are greater in some regional environments than in others, and the relative likelihood that an adolescent twin abstains, given that the co-twin does or that both parents do, was modulated by socioregional variation. These results illustrate how genetically informative data can enlighten prevention research by identifying target variables for intervention efforts.

The same investigators are performing a second study, on another sample of Finnish twins, similar in size and composition, but first assessed at earlier ages. They are studying subsamples of families at risk for alcoholism. Oversampling for risk is done by using a questionnaire to screen parents that has been validated against standard diagnostic criteria. At age 12 years, twin children from at-risk families are behaviorally differentiated in ratings that compare them with their classmate peers. Twins at risk for alcoholism are described by peers as more aggressive and less compliant. In the upper quartile of alcohol consumption at age 14 years, there are five times as many twins who were ranked by their peers as being in the lowest quartile of compliance. The behavioral dimensions shown to be relevant to risk were also shown to be moderately heritable, inviting more detailed genetic analyses as the twins moved through mid-adolescence and into a period of greater risk for early alcohol abuse.

Ireland

Scientists at Virginia Commonwealth University, Richmond, are studying families from Dublin, Belfast, and Galway to detect genes influencing predisposition to alcoholism. This is an important part of NIAAA's effort to conduct genetic linkage studies of alcohol dependence. To date, ascertainment and assessment have been completed on almost 300 families.

Italy

NIAAA participated in the Congresso Internazionale dei Docenti Universitari, Prevention Actions and Strategies for 2000, in Florence, Italy, on September 7–8, 2000. This congress included participation from Eastern and Western European countries working together to develop alcohol and health prevention priorities for the European Union. NIAAA participation was at the invitation of Italy, as an activity under the U.S.-Italy Science and Technology Agreement. Collaboration in the area of prevention research is a priority under this agreement.

Mauritius

Although aspects of the functioning of the autonomic and central nervous systems may predispose people to alcoholism in youth, there is a lack of long-term, prospective research on this topic. One study links past assessments of arousal via the nervous system at ages 3 and 11 years to current diagnoses of alcoholism and antisocial personality disorder at age 28 years. The investigators are studying 1,795 study participants from the general population of Mauritius who were tested at age 3 years in 1972 and retested at ages 8, 11, and 17 years. This information is also being linked to results of genetic testing of the participants. The data are being collected and analyzed.

New Zealand

New Zealand has the highest drowning rate in the world. The question of how alcohol may be a factor in drowning deaths in New Zealand is the focus of a study by researchers at the Center for Injury Research and Policy, Johns Hopkins University, Baltimore, Maryland. Preliminary data indicate that the quality and completeness of information from coroners' files is insufficient for an accurate estimate of the percentage of drownings in which alcohol was a factor.

Russia

Researchers from San Diego State University, California, together with scientists from the

State Research Institute of Psychiatry, Moscow, are studying alcohol-related neurodevelopmental disorders in children living in Russian orphanages and special boarding schools for the mentally handicapped. More than 1,700 children who were exposed to alcohol in utero were examined. The researchers are comparing children who were exposed to alcohol with those who were not exposed, for several neuropsychiatric dimensions (e.g., memory, attention, and cognition).

NIAAA is supporting scientists from Johns Hopkins University, Baltimore, in a study of mortality from alcohol-related injuries in Russia. These scientists, in collaboration with the National Center for Health Statistics, Centers for Disease Control and Prevention, are examining death certificates in Yakatinberg Oblast.

Medical education specialists from the University of Wisconsin, Madison, are working with specialists in infectious disease and narcology from Pavlov State Medical University, St. Petersburg. The goal is to develop a research-based curriculum for training of physicians and other health professionals working with patients who have HIV/AIDS and tuberculosis on how to deal with alcohol abuse and addiction.

Slovakia

Chronic alcohol consumption and chronic stress have each been shown to produce deleterious effects on bones, but the combined effects of both factors are not clear. Researchers at the University of New Jersey, Piscataway, and Rutgers University, New Brunswick, New Jersey, are working with investigators at the Slovak Academy of Sciences to understand the mechanisms of the development of osteoporosis in humans consuming a high level of alcohol and subjected to environmental stress. The researchers are using rats to evaluate the effects on bone by measuring bone quality and serum levels of osteocalcin, a bone protein. They evaluate bone quality by determining the strength required to break bones and the density gradient separation of finely powdered bone particles. The effects of stress are measured by evaluating biosynthesis of the enzymes of the catecholamine pathway. Preliminary findings led the researchers to conclude that decreased growth and bone osteocalcin in the rats were due to elevated corticosterone levels. Further experiments are being conducted to determine the interactive effects of ethanol and stress on bone quality.

South Africa

Scientists at Indiana University School of Medicine, Indianapolis, and the Foundation for Alcohol Related Research, University of Cape Town, are studying the genetic determinants of FAS. The genes for specific forms of alcohol dehydrogenase (ADH) in a group of children with FAS and their mothers were compared with the genes for forms of ADH in a control group of mothers who have normal children. ADH converts alcohol to acetaldehyde. The ADH2*2 allele, which produces a high-activity form of ADH, was significantly more common in the group of control mothers than in either the FAS children or their mothers. The results suggest that the form of ADH produced by this allele may have a protective effect against FAS. The presence of this allele has been associated with lower alcohol consumption in populations where the allele is more common.

