DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

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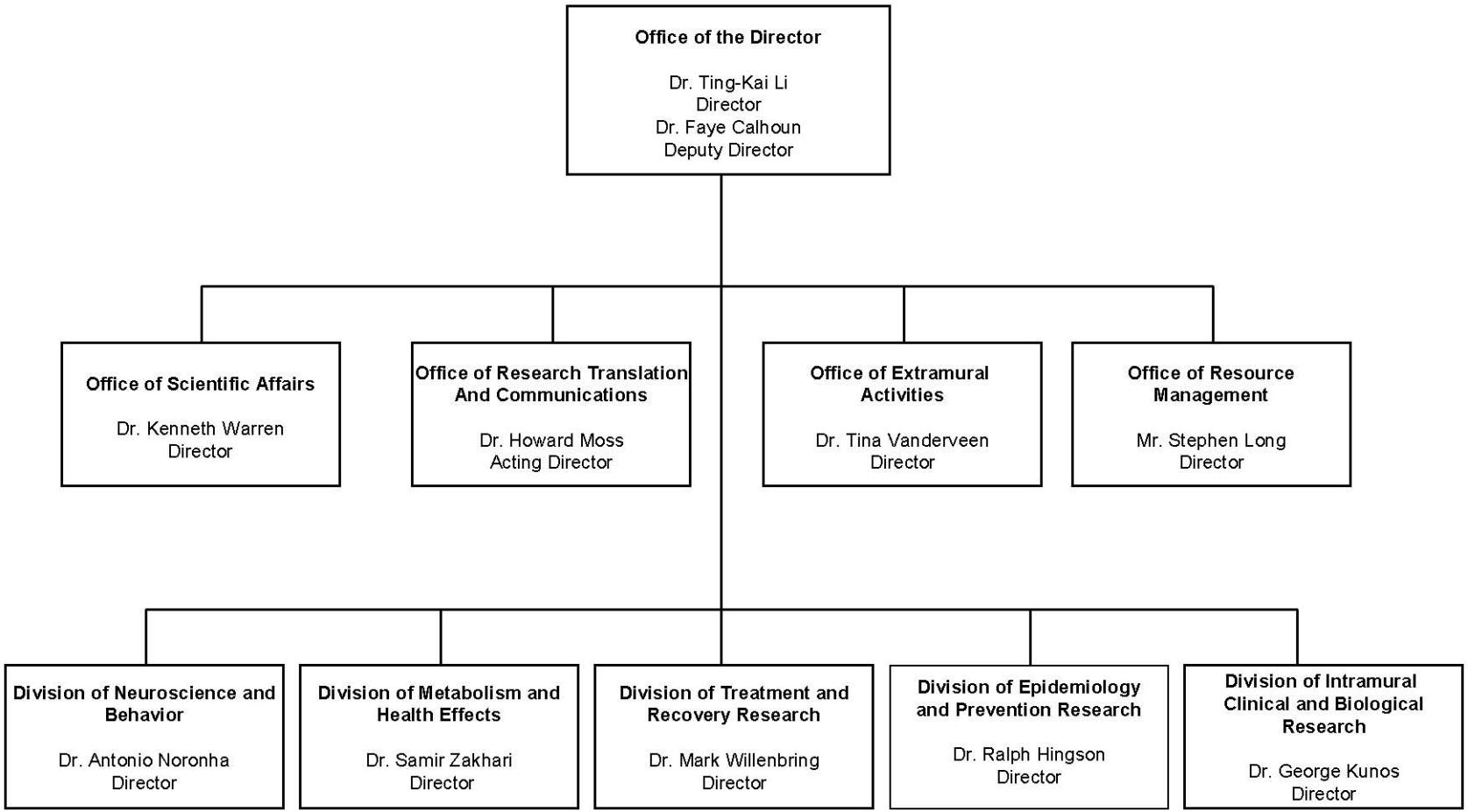

## NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

For carrying out section 301 and title IV of the Public Health Service Act with respect to alcohol abuse and alcoholism, [$440,333,000], *$433,318,000.*

[Department of Health and Human Services Appropriations Act, 2006]

