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National Institute on Alcohol Abuse and Alcoholism

INTRODUCTION

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is the primary Federal entity responsible for research on the causes, consequences, prevention, and treatment of alcohol-related problems. NIAAA conducts and supports biomedical and behavioral research into the effects of alcohol on the mind and body, prevention and treatment interventions, and the epidemiology of alcoholism and other alcohol-related problems.

NIAAA's international objectives are carried out through the International Research and Training Program. International activities throughout the offices and divisions of the Institute are coordinated through this Program. Using a variety of initiatives and mechanisms, NIAAA supports the research efforts of scientists worldwide who are investigating questions about alcohol use that are relevant to the U.S. population.

The International Research and Training Program serves as the point of contact for several bilateral agreements with foreign governments and multilateral agreements with international organizations. NIAAA is a designated World Health Organization (WHO) Collaborating Center for Research and Training on Alcohol Problems. The Program consists of international grants, medical education and research training, scientific exchange, and dissemination of information.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

NIAAA's very successful program of International Medical Education has been translated into five languages (Hungarian, Lithuanian, Polish, Russian, and Spanish) and implemented and evaluated in seven countries: Hungary, Lithuania, Mexico, Poland, Russia, the United States, and Venezuela. In fiscal year 1999 (FY 99), results from the ini-

tiative in Russia and Venezuela were added to those from earlier initiatives in Eastern Europe and Latin America. Plans are under way to test the model in Asia and Western Europe. Overall, the idea of screening and early intervention in primary care settings is valid for most countries, because of the small cost relative to the major health care costs and lost productivity of severe alcohol abuse and addiction.

NIAAA is involved in facilitating and participating in international research activities. The Institute sponsors a program announcement, Developmental Grants for Collaborative International Projects. This program teams established U.S. investigators with foreign investigators to develop new research projects on alcohol abuse and alcoholism that are the foundation for more intensive larger studies. Awards have been made for a number of projects over the past 3 years, and in FY 99, a new grant to evaluate a school-, home-, and community-based prevention intervention for sixth- and seventh-grade students in Moscow, Russia, was submitted and reviewed and will receive funding in FY 00.

Italy

An Exchange of Letters that identifies areas of cooperation in research on alcohol use between NIAAA and the Istituto Superiore di Sanità was signed by the directors of both institutes. This cooperation will facilitate U.S.-Italian collaborations in eight areas that are important to both countries: (1) moderation of alcohol consumption and reduction of cardiovascular disease; (2) study of alcohol use and health in aging populations; (3) prevention, early diagnosis, and treatment of alcohol-use disorders in primary care settings; (4) treatment efficacy; (5) medical education and training; (6) genetics; (7) development of standardized measures for international research on alcohol use; and (8) study of alcohol use and youth.

Russia

Since 1997, NIAAA has had the lead responsibility for research on alcohol-related problems, under the U.S.-Russia Binational Commission Subcommittee for Joint Activities on Identified Health Issues. The main emphasis on work with Russia is the formation of international teams of collaborators to develop and test effective screening and early intervention methods; prevention programs for preadolescents; and interventions aimed at reducing alcohol-related birth defects. Work with Russia in these areas significantly enhances the field as a whole and benefits the delivery of effective prevention and treatment in the United States.

In Russia, high rates of alcohol consumption have significant effects on health, including death from alcohol-related trauma. In FY 99, NIAAA, in collaboration with the National Center for Health Statistics and Johns Hopkins Center for Injury Research and Policy, Baltimore, Maryland, began a study to determine the relationship between alcohol use and the rising death rate in Russia from a number of violent causes, including drowning.

The Injury Mortality and the Role of Alcohol study is being conducted in Yekaterinburg and is building on earlier mortality studies that were conducted there by the National Center for Health Statistics. NIAAA support has allowed computer equipment to be provided to the Office of Health Statistics, at the coroner's office in Yekaterinburg, and a database of 1998-1999 deaths from injury in the city of Yekaterinburg has been established and will be extended into 2000. Demography experts from Russia and the United States will analyze the data and, for the first time, the Russian government will have access to the information necessary to define the extent of the problem and to develop appropriate prevention strategies.

Partners in Prevention, a highly productive collaboration between the University of Minnesota School of Public Health, Min-

neapolis, and the Institute Against Drug Trafficking, Moscow, completed a 2-year study testing the implementation of a school- and parent-based prevention program targeted to fifth graders in Moscow. The success of the program with parents, teachers, and school administrators has led to efforts toward its widespread dissemination throughout Russia. The Civilian Research and Development Foundation identified this project as an exemplary research study. The principal investigators for the project submitted a competitive grant application to test an expanded intervention on sixth and seventh graders and received funding to begin the project in the fall of 2000.

