NIAAA SPECTRUM

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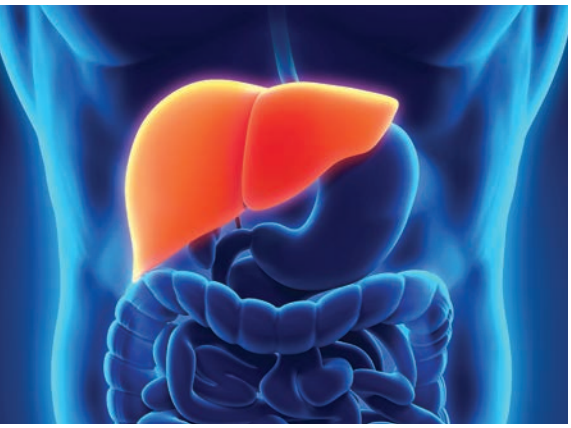
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Institute on Alcohol Abuse and Alcoholism

FEATURE

DRINKING AND THE LIVER: SEEKING BETTER TREATMENTS FOR ALCOHOLIC LIVER DISEASE



The liver is an impressive organ. Housed under the rib cage on the right side of the stomach, it performs hundreds of functions, from detoxifying the body of chemicals to metabolizing drugs, digesting foods, and making proteins important for blood clotting. Weighing in at three pounds, it is second in size only to the skin. Damage to this vital organ can be life-threatening, and excessive drinking continues to be one of the leading causes of liver disease. Alcohol was involved in 46 percent of the nearly 72,000 liver disease deaths in 2013.

As the head of NIAAA's Section on Liver Biology and Laboratory of Liver Diseases for the past 15 years, Bin Gao, M.D., Ph.D., works to understand alcoholic liver disease and to reduce illness and death caused by the disease.

"We have two major focuses—the first is to study the pathogenesis of alcoholic liver disease and the second is to try and find novel therapeutic targets," says Dr. Gao.

Alcoholic liver disease refers to a broad range of liver injury caused by drinking, he explains. Some forms are mild and reversible while others, such as cirrhosis and severe alcoholic hepatitis, are life-threatening and irreversible. Fatty liver disease, an early form of alcoholic liver disease marked by a build-up of fat in liver cells, occurs in almost all heavy drinkers, but liver damage can usually be reversed if an individual stops drinking. However, about 20 to 40 percent of heavy drinkers will develop more severe forms of alcoholic liver disease, including alcoholic hepatitis, which involves inflammation and swelling of the liver, and cirrhosis, a condition that can lead to liver failure as scar tissue accumulates on the organ.

In 2013, Dr. Gao's lab fundamentally changed how these more severe forms of the disease are studied when he and his team developed a clinically relevant animal model of alcoholic hepatitis. By incorporating both chronic and binge drinking, the model accurately replicates the kind of liver damage seen in people who are heavy drinkers.

"This model really mimics the drinking pattern in patients with alcoholic hepatitis, so it has now been used by many, many labs. It replaces the previous model that had been used over the past 40 years," says Dr. Gao.

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FEATURE

NIH HOLDS COMPETITION TO CREATE BETTER WEARABLE ALCOHOL BIOSENSOR

First prize winner will be awarded $200,000

To promote the development of a wearable, discreet device capable of measuring blood alcohol levels in real time, NIAAA has issued the Wearable Alcohol Biosensor Challenge. A wearable biosensor will aid researchers, clinicians, therapists, and individuals by providing more accurate data on how much an individual is drinking.

Current biosensor bracelets commonly used in the criminal justice system are effective but cumbersome and only take readings every 30 minutes. A winning prototype in the NIAAA Challenge would need to improve on existing technology by providing real-time monitoring in an inconspicuous package that appeals to the general public.

NIAAA is looking for innovation using a non-invasive design, which could take the form of jewelry, clothing, or another format that remains in contact with the body. The device must be able to measure blood alcohol level, interpret and store the data, or transmit it to a smartphone or other device by wireless transmission.

"This project is designed to stimulate investment from public and private sectors in the development of improved alcohol biosensors that will be appealing to researchers, treatment providers, and individuals," says George F. Koob, Ph.D., director of NIAAA.

A number of medical conditions are exacerbated by alcohol, including liver disease and HIV/AIDS. Research that seeks to understand the progression of these diseases and potential treatments depends on the ability to accurately measure alcohol use. Wearable alcohol biosensors will simplify the process for scientists, study participants, therapists, and individuals.