**National Institutes of Health**
**National Institute on Alcohol Abuse and Alcoholism**

**Amounts Available for Obligation 1/**

| Source of Funding | FY 2005 Actual | FY 2006 Appropriation | FY 2007 Estimate |
|---|---|---|---|
| Appropriation | $441,911,000 | $440,333,000 | $433,318,000 |
| Enacted Rescissions | (3,634,000) | (4,403,000) | 0 |
| Subtotal, Adjusted Appropriation | 438,277,000 | 435,930,000 | 433,318,000 |
| Real transfer under NIH Director's one-percent transfer authority for Roadmap | (2,771,000) | (3,896,000) | 0 |
| | 0 | 0 | 0 |
| Comparative transfer from OD for NIH Roadmap | 2,771,000 | 3,896,000 | 0 |
| | 0 | 0 | 0 |
| Subtotal, adjusted budget authority | 438,277,000 | 435,930,000 | 433,318,000 |
| Unobligated Balance, start of year | 0 | 0 | 0 |
| Revenue from Breast Cancer Stamp 2/ | 0 | | |
| Unobligated Balance, end of year | 0 | 0 | 0 |
| Subtotal, adjusted budget authority | 438,277,000 | 435,930,000 | 433,318,000 |
| Unobligated balance lapsing | (3,000) | 0 | 0 |
| Total obligations | 438,274,000 | 435,930,000 | 433,318,000 |

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2005 - $1,629,000 FY 2006 - $1,629,000 FY 2007 - $1,629,000
Excludes $7,241 in FY 2005 and $7,737 in FY 2006 for royalties.

## Justification

## National Institute on Alcohol Abuse and Alcoholism

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Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.

Budget Authority:

| FY 2005 Actual | | FY 2006 Appropriation | | FY 2007 Estimate | | Increase or Decrease | |
|---|---|---|---|---|---|---|---|
| FTEs | BA | FTEs | BA | FTEs | BA | FTEs | BA |
| 233 | $438,277,000 | 227 | $435,930,000 | 227 | $433,318,000 | 1 | -$2,612,000 |

This document provides justification for the Fiscal Year 2007 activities of the National Institute on Alcohol Abuse and Alcoholism, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2007 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)." Detailed information on the NIH Roadmap for Medical Research may be found in the Overview section.

## Introduction

Alcohol is the third leading cause of preventable death in the United States, according to the Centers for Disease Control and Prevention.[1] In addition to associations with mortality, drinking too much, too fast, and too often can be a direct cause of harm to the individual's health, the health of others, and society at-large. Health consequences of excessive alcohol use include toxic effects on numerous organs resulting in liver disease, pancreatitis, weakness of the heart muscle, and elevated cancer risk.

Fundamental to the connection between alcohol use and adverse medical consequences, are two basic questions: *(1) Why are some people (~70 percent of the population)[2] able to drink moderately, while others (~5 percent of the population)[3] become alcohol dependent (alcoholic) and (2) among those who use alcohol in excess, why are some (~30 percent of the population)[4] more vulnerable than others to alcohol-induced tissue damage?*

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[1] Mokdad AH, Marks JS, Stroup DF, Gerberding JL. JAMA. 2004. 29:1238-45.

[2] NIAAA National Survey on Alcohol and Related Conditions, (2001-2002)

[3] Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, Pickering RP. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991-1992 and 2001-2002. Drug Alcohol Depend. 2004 Jun 11;74(3):223-34.

[4] Grant BF, Dufour MC, Harford TC. Semin Liver Disease. 1988. Feb;8(1):12-25

Three decades of research have shown that there are factors contributing to the risk for the development of alcoholism arising from an individual's biology or genetics as well his/her environment. Indeed, studies have shown that about half of the risk for the development of alcoholism is genetic with the other half environmental. Among the environmental contributors to the risk for alcohol dependence are cultural, family, and social factors promoting and modeling the consumption of alcohol, easy access and inexpensive availability of alcohol, and a lack of enforcement of regulatory policies around the sale and distribution of alcohol.

Research on the genetic contributors to alcoholism has revealed a number of genes that afford either decreased or increased risk. These genes may be specific for the effects or metabolism of alcohol or they may also be non-specific in the sense that they promote other mental disorders associated with a high degree of comorbidity with alcohol problems. For example, research has identified specific genetic variants for alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), major components of the alcohol metabolic pathway, that protect against the development of alcohol use disorders. On the other hand, ongoing research has suggested that variations in the sequence of genes related to specific biological systems may *increase* vulnerability to alcohol use disorders. These risk genes include those coding for a type of GABA receptor, a subtype of the acetylcholine receptor, a gene that encodes a type of opiate receptor, a gene that encodes a serotonin transporter, and a gene that encodes for a peptide involved in appetite and anxiety called NPY.