Activities With International and Multinational Organizations

International Society for Biomedical Research on Alcoholism

NIAAA, the National Institute on Alcoholism in Japan, and Keio University cosponsored a workshop for new foreign investigators performing research on alcohol. The workshop focused on strategies for publishing scientific articles in English-language journals. Editors from five major publications on alcohol research took part in the interactive workshop that allowed investigators to bring articles they were working on for discussion and revision.

In addition, NIAAA will sponsor an international symposium on FAS, entitled Prenatal Alcohol Exposure: Advancing Knowledge Through International Collaborations, to be held in Valencia, Spain, on September 9–12, 2001. The meeting will feature speakers representing work in Germany, Japan, Russia, and South Africa.

International Council on Alcohol and Addictions

The 43rd International Conference on the Prevention and Treatment of Dependencies took place in Manama, Bahrain, in September 2000. NIAAA sponsored a symposium for specialists and policy makers on treatment of addiction that highlighted advances in prevention research and studies on gender and alcohol.

International Research Group on Gender and Alcohol

A 20-year study on problem drinking in women by researchers from the University of North Dakota, Grand Forks, includes a component on cross-national variation in women's drinking behavior and its antecedents and consequences. NIAAA has supported this work, which is carried out in collaboration with members of the International Research Group on Gender and Alcohol. This international team of researchers has found that, although gender ratios for specific drinking measures vary considerably across societies, the data confirm findings of other studies—that men consistently exceed women in average drinking frequency and in the quantity of alcohol consumed per drinking occasion. Across the countries studied, women were almost as likely as men to be current drinkers, but lifetime abstention from alcohol was more common among women than among men. The data suggest that any convergence in women's and men's drinking behavior has not progressed very far. For both sexes, the likelihood of abstaining from alcohol increased with increasing age. Across age groups, older drinkers drank smaller quantities of alcohol per occasion than younger drinkers did, but frequency of drinking did not change consistently with age.

World Health Organization

NIAAA supports the WHO-NIH Joint Project on Disablement. The major objective of this program is the development of an instrument that measures disability in patients who have mental disorders or disorders of alcohol use or drug use. An additional study of the State and Trait Markers of Heavy Alcohol Consumption is being conducted with support from NIAAA, WHO, and the International Society for Biomedical Research on Alcoholism.

Intramural Programs and Activities

During FY 00, 33 Postdoctoral Fellows representing 11 countries received training

under the mentorship of the senior scientists in the Division of Intramural Clinical and Biological Research. Twelve Senior Researchers and Guest Researchers representing nine countries conducted collaborative research projects along with senior scientists in the Division. In addition, staff in several of the Division's laboratories conducted joint research projects with scientists at foreign research institutions and made numerous scientific presentations at foreign institutions and meetings of international professional societies.

Laboratory of Membrane Biochemistry and Biophysics

In the Laboratory of Membrane Biochemistry and Biophysics, four studies are under way with investigators at foreign institutions. First, the Laboratory is working with scientists at the University of Leipzig, Germany, on a project to study (1) the structure and dynamics of membranes composed of lipids with polyunsaturated fatty acids, (2) lipid–protein interactions related to lipid polyunsaturation and alcoholism, and (3) the interaction of alcohol with proteins and lipids in biological membranes. Second, collaboration with the University of Barcelona, Spain, led to a publication discussing the implications of thiamine deficiency in cancer. Third, joint studies are being conducted with scientists at Oxford University, England, involving the effects of ethanol-induced change in hepatic voltage on (1) the gradients of all the amino acids between portal vein blood and liver and (2) the gradients of the nine major inorganic ions between intracellular and extracellular space in rats living in vivo. Finally, NIAAA staff and staff at Tottori University, Yonaga, Japan, are investigating the effects of ketone bodies on two neuronal culture models of common degenerative neurological diseases.

Laboratory of Molecular and Cellular Neurobiology

Scientists at the Laboratory of Molecular and Cellular Neurobiology are working with scientists at the National Center for Scientific Research, Strasbourg, France, to investigate alcohol actions on neuronal neurotransmitter receptors, by using electrophysiological techniques.

Laboratory of Neurogenetics

In a joint study of the Laboratory of Neurogenetics with the University of Helsinki, Finland, there was no significant association or linkage between OPRM1 (a μ opioid receptor) and alcohol dependence in three population samples. These results strongly suggest that variation at the μ opioid receptor is not involved in vulnerability to alcohol dependence.

Three studies are under way with the University of Pisa, Italy. The first study replicated an earlier finding that a variant in the promoter region of the gene for the serotonin 2A receptor is associated with anorexia nervosa, but not bulimia nervosa. The second study uses analysis with single-strand, conformational polymorphisms to screen the TDO2 gene for polymorphisms, to assess functionality, and to search for disease associations. The researchers successfully amplified most of the coding regions (11 of 12 exons and short regions of the introns), and they performed screening across populations with such conditions as anorexia, bulimia, major depression, autism, and alcoholism. In the third study, the scientists identified the 5HTTLPR promoter in a variety of populations with psychiatric conditions, including individuals with alcoholism.

In work with the Natal Institute of Immunology, South Africa, the investigators are constructing haplotypes from the collected genotypes and the parameters of population genetics to compare population diversities and associations between haplotypes and populations.

A study in collaboration with Karolinska Institute, Stockholm, Sweden, showed that the 5HT2A-1438G>A promoter variant is linked to anxiety-related conditions, including obsessive–compulsive disorder, seasonal affective disorder, and anorexia nervosa.