Well-calibrated alcohol biosensors will provide an objective measure of alcohol

consumption, and participants will be able to avoid the inconvenience and discomfort of having blood drawn at regular intervals. The data collected would also be more accurate than self-report. In addition, people concerned with their personal drinking, or who are in treatment for alcohol problems, will be able to use the devices without stigma.

Competition submissions should include a working prototype, data

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NEWS FROM THE FIELD

STUDY DEFINES BRAIN AND BEHAVIORAL EFFECTS OF TEEN BINGE DRINKING

Adolescent binge drinking can disrupt gene regulation and brain development in ways that promote anxiety and excessive drinking behaviors which can persist into adulthood, according to a study published online in the journal *Neurobiology of Disease*.

These behaviors likely were the result of epigenetic changes, which are chemical modifications to DNA or DNA proteins that regulate gene activity without making changes to the underlying DNA sequence.

Previous studies have shown that people who start drinking before the age of 15 are four times more likely to meet the criteria for alcohol dependence at some point in their lives than those who delay drinking until age 21, and that young people consume more than 90 percent of their alcohol by binge drinking.

Researchers led by Subhash C. Pandey, Ph.D., of the University of Illinois at Chicago and a Research Career Scientist at Jesse Brown Veteran Affairs Medical Center in Chicago, investigated the effects of intermittent binge alcohol exposure during the adolescent stage of development in rats. To model adolescent binge drinking in humans, the researchers gave 28-day-old rats alcohol for 2 days in a row, followed by 2 days off, and repeated this pattern for 13 days. Some rats were followed into

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To further validate the new animal model, Dr. Gao recently worked with several clinical investigators to compare its gene profile with liver samples from patients with alcoholic hepatitis. The researchers identified several key factors that promote inflammation present in both samples, suggesting they may contribute to the progression of alcoholic hepatitis.

Dr. Gao's lab has also made strides toward the development of new medications to treat alcoholic hepatitis. Currently there are no effective drug treatments for the disease. The mortality rate for patients who seek treatment for severe alcoholic hepatitis is estimated to be about 50 percent.

Fortunately, Dr. Gao's work is moving us closer to some answers. For more than 10 years, his lab has investigated interleukin–22 (IL–22), a cytokine, or cell signaling molecule that is produced by immune cells. In 2004, the team discovered that IL–22 helps protect against liver damage and is a key survival factor for liver cells. Later, many follow-up studies by Dr. Gao's group and other researchers demonstrated that IL–22 is also an important factor in protecting against cell damage in other organs, including the kidney, pancreas, lung, and gut.

"This is probably the only cytokine produced by immune cells that does not target immune cells, because they have no receptor for this cytokine. Instead the main target is epithelial cells in the body. In the liver this is mainly hepatocytes [chief cells of the liver] so it's very, very specific," explains Dr. Gao.

Dr. Gao hopes that this specificity translates into a drug with few side effects. Clinical trials are currently underway to test an experimental drug that targets IL–22 in alcoholic hepatitis patients.

As part of the broader NIAAA research community, Dr. Gao is not alone in this quest to understand the effect of alcohol on the liver. Several NIAAA-funded extramural research consortia are also involved in the search for novel therapeutics to treat alcoholic hepatitis. The DASH (Defeat Alcoholic Steatohepatitis) and TREAT (Translational Research and Evolving Alcoholic Hepatitis Treatment) consortia are testing new therapies, including probiotics; an IL–1 inhibitor; an activator of the farnesoid X receptor; and immunoglobulin, which binds lipopolysaccharide in the gastrointestinal tract. The InTeam (Integrated Approaches for Identifying Molecular Targets in Alcoholic Hepatitis) consortium is conducting translational research to look for novel therapeutic targets, and the Southern California Alcoholic Hepatitis Consortium is studying inflammatory mechanisms in alcoholic hepatitis.

Ultimately, the future of treatment for alcoholic liver disease may lie in combination therapies. Physicians currently use a variety of anti-inflammatory drugs to suppress inflammation, as well as drugs that both protect against liver cell injury and promote their regeneration.

As Dr. Gao explains, "Alcoholic liver disease is not a single disease. The future is probably combination therapy with several different strategies or drugs in order to treat those patients."

adulthood and observed for abnormal behaviors. They were offered both alcohol and water, and their alcohol-drinking behavior was monitored.