While important research continues on the role of gene sequences in the vulnerability for alcoholism and/or alcohol-related organ pathologies, alcohol researchers are now embarking on a new and important direction. This new direction explores how the patterns of gene expression that occur as a consequence of chemical modifications of the DNA molecule itself, or its protein packaging (i.e., the chromosome), contributes to the risk for alcoholism and alcohol-related organ pathologies. These effects, which alter patterns of gene expression, are collectively referred to as "epigenetic" phenomena. The epigenetic modification of DNA may silence specific genes. Chemical modifications of histones, the protein packaging for DNA, may either activate or silence the expression of genes. Researchers are now beginning to investigate if and how exposure to alcohol or one of its metabolites can produce these epigenetic effects that ultimately lead to tissue injury. Research has recently shown that alcohol or the final product of its metabolism, acetate, can bring about the chemical modification of a specific histone, and that one of the consequences of this epigenetic event is an increase in the transcription of the ADH gene itself. It is also known that alcohol can alter the level of a specific metabolite that is required for the chemical modification of DNA.

Epigenetic modifications may be transmitted as the cell divides such that the modifications may be retained throughout the lifespan. Importantly, epigenetic changes also have the potential to be passed on to the next generation, producing injury or abnormal physiology in the offspring. Thus, the impact of drinking too much and too often might also be passed onto the next generation.

Research on alcohol and health supported by NIAAA is at the forefront of the remarkable progress in genetics, molecular biology, and the complex mechanisms by which environmental factors interact with biological ones. Through this research, we will gain a clearer understanding

of the origins of alcohol dependence and alcohol-induced diseases, as well as offer an unprecedented opportunity to prevent and treat these disorders.

## Story of Discovery
## A Pathway to Alcohol Dependence

People drink for a variety of reasons including mood changes, life circumstances, and social situations. Most have no problem limiting their alcohol intake. But in some – almost 16 million Americans over the age of 17 – they lose control of drinking, exhibit an obsessive compulsive drinking pattern of behavior and they become alcohol dependent (alcoholic). What happens in the brain that leads to alcoholism (alcohol dependence)? Why is it important to know?

Alcohol exposure can change some of the inner workings of brain cells when someone drinks chronically and heavily. These changes as the brain adapts to alcohol become the biological basis of the addiction to or dependence on alcohol. The more closely we can pinpoint where and how these changes occur in the brain, the better molecular targets we have to direct the development of medicines that can alter the addictive process.

This story of discovery shows how two independent lines of research advanced, and were then brought together to reveal a neurobiological pathway that provides important clues about the potential role that anxiety may play in human alcoholism – and reveal potential points for targeted therapy of anxiety-related alcoholism. Importantly, this pathway may underlie a genetic predisposition and vulnerability to alcohol dependence.

Anxiety is regulated by a specific area of the brain, the amygdala. Some researchers have suggested that high levels of anxiety may predispose certain individuals to becoming alcoholic. Anxiety may also contribute to relapse in abstaining alcoholics. The identification of a common brain mechanism within the amygdala that can regulate both anxiety and alcohol consumption provides strong support that this mechanism contributes to excessive consumption of alcohol and ultimately a loss of control over alcohol intake.

One element of the neurobiological pathway in the amygdala is NPY (short for neuropeptide Y). There is a relationship between NPY levels in the brain and how much alcohol drinking occurs – the higher the NPY level, the less one consumes alcohol. But this NPY regulatory mechanism doesn't work anymore with chronic, heavy alcohol exposure. In this latter case, NPY levels no longer go up in response to alcohol consumption. This was further shown by scientists who created a scenario similar to chronic alcohol exposure by deleting the gene that produces NPY in animals. These genetically-modified animals are more anxious and naturally drank more alcohol than normal animals.

These simple statements belie the elegant studies on NPY, from the 1990s through the present, upon which they're based, and the technological advances that enabled progress. By the late 1990s, researchers had begun to ask if medicines that boosted NPY might be useful in treating alcohol dependence. Scientists are continuing this line of study, to find out (1) if boosting NPY would have this effect and, (2) if so, where in the inner workings of brain cells they should aim pharmaceuticals.

A different line of research provided an important clue about the NPY story and established the second element of the neurobiological pathway. It has to do with a signaling mechanism in brain cells called the cAMP pathway, short for the molecule, 3', 5'-cyclic adenosine monophosphate.

The cAMP pathway is an important regulator of biological function. Activation of this pathway will result in changes in the activity and function of many cells. In the brain, the cAMP pathway can affect the communication between nerve cells, thereby altering neuronal physiology and behavior. In the late 1970s, alcohol researchers had begun to ask if alcohol affected the cAMP pathway in ways that could lead to alcohol dependence. This search was enabled by the work of many scientists who had delineated, beginning in the 1970s and continuing through the 1980s, the details of the intricate steps of the cAMP pathway.