A comprehensive study of risk factors for alcohol use in women of childbearing age was completed by the Pavlov State Medical Academy, St. Petersburg, who worked closely with the University of North Dakota School of Medicine and Health Sciences, Grand Forks. Results of this survey of 1,000 individuals are being used to develop programs for prevention of alcohol abuse for Russian women who are pregnant or planning to become pregnant.

Alcohol-related birth defects, including fetal alcohol syndrome (FAS), are the focus of a collaborative partnership between the Center for Behavioral Teratology, San Diego State University, California, and the Institute of Psychiatry, Moscow. U.S. experts in research on the fetal effects of maternal alcohol consumption have teamed with Russian experts in mental retardation, pediatrics, and epidemiology to determine the nature and extent of alcohol-related birth defects in Russian children. Study results will be used to develop better diagnostic and referral systems and educational interventions.

NIAAA and the First Moscow Medical Academy are working together to transfer research-based knowledge about the prevention and treatment of alcohol-use disorders into the Russian medical education system. This highly successful initiative focuses on developing faculty in the primary care specialties to improve teaching and clinical skills in the early identification and treatment of alcohol-related problems. Faculty from 18 departments of family medicine at Russian medical academies have been trained and are part of an ongoing research

effort to contribute to new developments in Russian preventive medicine.

South Africa

A highly productive collaborative research program on FAS has been undertaken in the Western Cape province of South Africa. This work involves leading scientists from the United States and South Africa. The project is included as a significant agenda item for the Health Working Group of the Gore-Mbeki Binational Commission. The overall goals are as follows:

1. to build a multidisciplinary and multicultural team of scientists and clinicians from universities in the United States and South Africa;

2. to work with the government and non-governmental organizations of South Africa in developing capabilities and methods to 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 the 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 the team approach.

Significant progress has been made in establishing a minimum prevalence of FAS among first-grade students in one city in the Western Cape. The results of two screening and diagnostic efforts indicate a prevalence of 5%–7% among the 1,800 students examined. Diagnosis involves maternal interviews, neurobehavioral testing, and examination by a dysmorphologist. The screening methods developed and used will be the standard for active case studies in the United States, and the publication of research reports is in progress. Initial developmental testing of children with FAS and control subjects indicates a specific pattern of deficits and strengths. Plans have been made to strengthen and expand the testing procedures to clarify the findings. The methods used and tests selected were developed by U.S. scientists expert in assessing Native American children with FAS, in collaboration with South African specialists in child development. Metabolism and genetic pilot

projects are under way to determine why some women who drink similar amounts of alcohol have affected children and some have normal children.

The General Electric Corporation, Milwaukee, Wisconsin, donated ultrasonography equipment to monitor alcohol-related, high-risk pregnancies in this area of the Western Cape. Ultrasonograms may provide information to assist in prenatal diagnosis of alcohol-related fetal heart problems, which may lead to early interventions. The city that serves as the study site is in the process of launching a campaign for prevention of alcohol abuse as a result of a workshop and prevention training effort provided by the U.S. team. The team developed plans to implement aspects of the procedures and methods used in South Africa, in Washington, D.C., and other sites in the United States.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Australia

Using data from Australia's twin registry, scientists from the Queensland Institute of Medical Research, Brisbane, and the University of Missouri, Columbia, are studying the relationship between alcohol dependence and conduct disorder and their genetic transmission. This study is the first time a two-generation, twin-family design has been implemented in a study on alcoholism.

Another project at the Queensland Institute is a longitudinal study to examine the persistence of and change in drinking habits by following twin pairs born between 1964 and 1971.

Canada

Researchers at the University of Guelph, Ontario, are studying alcohol-induced liver damage in situ by using a unique noninvasive technique called functional magnetic resonance imaging. The technique will measure changes in oxygen levels in the sinusoids of the liver of rats receiving long-term ethanol treatment alone or simultaneously subjected to challenge with ethanol or hypoxia. Oxygen levels in the liver are elevated to determine whether ethanol treatment leads to hypoxia, which plays an important

role as a cause of early ethanol-induced liver injury. Results of this project will help in the development of a simple, noninvasive, clinical diagnostic test for early prediction of liver disease in persons with alcoholism.

In experimental animals, chronic ethanol intake during pregnancy 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, investigators at the University of British Columbia, Vancouver, are using an animal model to investigate the effects of chronic alcohol consumption on calcium regulation and bone during pregnancy in both the mother and the 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 lack of regulation of calcium levels in the mother.