Rats exposed to alcohol during adolescence exhibited changes in behavior that lasted into adulthood, long after their adolescent binge exposure to alcohol had ended. For example, they showed increased anxiety-like behaviors and drank more alcohol in adulthood.

Prior research has implicated a brain structure known as the amygdala in anxiety and alcohol-drinking behaviors. When Dr. Pandey and his colleagues analyzed the amygdalas of alcohol-exposed rats in their study, they found that the complex of DNA and histone proteins within the amygdala cell nuclei appeared to be tightly wrapped. They also found increased levels of a protein called HDAC2, which modifies histones in a way that causes DNA to be wound tighter around them. Collectively, these kinds of changes to DNA or its associated proteins, which change its function but do not affect the DNA sequence, are referred to as epigenetic changes.

Dr. Pandey and his team found that the epigenetic changes they observed in alcohol-exposed rats were linked to lowered expression of two genes—brain-derived neurotrophic factor and activity-regulated cytoskeleton-associated protein—that nerve cells need to form new connections with each other. The diminished expression of the genes persisted into adulthood, even if alcohol exposure was stopped weeks before, and the researchers observed diminished nerve connectivity in the amygdalas of these affected adult rats. The researchers then showed that a drug which blocks the activity of HDAC2 could loosen the coiling of DNA in the amygdala cell nuclei of alcohol-exposed rats, and thus increase the expression of the gene needed for nerve cell connectivity in those animals. The animals then also exhibited less anxiety and reduced alcohol intake.

Source:
Pandey, S.C.; Sakharkar, A.J.; Tang, L.; and Zhang, H. Potential role of adolescent alcohol exposure-induced amygdaloid histone modifications in anxiety and alcohol intake during adulthood. *Neurobiology of Disease*. March 24, 2015 [Epub ahead of print] PMID: 25814047

SPOTLIGHT

NEW NESARC DATA AVAILABLE

NIAAA's fourth national epidemiologic survey is complete, and information about accessing the data is now available on the NIAAA Web site. The National Epidemiologic Survey on Alcohol and Related Conditions–III (NESARC–III) includes information on alcohol and drug use and disorders, related risk factors, and associated physical and mental disabilities. Over the course of a year, beginning in February 2012, data were collected from 36,309 subjects using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS–5). Saliva was also collected and is being stored for future DNA analysis. NESARC–III is a cross-sectional survey, based on a nationally representative sample of the civilian non-institutionalized population of the United States aged 18 years and older. It was sponsored, designed, and directed by NIAAA.

NIAAA encourages investigators to use this important data resource. To request access to the NESARC–III, follow the procedures outlined on the Web site, including completing and signing the Data Use Agreement.

For information, visit http://www.niaaa.nih.gov/research/nesarc-iii.

SPOTLIGHT

DR. GEORGE KOOB SPEAKS AT CONGRESSIONAL BRIEFING ON ALCOHOL AND PREGNANCY

Dr. George Koob speaking at the Friends of NIAAA–sponsored Congressional Briefing, Alcohol and Pregnancy: An Overview of Fetal Alcohol Spectrum Disorders, on April 13, 2015.

The briefing included presentations by Dr. Kenneth Warren, NIAAA Deputy Director; Kathleen Mitchell, National Organization on Fetal Alcohol Syndrome (NOFAS); and Dr. Edward Riley, San Diego State University.

SPOTLIGHT

DR. SANJAY GUPTA VISITS THE NIAAA BAR LAB

CNN Chief Medical Correspondent and neurosurgeon, Sanjay Gupta, M.D., (middle) met with NIAAA Director George Koob, Ph.D., (right) at NIAAA's research laboratory designed as a virtual bar when he visited NIH on March 25, 2015, to deliver the annual J. Edward Rall Cultural Lecture. Dr. Gupta hopes to use information from this meeting and subsequent discussions for a possible future CNN story about NIAAA's research on developing medications to help people with alcohol use disorder. Lorenzo Leggio, M.D., Ph.D., M.Sc., (left), of the NIAAA and NIDA Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology also participated in the visit. Through the NIH and NIAAA Communications offices, Dr. Gupta was offered several options for his Clinical Center visit and selected only this NIAAA lab for a personal tour and interview. Dr. Leggio uses the virtual bar to explore alcohol triggers and to test potential new medications.