The alcohol researchers found that *acute* exposure to alcohol caused an increase in the levels of cAMP in cultured brain cells. However, after *chronic* alcohol exposure of the cells that boost in cAMP levels in response to acute alcohol no longer occurred. Clearly, chronic alcohol exposure was causing adaptive changes in the biological response of the cells. Additionally, a similar result was found for a protein, CREB (cAMP response element-binding protein), whose activity is modulated by the cAMP pathway. CREB is a transcription factor that "turns on" genes in response to the cAMP signal, thereby resulting in the increased production of proteins such as NPY. Researchers found that acute exposure of cultured brain cells as well as live animals to alcohol caused an increase in the level of activated CREB protein. Increases in activated CREB were not found after chronic alcohol exposure both in cultured cells and in brain cells prepared from chronic alcohol-exposed animals. The cells had undergone long-term adaptations to chronic alcohol exposure, and lower CREB activity was one of them.

These results implicate a neurobiological pathway consisting of cAMP signaling, CREB activation, and the generation of NPY - in modulating neuronal function and alcohol drinking behavior. Two recent studies now show that this pathway both underlies the relationship between anxiety and alcohol drinking and suggests there is a genetic predisposition to excessive alcohol drinking.

In the first study, scientists deleted part of the gene that produces CREB itself in mice, meaning that less CREB protein is produced in these animals. Compared with normal animals, these animals were found to also have reduced levels of activated CREB and produced less NPY in the amygdala, the region of the brain that regulates anxiety. Importantly, the mice with reduced CREB showed more innate anxiety behavior, and drank more alcohol than normal mice.

The second study not only further supports the association of this brain pathway with anxiety and alcohol consumption, but suggests that genetic variation of this pathway places individuals at greater risk to excessive alcohol drinking. Rats selectively bred to prefer alcohol normally drink alcohol to levels that exceed the legal limit of intoxication in humans (i.e., 80 mg percent), and drink about five to ten times more alcohol than rats bred to not prefer alcohol. The alcohol-preferring animals were found to have lower activated CREB as well as lower NPY levels in the amygdala relative to the alcohol non-preferring rats. Further, the alcohol-preferring rats were innately more anxious than the non-preferring rats. Interestingly, the neurobiological pathway of one strain could be pharmacologically manipulated such that the animals now showed anxiety and alcohol drinking behaviors that resembled the other strain.

Cellular adaptation to chronic alcohol exposure resulting in decreased cAMP signaling, decreased CREB activation, and decreased NPY production—seems to be an important substrate in the transition from reward-driven social drinking to compulsive, relief (from withdrawal)-driven alcohol drinking. An innate dysregulation of this pathway may also influence why some individuals drink alcohol excessively from the outset and others do not. Supporting this, a change in the NPY gene was recently found by NIAAA scientists to protect people from becoming alcohol dependent, possibly by enhancing NPY function.

The animal studies point to a brain mechanism that explains the link between anxiety and alcohol drinking. Moreover, these studies provide evidence that genetic alteration of the neurobiological pathway might be a risk factor for developing alcohol dependence. These findings bring us closer to understanding one of the biological roots of the heterogeneous complex disorder alcoholism, a devastating disease, and to more accurate targets for medicines to treat it.

## SELECTED ADVANCES IN ALCOHOL RESEARCH

**Naltrexone Keeps Slip-Ups From Becoming Relapses Early in Alcohol Treatment** – The first United States "effectiveness study" of the alcohol treatment naltrexone showed that it helps patients who have trouble abstaining early in treatment, a common point of relapse in recovering alcoholics. The studies that led to naltrexone's approval by the Food and Drug Administration revealed that it reduced relapse rates in tightly-controlled patient populations. However, clinical trials in real-world settings, where selection criteria, treatment regimens, and types of patients are less restrictive, and the patients' adherence varies, can produce results that deviate from those seen in initial trials. Thus, effectiveness trials demonstrate how well therapeutics function in actual patient-care situations.

In this effectiveness study of naltrexone, the drug benefit was limited to those patients who had brief drinking episodes or "slips" early in treatment. It kept their slips from progressing to full-blown relapses. Effectiveness studies are intended to show what populations benefit from the treatments being tested, and this one provides information that is immediately applicable by patients and practitioners.

**How Alcohol Tips the Life-and-Death Balance in Liver Cells –** Alcohol can have toxic effects on any tissue in the body, resulting in organ damage. Heavy drinking is one of the most common causes of liver damage, and there is no FDA-approved treatment for alcoholic liver disease. Scientists recently found that a known molecular pathway in cancer cell death also contributes to the development of alcohol-induced liver damage. This pathway is known as PTEN (*Phosphatase and Tensin homologue deleted on chromosome TEN*).