Researchers at the Addiction and Mental Health Services Corporation, Ontario, are investigating the impact of self-help interventions in a general population. This project uses an experimental trial to assess the effectiveness of self-help books and personalized assessment feedback interventions, both separately and in combination.

Investigators at the Pacific Institute for Research and Evaluation, Bethesda, Maryland, and the Driver Control Board of Alberta are taking advantage of legislation in Alberta to conduct studies on the effectiveness of breath-activated alcohol safety interlocks on the vehicles of drivers who have been convicted of offenses for driving under the influence (DUI) of alcohol. A breath-activated alcohol safety interlock prevents a vehicle from starting until the driver breathes into an apparatus that measures blood alcohol level. The vehicle will not start if any alcohol registers on the scale. The project examines the effectiveness of the interlocks in preventing involvement in crashes and recidivism of DUI offenses among first offenders. It also evaluates the potential of a parallel case management intervention to provide continuing health services in an attempt to reduce recidivism.

Researchers at the Addiction Research

Foundation, Toronto, Ontario, are conducting a historical case study of the London Gin Epidemic (1720–1751) and the Gin Act of 1736, to determine factors that influence the formulation of alcohol control policy and its impact on alcohol consumption. They determined that class, gender, and social networks were key factors and are now focusing on the impact of standard of living, legislative constraints, and alcohol prices and taxes.

England

Although aspects of autonomic and central nervous system functioning may predispose individuals to alcoholism in youth, there is a lack of long-term prospective research on this topic. Investigators at the University of Southern California, Los Angeles, and the University of York, England, are collaborating to study (1) deficits in the autonomic nervous system and the central nervous system (i.e., low arousal) and (2) increased alcoholism in criminals with antisocial personality disorder (schizotypal criminals). This study links past assessments of nervous system arousal at ages 3 and 11 years to current diagnoses of alcoholism and antisocial personality at age 28 years. The 1,795 study subjects are from the general population of Mauritius; they were tested at age 3 years in 1972 and retested at ages 8, 11, and 17 years. Findings suggest that schizotypal persons are a relatively distinct group, which is most strongly indicated by increased alcoholism and less strongly indicated by reduced orienting response. The investigators hypothesize that reduced orienting in schizotypal persons may partly reflect dysfunction in the prefrontal brain, which increases risk for alcoholism.

Finland

Researchers at the University of Indiana, Indianapolis, analyzed data from an age-standardized, population-based sample of 5,700 Finnish twins. They showed that socio-regional variation, reciprocal sibling interactions, and parental drinking patterns influence abstinence from alcohol at ages up to 16 years more than genetic factors do. These results demonstrate how genetically informative data can guide prevention efforts by identifying target variables.

In a second study, this research group is using structured interviews and school-based

peer and teacher ratings to analyze subsamples of Finnish families with a high percentage of members at risk for alcoholism. Findings show that, at age 12 years, twin children from at-risk families are behaviorally differentiated in ratings by their classmate peers: these twins are more aggressive and less compliant and are reported to consume more alcohol at age 14 years. The behavioral dimensions shown to be relevant to risk are also shown to be moderately heritable, inviting more detailed genetic analyses as the twins move through mid-adolescence and into a period of greater risk for early alcohol abuse.

Italy

Bowman Gray School of Medicine, Winston-Salem, North Carolina, and the University of Cagliari, Sardinia, completed a joint study that characterizes the neuropharmacological basis of the subjective effects of alcohol in selected rat lines. These rats were bred in Italy for alcohol preference or nonpreference. The rats with alcohol preference displayed behaviors indicating anxiety; the rats that did not prefer alcohol did not display anxiety. These findings allowed investigators to examine the link between antigenic phenotype and high alcohol consumption.

Mexico

Researchers from the Pacific Institute for Research and Evaluation, Bethesda, Maryland, are evaluating efforts to reduce “binge” drinking on the U.S.-Mexico border near Tijuana, Mexico. Tijuana, with a drinking age of 18 years, low prices for alcohol, and a cluster of 39 bars in a four-block area, caters to young drinkers from San Diego, California. Breath test surveys of those reentering San Diego after a night of drinking in Tijuana indicate that approximately 30% have blood alcohol concentrations higher than 0.08. The Safe Border Project, which is being evaluated in this study, is a coordinated community effort featuring enhanced enforcement of drinking laws; a center to offer logistic support for detaining highly impaired persons crossing the border and for providing transportation home; and a strong media advocacy program.