SPOTLIGHT

NIAAA CHATS WITH STUDENTS ABOUT ALCOHOL ON DRUG FACTS CHAT DAY

For the fifth year in a row, NIAAA participated in Drug Facts Chat Day, an annual live online chat hosted by the National Institute on Drug Abuse (NIDA). During Chat Day, high school students from around the country ask thousands of questions about drugs and alcohol. Subject matter experts from NIAAA, NIDA, the National Institute of Mental Health (NIMH), and the U.S. Food and Drug Administration (FDA) respond in real time with science-based answers. Each expert is paired with an editor to ensure answers are understandable. Because the chat is anonymous, students feel comfortable asking about topics that can be tough to address face to face.

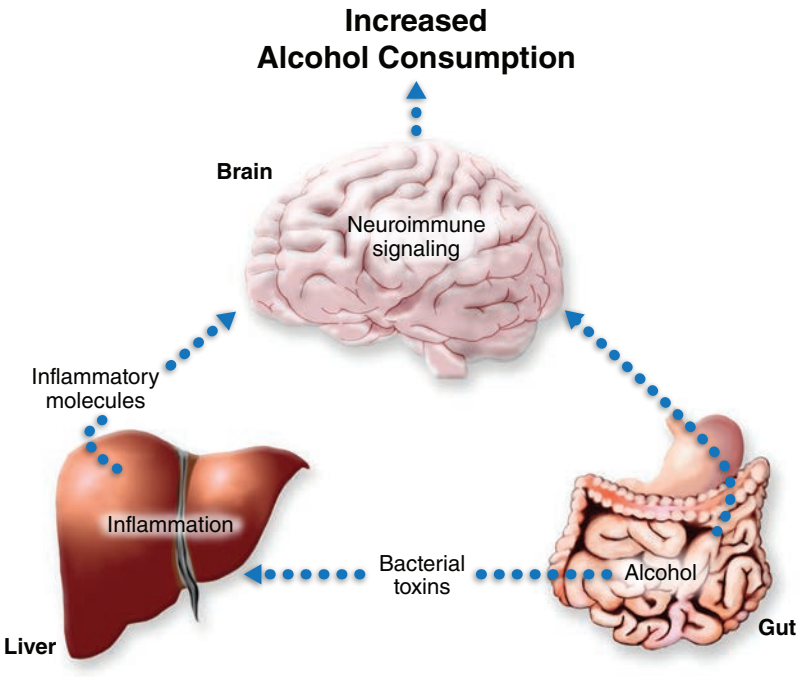
As in past years, Aaron White, Ph.D., Senior Scientific Advisor to the Director, was paired with editors Shuly Babitz and Erin Bryant, both in the Communications and Public Liaison Branch (CPLB). Together, the team fielded more than 230 alcohol-related questions. Common ones included: How many teen lives are lost to alcohol; what is alcohol made from; how does alcohol damage the liver, brain, and the rest of the body; and can you drink during pregnancy? For these questions, the NIAAA team offered factual answers and links to resources, including *Rethinking Drinking: Alcohol and Your Health*, *Beyond Hangovers: Understanding Alcohol's Impact on Your Health*, and the Cool Spot Web site. Some questions required a bit more creativity to answer effectively, including what happens when my dog drinks alcohol and why does alcohol make me dance better.

Aaron White and Shuly Babitz answer questions from high school students at Drug Facts Chat Day.

"I always enjoy answering the questions students have during Chat Day. This is a great opportunity to hear what kids are curious about and offer them solid, scientific information," said Dr. White.

A CLOSER LOOK

A GUT REACTION: THE GUT-LIVER-BRAIN AXIS AND ALCOHOL USE DISORDER



Adapted from: Mayfield, Ferguson, and Harris (2013)

Recent research has implicated immune signaling in the gastrointestinal tract, liver, and brain in the development of alcohol use disorder (AUD). The human gastrointestinal tract, or gut, is home to trillions of microorganisms. Researchers have found that excessive alcohol consumption makes it easier for bacterial toxins in the gut to escape into the bloodstream. Once in circulation, these toxins can trigger an inflammatory response in the liver and other organs.

Scientists have long known that liver inflammation resulting from long-term, excessive drinking can lead to alcoholic liver disease. Newer research suggests that inflammatory molecules generated in the liver could partly contribute to an immune response in the brain. Studies have found that alcohol also directly triggers immune signaling in the brain. Several lines of evidence suggest that this neuroimmune signaling, in turn, contributes to increased alcohol consumption and the development of AUD.