When PTEN leads to the death of cancer cells, that's beneficial. However, alcohol also causes an overproduction of PTEN that tips the balance of other cell-survival and cell-death pathways in liver cells toward death. Underlying this process is the disruption of a membrane around a crucial cell compartment, the mitochondrion, which kills the liver cell.

When researchers suppressed the alcohol-induced stimulation of PTEN, the deleterious changes in other cell-survival and cell-death pathways resolved; mitochondrial membranes remained intact; and liver cells survived. The elucidation of PTEN's role in causing alcohol-induced liver-damage provides an important molecular target for the development of medications that can prevent alcoholic liver disease.

**Alcohol Impairs Motor Coordination by Enhancement of Extrasynaptic GABA receptors** – Alcohol disrupts learning, memory, motor coordination, and cognitive processing by altering how brain cells communicate with one another. Among the key molecular targets of alcohol action are receptors for the inhibitory neurotransmitter GABA (gamma-aminobutyric acid). Alcohol is thought to exert many of its depressant, anxiolytic, and other actions by enhancing the effectiveness of GABA at inhibitory synaptic junctions between neurons.

Scientists focused on so-called "extrasynaptic" GABA receptors in granule cells of the cerebellum, a part of the brain that coordinates motor behaviors. These receptors, which are

located on a part of the cell body away from synaptic junctions, were found to be unusually sensitive to modest concentrations of alcohol. The most sensitive form of extrasynaptic receptors consisted of a specific combination of protein subunits (alpha6beta3delta). A single amino-acid substitution (R100Q) in the alpha6 subunit selectively increased the alcohol sensitivity of these GABA receptors. In behavioral tests, rats possessing naturally-occurring variants in the alpha6 protein exhibited significant differences in the impairment of motor coordination produced by alcohol.

This study has uncovered an important new target of alcohol action, namely the extrasynaptic GABA receptors in cerebellar granule cells. The results provide strong evidence that alcohol impairs motor coordination by enhancing the function of these receptors. Moreover, subtle changes in the composition of these proteins can produce major changes in alcohol sensitivity, leading to enhanced behavioral consequences of intoxication.

**Insulin Signaling in the Nervous System Affects Sensitivity to Alcohol** – Although insulin is most widely thought of as a blood-sugar regulator, it regulates many other cellular processes. New research shows that cells producing insulin-like substances in the brain regulate sensitivity to alcohol. This is an important finding, because sensitivity to alcohol is one of the factors that affect how much people drink. Low alcohol sensitivity – the ability to handle a comparatively large amount of alcohol without feeling its intoxicating effects – is a potential risk factor for heavy drinking and alcoholism. Scientists found that the human equivalent of brain cells in fruit flies produce insulin-like substances which influence alcohol sensitivity.

This research shows that cells that produce insulin-like substances in the brain regulate alcohol sensitivity as well as offer a potential mechanism. Understanding brain mechanisms that contribute to alcohol sensitivity is essential to understanding how to prevent and treat alcohol-use disorders. These findings suggest that this pathway may be an important target for a therapeutic intervention of alcoholism.

**Alcohol Researchers Find Fat-Promoting Receptor in Liver Cells** – Obesity is a major, proven health risk. Alcohol researchers have revealed a new reason that a specific receptor has implications for obesity. Scientists knew that the CB1 receptor stimulates appetite when naturally occurring chemicals called endocannabinoids activate it in brain cells. Now, alcohol researchers have shown that CB1 receptors also are present in the liver, where they directly stimulate fat production when activated by endocannabinoids.

NIAAA studies fat synthesis and metabolism because of its well-established research on liver disease. Excess alcohol causes fat build-up in the liver, a precursor of alcoholic liver disease, and understanding the mechanisms underlying this accumulation of fat is essential to finding treatments.

As scientists find out more about the biological mechanisms that contribute to fat synthesis, fat metabolism, and obesity, they identify more effective molecular points for intervention. Already, a weight-loss drug that inhibits the CB1 receptor is being developed by a French company.

## NEW OR EXPANDED INITIATIVES IN ALCOHOL RESEARCH

**Alcohol, Gene Expression, and Disease** – Alcohol is toxic when ingested in excess. It can have wide spread effects throughout the body resulting in disease to many organs. This new initiative will explore and increase our understanding of one of the routes through which alcohol may lead to disease, specifically through the chemical modification of the genetic material of the cell, the DNA, and of the proteins, called histones, which are a part of the packaging of DNA in chromosome structures. Histones play essential roles in the expression of the genetic information contained within the DNA of the chromosome.