Investigators from the Mexican Institute of Psychiatry, Mexico City, and the Alcohol Research Center, Berkeley, California, completed a test of screening instruments for

use in emergency department settings. The instruments were tested on samples of Mexican and Mexican-American patients, and results were compared with results in samples of Hispanics from the general U.S. population. The data suggest different performance of screening instruments among Hispanics in the general population than among Hispanics in Mexico and in the United States. The study also indicated an instrument that may be most useful in identifying alcohol-use disorders in the Hispanic general population.

New Zealand

Researchers from Johns Hopkins Center for Injury Research and Policy, Baltimore, are working in New Zealand on a study of alcohol-related drowning and serious boating injuries. This project extends research conducted in Maryland and North Carolina into New Zealand, where a review of coroner's records and data gathered from police reports and inquest statements will provide the first comprehensive data on involvement of alcohol use in boating injuries.

Poland

The Institute of Psychiatry and Neurology, Warsaw, Poland, and the University of Wisconsin, Madison, completed work on a clinical trial of early intervention in alcohol use in primary care settings. Preliminary results indicate that intervention with patients in the Polish primary health care system who are at risk for alcohol abuse is effective in reducing drinking.

Russia

Researchers at Yale University, New Haven, Connecticut, and the Leningrad Regional Dispensary of Narcology, St. Petersburg, successfully completed a study of interactive ethanol-like cognitive and behavioral effects of nimodipine and ketamine in abstinent persons with alcoholism.

Slovakia

Chronic alcohol consumption alone and chronic stress alone have been shown to produce deleterious effects on bones, but the combined effects of both factors are not clear. Investigators at Rutgers, the State University of New Jersey, Piscataway, and the Slovak Academy of Sciences are collaborating to understand the mechanisms of the

development of osteoporosis that occurs at high levels of alcohol consumption accompanied by environmental stress. The experiments are being conducted on rats. Effects on bone are being evaluated by measuring bone quality and serum levels of osteocalcin, a bone protein. Bone quality is determined by measurement of strength required to break bones and density gradient separation of finely powdered bone particles. The effects of stress are monitored by evaluating biosynthesis of the enzymes of the catecholamine pathway. Researchers at the Slovak Academy of Sciences are investigating the effects of chronic alcohol consumption and stress on plasma catecholamine levels, biosynthesis of catecholamines, and gene expression of catecholamine biosynthetic enzymes. This collaborative study may unravel the mechanisms of interactive effects of alcohol and stress on various bone disorders, including osteoporosis.

South Africa

Investigators at Indiana University School of Medicine and the University of Cape Town School of Medicine are using ultrasonography to identify the effects of alcohol on the fetus. These effects will be correlated with maternal drinking patterns and genotype for alcohol-metabolizing enzyme. To date, 42 children who have FAS, their mothers, and 95 control subjects have been entered in the study and genotyped for alcohol dehydrogenase and aldehyde dehydrogenase alleles.

NIAAA is supporting a scientific meeting entitled Addressing Addiction Through Health and Social Systems, which is scheduled to be held in Cape Town, on September 21–25, 2000. This is the ninth annual meeting of the International Conference on Treatment of Addictive Behaviors. It brings together clinical and scientific colleagues to address treatment issues and to bring research findings into clinical practice. Professionals from throughout South Africa, as well as a number of developed and developing countries, will convene to determine how best to identify and intervene with people who use alcohol or drugs or have other addictive behaviors.

Activities With International and Multinational Organizations **International Council on Alcohol and Addictions**

NIAAA sponsored an important symposium at the 38th International Congress on Alcohol, Drugs, and other Dependencies, the annual meeting of the International Council on Alcohol and Addictions. The symposium, Contemporary Treatment for Alcohol Problems and the Role of Research, highlighted recent advances in research that are improving clinical treatment. Sessions included presentation of findings from studies of behavioral treatment; advances in neuroscience that have led to new pharmacological therapies for treatment of addictions; new understandings about patient motivation to change behavior and how this knowledge can be applied to treatment of alcohol abuse and addiction; and the latest research in treating alcohol addiction in women and adolescents.

World Health Organization

NIAAA continues to have a significant role in the WHO-NIH (National Institutes of Health) Joint Project on Disablement. The major objective of the program is to develop an instrument that will measure disability in patients who have mental disorders, alcohol-use or drug-use disorders, or combinations of these disorders. Such an instrument is very much needed in epidemiologic, clinical, and health services research on these disorders.

The Institute also supports a joint effort between WHO and the International Society for Biomedical Research on Alcoholism to study State and Trait Markers of Heavy Alcohol Consumption and Alcoholism. The first goal of this project is to develop biological screening tools that can, with good sensitivity and specificity, identify problem drinkers. The second goal is to begin to develop diagnostic "trait" markers that would provide information on genetically determined predisposing and protective factors in the development of alcoholism.