Neuroimmune signaling and the activity of immune-related genes in the brain are increased in mouse models of chronic alcohol consumption, whereas mice lacking neuroimmune-related genes drink less alcohol than mice with these genes. Research with rodents has also found that administration of bacterial toxins increases alcohol consumption and that certain immune factors act through the brain's stress systems to promote anxiety following alcohol withdrawal.

Research with humans also supports a role of the neuroimmune system in the development of problem alcohol use. For example, the activity of inflammatory molecules and immune-related genes is altered in the brains of individuals with AUD, and variants of certain immune-related genes are associated with an increased risk for AUD. In addition, alcohol craving and consumption correlate with levels of inflammatory molecules and bacterial toxins circulating in the blood of people diagnosed with AUD.

Taken together, these data suggest that immune pathways may be promising targets for treating AUD. Indeed, anti-inflammatory compounds have been shown to reduce alcohol consumption in animal models of alcohol dependence, suggesting that pharmacological modulation of immune pathways may be an effective treatment strategy for AUD. Going forward, NIAAA will support research to evaluate additional anti-inflammatory agents as possible treatments for AUD and support studies to further illuminate how the gut, liver, and brain interact to promote AUD and other alcohol-related diseases.

Sources:
Crews, F.T.; Qin, L.; Sheedy, D.; et al. High mobility group box 1/Toll-like receptor danger signaling increases brain neuroimmune activation in alcohol dependence. *Biological Psychiatry* 73(7):602, 2013. PMID: 23206318

Knapp, D.J.; Whitman, B.A.; Wills, T.A.; et al. Cytokine involvement in stress may depend on corticotrophin releasing factor to sensitize ethanol withdrawal anxiety. *Brain, Behavior, and Immunity* 25:S146–S154, 2011. PMID: 21377524

Mayfield J.; Ferguson L.; and Harris R.A. Neuroimmune signaling: A key component of alcohol abuse. *Current Opinions in Neurobiology* 23(4):513–520, 2013. PMID: 23434064

Wang, H.J.; Zakhari, S.; and Jung, M.K. Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. *World Journal of Gastroenterology* 16(11):1304–1313, 2010. PMID: 20238396

5 QUESTIONS WITH . . .

PEGGY MURRAY, PH.D.,

Director, Global Alcohol Research Program, Office of the Director, NIAAA

1 What is the Global Health Research Program at NIAAA?

The Global Alcohol Research Program is an NIAAA-wide initiative that spans several offices and divisions in the Institute. It has two main goals—to further NIAAA's research agenda through the development of scientific collaborations among U.S. and foreign investigators, and second, to disseminate throughout the world our alcohol research-based knowledge—including the health effects of alcohol, biomedical and epidemiological discoveries that underlie effective treatment and prevention interventions for alcohol use disorder, and scientific findings from the clinical development and testing of effective treatments and prevention interventions.

2 Why is global research an important component of NIAAA's portfolio?

First of all, we recognize that alcohol misuse is a problem worldwide, and global challenges require global solutions. Alcohol is consumed all over the world, and alcohol-related problems are not unique to any particular country. Research on alcohol use disorder is conducted in many countries throughout the world, and supported by government and non-government organizations.

The World Health Organization (WHO) has estimated that there are about 2 billion people worldwide who consume alcoholic beverages, with 76.3 million diagnosed with alcohol use disorder. The global public health burden related to alcohol consumption in terms of both morbidity and mortality is substantial in most parts of the world. WHO estimates that alcohol consumption causes 3.2 percent of deaths (1.8 million) and 4.0 percent of the disability-adjusted life-years lost (58.3 million) worldwide. Alcohol consumption is the leading risk factor for disease burden in developing countries, and the third largest risk factor in developed countries. Clearly, alcohol problems are of an international scope and are a source of international public health concern.

Global research can also facilitate the development of new scientific discoveries. Collaborative research involving U.S. and non-U.S. research centers provides a unique opportunity to expand our knowledge about alcohol's effects, particularly when it affords the opportunity for the interaction of investigators and laboratories with unique skills, and the access of U.S. and non-U.S. investigators to resources, including scientific personnel not otherwise available to them. These resources can also include policy differences (legal minimum drinking age, legal maximum blood alcohol concentration [BAC] limits for driving); access to twin registries not found in the United States; and unique populations, such as large numbers of children with fetal alcohol spectrum disorders.