Both DNA and histones may be modified by enzymes within the cell through the addition of various chemical entities, including one known as the methyl group (a process called methylation). Research has shown that heavy alcohol use can change the levels of key metabolites involved in the attachment of methyl groups to DNA and histones. By changing the methylation pattern of either DNA or histones, certain genes may be expressed in excess, while others may be silenced. This can have important consequences for the physiology of the cell, potentially leading to disease and even to some cancers.

Another way that the structure of histones may be altered is through the attachment of another chemical entity known as an acetyl group (the process of acetylation). Alcohol can stimulate the attachment of the acetyl group to histones. Recently, researchers have found that the final product of alcohol metabolism, a chemical called acetate, has the same effect as alcohol in stimulating the acetylation of the histone protein.

Overall, the initiative will uncover the mechanisms by which alcohol alters the gene structure and expression through chemical modification of DNA and histones. The consequences of these changes on physiology and disease will be investigated, and in the long-term, molecular targets will be identified for pharmaceutical interventions to prevent alcohol-induced disease.

**Drinking During Adolescence: Alcohol's Effects on the Developing Brain** – Alcohol is the drug most commonly used by youth.[5] For example, according to 2004 data from Monitoring the Future, 76.8 percent of 12$^{th}$ graders have used alcohol, 52.8 percent have used cigarettes and 45.7 percent have used marijuana at least once in their lifetime. And much of this drinking is at high levels; again according to 2004 data from Monitoring the Future, 11.4 percent of 8$^{th}$ graders, 22.0 percent of 10$^{th}$ graders and 29.2 percent of 12$^{th}$ graders report drinking 5 or more drinks in a row in the past two weeks. This drinking pattern, common to many young people, has been called "binge" drinking (consuming 5 or more drinks within 2 hours), and is a particularly hazardous pattern of drinking. Despite the widespread use of alcohol by adolescents, the short- and long-term effects of drinking on brain development are not yet well characterized. Studies in this area are critical, because the brain is still undergoing programmed growth and differentiation in adolescence. Therefore, even transient brain changes have the potential to change lifetime academic, vocational, social, and emotional trajectories.

[5] Johnston, L. D., O'Malley, P. M., Bachman, J. G., & Schulenberg, J. E. (2005). *Monitoring the Future national survey results on drug use, 1975-2004. Volume I: Secondary school students* (NIH Publication No. 05-5727). Bethesda, MD: National Institute on Drug Abuse

Preliminary research with animals and humans suggests that alcohol may perturb normal brain development in adolescence and young adulthood, thereby altering neurophysiology and associated behavioral function. We also know that people who begin drinking earlier, rather than later, in youth are far more likely to report meeting the criteria for alcoholism (alcohol dependence) in their life. These facts, taken together, suggest that alcohol drinking by youth has consequences that go beyond social and psychological problems, and may include specific biological changes in brain structures and function. The mechanisms that may underlie such changes have been called epigenetic, in that alterations in the expression pattern of important genes at one point in life may influence health and illness patterns in an enduring fashion over the lifespan.

This initiative is intended to determine whether drinking during adolescence: (1) affects developing brain structures and systems that regulate behavior, (2) results in acute neurophysiological or neuropsychological changes that are linked to brain changes, and (3) has long-term neurophysiological and behavioral effects, and, if so, whether they are permanent or reversible. In addition, this initiative will address: the biological mechanisms that underlie alcohol-related changes in neurophysiology during brain development; alcohol dosage and drinking patterns that result in these brain changes (youth drink less often than adults, but when they do drink, they tend to binge); and factors that promote these changes or protect against them.

**Medications Development** –
*1. Enhancing Early Human Clinical Trials of Medications for Alcohol Dependence* – This component will reduce the time that it takes to move from identification of promising compounds to initial human efficacy trials, to help speed development of anti-craving medications for alcohol dependence.

The most promising advance in treatment of alcohol dependence is the development of anti-craving medications. Craving for alcohol is a common cause of relapse among alcohol dependent individuals in treatment. Currently, only two such compounds are available for this use. Although many compounds with potential have been identified, testing efficacy in humans has been a lengthy and expensive process. In particular, the extramural grant process depends on the initiative of individual investigators, and takes several years to produce results. Additional mechanisms are needed to speed up the development of anti-craving medications.

This research will develop an enduring infrastructure for early Phase II human trials of multiple compounds, enabling faster determination of which of them merit advancement to large, multi-site studies. A contract mechanism will enable the early Phase II trials to start more quickly and to be completed within two years, rather than the usual five years, using methodology standardized across studies.

Compounds that show promise in these early trials ultimately may merit a New Drug Application (NDA) through the Food and Drug Administration. A network of clinical sites that conduct early Phase II trials will use protocols designed to facilitate the NDA process for compounds reaching that stage.