Intramural Programs and Activities

During FY 99, 24 scientists representing 12 countries conducted research in NIAAA's intramural laboratories. In addition, NIAAA intramural scientists were involved in a

number of collaborative projects with researchers in foreign laboratories.

Laboratory of Clinical Studies

The Laboratory of Clinical Studies is performing research in conjunction with University College, London, England, and the University of Haifa, Israel. These projects aim to uncover, assess, and contrast mechanisms that are responsible for impairments in cognitive functioning in different forms of neuropsychiatric disorders. The emphasis is on syndromes associated with alcohol abuse and on understanding how drugs alter cognitive functioning and memory in persons with alcoholism. Together with scientists at the University of Würzburg, Germany, and Karolinska Hospital, Stockholm, and Uppsala University, Sweden, NIAAA scientists have developed a primate model to investigate the role of genes and environment in alcohol abuse, by using a developmental paradigm.

Laboratory of Genetics

In the Laboratory of Genetics, scientists from the University of Helsinki, Finland, are working with NIAAA intramural scientists on studies of individuals and animals with genetic defects in serotonin function that can shed light on the role of this neurotransmitter in behavior. They are also looking at the role of milder functional variants in serotonin genes in predisposing individuals to psychopathologic conditions and alcoholism. Work in conjunction with Karolinska Hospital, Stockholm, is focused on the identification of individuals with a deficit of serotonin metabolism in the central nervous system, which is postulated to be connected with behaviors characterized by deficient impulse control, including alcoholism.

Researchers from NIAAA, McGill Univer-

sity, Montreal, Quebec, the University of Helsinki, Finland, and the University of Pisa, Italy, are conducting a study of TD02 gene polymorphisms. Through screening, they are assessing functionality and searching for disease associations based on the possibility that genetic defects in the enzymes involved in serotonin metabolism may contribute to a wide range of neuropsychiatric diseases, from eating disorders and obsessive-compulsive disorders and alcoholism to autism.

Scientists from NIAAA, Seoul National University, Korea, and the Taipei Blood Center, Taiwan, are studying sequence variation in the nonpseudautosomal region of the Y chromosome in the Hominidae family of primates and between genuses in the Hominidae family. The findings could elucidate Y chromosome evolution and paternal history in the human population.

Finally, the Netherlands Institute for Public Health, Leiden, is working with NIAAA to study the effects of alcohol intake on genomic DNA.

Laboratory of Membrane Biochemistry and Biophysics

In the Laboratory of Membrane Biochemistry and Biophysics, five studies are being conducted that involve collaboration with foreign institutions.

Researchers at the Institute of Nutrition and Food Technology, University of Chile, Santiago, are studying desaturation of essential fatty acids, by using stable isotope gas chromatography mass spectroscopy. This metabolic study of persons with alcoholism suggests new mechanisms that may underlie effects of fatty-acid concentrations in tissues.

A collaboration with scientists from NIAAA, Oxford University, England, and Tottori University, Japan, is aimed at increasing understanding of the metabolic dis-

order common to many diseases. Findings may lead to the possibility of dietary treatments for conditions such as Parkinson's disease and Alzheimer's disease. In another joint study with Oxford University, scientists are investigating Ion Gradients and Metabolic Energy in Animal Tissue, in an effort to improve treatment for patients with trauma, burns, or postsurgical resuscitation.

Using nuclear magnetic resonance imaging, scientists in the Laboratory of Membrane Biochemistry and Biophysics are investigating cell membrane structure in collaboration with scientists at the University of Leipzig, Germany. They are exploring the interaction of alcohol with proteins and lipids in biological membranes and the structure and dynamics of membranes composed of lipids with polyunsaturated fatty acids and β lipid-protein interactions related to alcoholism and lipid polysaturation.

Okayama University Medical School, Japan, is working with NIAAA intramural scientists on nutritional effects on the composition of essential fatty acids. They are performing an investigation of dietary deficiency in omega-3 fatty acids during the crucial period of development of the nervous system in infants.

Laboratory of Molecular and Cellular Neurobiology

The Laboratory of Molecular and Cellular Neurobiology, in collaboration with the University of Helsinki, Finland, is investigating the molecular basis of the actions of alcohol in the nervous system, by using techniques of molecular biology. A collaboration with the Tonji Medical University, China, is using electrophysiological techniques to study alcohol actions on neuronal neurotransmitter receptors.