In addition, NIAAA uses the results of its funded studies (both domestic and international) to inform U.S. government policy positions at the United Nations General Assembly, the World Health Assembly, and meetings of the Organization of Economic Co-Operation and Development (OECD), as well as other global entities. Senior staff at NIAAA, both in the intramural and extramural Divisions, as well as our extramural grantees, provide scientific advice to WHO, its regional offices, and member states in support of the Global Strategy to Reduce Alcohol-Related Harms. Given alcohol's complex and well-documented role as a factor in violence, NIAAA has provided important funding and leadership to the National Academies of Science/Institute of Medicine Forum on Global Violence Prevention.

3 What are some of the areas of alcohol research where international collaborations have made the most difference?

Participation of international investigators on some of NIAAA's research consortia, such as the Integrative Neuroscience Initiative on Alcoholism (INIA) and the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), has enhanced our work and led to discoveries not otherwise possible. For example, Professor Brigitte Kieffer, of the Douglas Institute at McGill University and formerly of the IGBMC and INSERM in France, and recent winner of the Prix L'Oréal-UNESCO, brings unique expertise in genetic engineering to the INIA consortium that has shed light on molecular bases of the reward circuitry changes in the brain associated with alcohol dependence. In terms of unique study populations, CIFASD researchers have completed a clinical trial in the Ukraine that has produced findings to support the idea that nutritional

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FEATURE: *NIH Holds Competition. . . Continued from page 2*

proving its functionality and reliability, as well as photos and videos. Submissions will be accepted until December 1, 2015. Judging is expected to begin in January 2016, with winners announced on or after February 15, 2016. The first prize winner will be awarded $200,000; the second prize winner will receive $100,000.

For more contest details, go to the Federal Register announcement (https://www.federalregister.gov/articles/2015/03/02/2015-04254/announcement-of-requirements-and-registration-for-a-wearable-alcohol-biosensor-challenge#h-3).

Competition contact is M. Katherine Jung, Ph.D., program director, NIAAA Division of Metabolism and Health Effects: NIAAAChallengePrize@mail.nih.gov.

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supplementation in women who have continued to drink during their pregnancy can improve cognitive function and physical health in their children who have been exposed to alcohol in utero. CIFASD also has taken advantage of the unique resources and expertise of Dr. Peter Hammond of University College, London, who is using state-of-the-art 3D facial imaging to enhance the diagnosis of FASD, allow telemedicine approaches, and enable the screening and identification of large numbers of potentially affected children.

4 Where do you see the program moving in the next few years?

The program will continue to facilitate the development of research collaborations with major scientific programs in other countries, such as INSERM in France. An important piece of this initiative is the continued support of mutual laboratory visits by post docs in the United States and foreign countries. The sharing of experience and perspectives that leads to lifelong collaborative relationships will continue to produce important findings in the long term. Another focus will be to further the recognition of NIAAA, and its body of funded research, as a source of important and credible information and expertise in the development of global health policy, including global alcohol policy. For instance, the United Nations Non-Communicable Disease (NCD) Initiative has identified a 10 percent reduction in heavy episodic drinking as one of the four targets member states should concentrate on in order to prevent NCD's. Our research will be an important tool for countries as they develop programs to meet that target. Finally, we will continue to find creative ways to bring international scientific expertise into our major research projects, such as the development of medications to treat alcohol addiction and the study of how alcohol and other substances of abuse may affect adolescent brain development (i.e., the ABCD Study.)

5 How did you become involved in the Global research program at NIAAA?

My educational background is in health and social policy, and I have always been interested in the development of policy, both internationally and domestically, especially the exigency to use the best current research to inform policy development. I was working in another Division of NIAAA when a position in the International Affairs Office (so named at the time) opened up. I went for it and have been grateful for the tremendous opportunities it has afforded me.

ABOUT US

NIAAA Spectrum is NIAAA's Webzine. With engaging feature articles, short news updates, and colorful graphics, *NIAAA Spectrum* offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences.

Each issue includes feature-length stories, new research findings from the field, image and data analyses, and an interview with an NIAAA staff member or alcohol researcher. *NIAAA Spectrum* is published three times a year.

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