*2. Developing Animal Screens for Medication Efficacy in Alcohol Dependence* – In this component, we will address three over-arching issues. (1) Only two anti-craving medications for treating alcohol dependence have been brought to the U.S. market in the last fifteen years, and there is a substantial need for additional medications. (2) Phase I and II human trials are expensive and time consuming, but there is no demonstrated way to pre-screen for the compounds most likely to show efficacy in humans. (3) Pharmaceutical companies will be more likely to invest in drug development for treating alcohol-use disorders if a screen exists that increases the efficiency of the process.

This research will determine if existing animal models that reflect various aspects of alcohol dependence predict efficacy of treatment compounds in Phase II human trials. Our intent is to (1) expedite discovery of more compounds with potential as treatments; (2) predict earlier in the testing process whether these compounds are likely to reduce drinking and merit Phase I and Phase II testing; and (3) provide pharmaceutical companies with preliminary data on promising compounds – the kind of data that they traditionally have not pursued – to encourage the companies to develop them further and to bring to market those that are proven efficacious.

The NIH Roadmap Molecular Libraries Initiative will be a valuable resource for this project, which will be funded through an efficient contract mechanism. In addition, we will collaborate with other NIH Institutes conducting high-throughput screening to share information about compounds that appear to have potential for treating more than one type of disease. For example, some compounds being tested for treatment of seizures by the National Institute of Neurological Disorders and Stroke also have potential for treating alcohol dependence.

**Alcohol-Exacerbated HIV Dementia: Developing Preventive Agents** – The human immunodeficiency virus (HIV) often invades the central nervous system (CNS) of people with AIDS, causing dementia. Heavy alcohol use exacerbates HIV infection of the brain, adding to morbidity and mortality. This initiative will focus on developing neuroprotective agents that will prevent, or reduce damage from, alcohol-exacerbated dementia in people with AIDS.

To develop protective agents, it is essential that we tease apart the potential sources of neurologic damage in HIV-positive, heavy-drinking individuals. Potential sources include: (1) direct toxic effects of alcohol on CNS tissue, (2) neurologic consequences of systemic HIV disease, and (3) the synergistic effects of these sources.

Alcohol aggravates HIV damage to the brain by (1) damaging mechanisms that prevent the virus from circulating into the brain via the blood – that is, through the "blood-brain barrier," and (2) increasing inflammation, which leads to injury to brain cells and diminished ability of the immune system to adapt to the virus. Investigators will use cellular and animal models to test whether stimulating a naturally occurring protein called PPAR-gamma (peroxisome proliferator-activated receptor gamma) will: (1) improve the ability of the blood-brain barrier to prevent HIV from entering the brain, and (2) protect brain cells damaged by alcohol and immune cells (macrophages) infected by HIV from further injury. Agents that stimulate PPAR-gamma are approved for clinical use, which will permit rapid translation of experimental findings into therapeutic applications.

In addition, the neurological damage caused by the combined effects of alcohol and HIV/AIDS may lead to neural tissue destruction in brain regions that regulate cognitive functioning required for the engagement in planned behavior. Such damage would directly impair the ability of individuals to adhere to complex antiretroviral medication therapies, potentially raising the likelihood of HIV progression and a global worsening of the patient's clinical status. This initiative also will test the neuroprotective effects of strategies that improve adherence to treatment; for example, strict monitoring, simplified regimens, and differently structured regimens.

## OTHER AREAS OF INTEREST

A revised *Helping Patients Who Drink Too Much—A Clinician's Guide* was released in July to help health care practitioners identify and care for patients with heavy drinking and alcohol use disorders. The *Guide* provides a research-based approach to alcohol screening and brief interventions for both primary care and mental health clinicians. It updates earlier NIAAA guidelines, which focused solely on primary care providers and used a lengthier screening process. Included in the new *Guide* are an optional written self-report screening tool (the AUDIT) in both English and Spanish; a new section about prescribing medications for alcohol dependence; new forms for recording patient baseline and progress notes; and a pocket-sized summary version of the *Guide*. Over 20,000 copies of the *Guide* have been distributed and another 100,000 copies are being printed. The *Guide* can be viewed online at the NIAAA website under publications/professional education materials.
http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf

As a follow-up to the *Guide*, additional products and initiatives are being contemplated in order to increase screening and brief intervention for heavy drinking in medical settings. Under discussion is a guide for nurses to assist doctors prescribing anti-craving medications by providing brief counseling. We are also exploring the development of a DVD with video clips and other instructional materials illustrating the use of the *Guide* in clinical practice and made available for download from the web. Finally, a patient education pamphlet regarding drinking limits, symptoms of alcohol use disorders, self-management principles, and medication information is being considered as a collaborative project with Center for Substance Abuse Treatment, a component of the Substance Abuse and Mental Health Services Administration.

## NIH ROADMAP AND ALCOHOL RESEARCH

NIAAA continues to contribute to, and benefit from, the important research initiatives under the NIH Roadmap. This research framework is designed to enhance biomedical and behavioral research, ultimately accelerating the translation of basic science findings into clinical practice. While NIAAA investigators will benefit from all of the Roadmap initiatives, several of the initiatives are expected to have particular importance to the alcohol research field.

Alcohol's actions are derived from the complex interaction of this relatively small molecule with the various structural and functional components of the cell. Many of these components are proteins, and comprise, what is now known as, the cell's proteome. Other components, from the lipids in the membrane structure, to the intermediate metabolites that are the substrates for the

many enzyme reactions within the cell, comprise the metabolome. Proteomic and metabolomics research tools, stimulated by the NIH Roadmap, are already providing valuable insights into alcohol's effects on the nervous system, and elucidating the mechanisms of alcohol-induced disease and organ damage. This research paradigm also holds the promise to reveal important protein or metabolic biomarkers that could lead to early clinical diagnosis of alcohol-induced organ injury. The findings may also be of importance in identifying the molecular targets of alcohol's actions, thereby providing the potential to develop novel, and more specific therapeutics for alcohol-related disease.

Also of high importance to NIAAA are the Roadmap initiatives to enhance the clinical research enterprise. NIAAA is committed to clinical research regarding diagnosis and treatment of alcohol use disorders and alcohol-associated organ damage. Within the framework of the NIH Roadmap, NIAAA research will capitalize on the development of the National Electronics Clinical Trials and Research Network (NECTAR). NECTAR is a nationwide effort to create an organization of clinical field sites and investigators that standardize research protocols and share and archive scientific data using a common clinical data reporting format. This research infrastructure will facilitate the efficient conduct of large-scale clinical trials of emerging therapeutics for alcohol use disorders and alcohol-related organ damage, thereby hastening the progress of promising medications into clinical practice. Initially, this Roadmap-associated effort will be coordinated by NIAAA's Phase II Clinical Trials group for the clinical testing of promising new compounds that reduce the craving for alcohol in early stages of recovery, and help the long-term outcomes of the alcohol dependent patient. Alcohol research will benefit from the Clinical and Translational Sciences Award that is designed to accelerate the development of new treatments, including the training of clinical investigators.

## NIH NEUROSCIENCE BLUEPRINT

The NIH Neuroscience Blueprint enhances cooperative activities among 15 NIH Institutes and Centers that support research on the nervous system. By pooling resources and expertise, the Blueprint takes advantage of economies of scale, confronts challenges too large for any single Institute or Center (IC), and develops research tools and infrastructure that serve the entire neuroscience community. "Best practices" developed at a single IC are implemented more widely; planning is coordinated at the early concept stage; resources established by one IC are opened to neuroscientists supported by others; and multi-Institute working groups focus on diseases and cross-cutting scientific issues.

The first series of Blueprint initiatives began in 2005 with additional projects added in 2006. These projects are expected to yield important dividends for alcohol research. One of the first initiatives under the Blueprint was the establishment of training programs in neuroimaging. These programs will provide training in multiple areas related to imaging including the physics of imaging technologies, the chemistry of ligand development, the bioengineering of imaging technology, and the application of these domains to neuroscience research. The cadre of investigators trained through this initiative will advance the alcohol research field through technology development, and the translation of basic science findings to the clinical research arena

Another Blueprint activity, the Unified Measures of Neural and Behavioral Health initiative is developing a set of standard measures of cognitive and emotional function that will provide alcohol researchers with a common language for collecting, sharing and understanding alcohol effects on neural and behavioral functions. This should reduce conceptual and methodological ambiguities, facilitate collaborative research, and improve the overall efficacy of research on neurobehavioral effects of alcohol.

A particularly important Blueprint activity for NIAAA's Underage Drinking Initiative is the Diffusion Tensor Imaging component of the Pediatric MRI Study of Normal Brain Development. This project will provide a database representing normal brain development from newborns through young adulthood, which can serve as a comparative tool for the study of behavioral and neurological disorders. Given the high frequency of drinking in adolescence, and alcohol's potential impact on brain development, this database will be a key resource that will allow alcohol investigators to compare brain development data from youth who began drinking in adolescence to standardized control groups of the same age, and to continue to follow and compare these individuals in a longitudinal manner, from youth, through adolescence and into young adulthood.

## AIDS ACTIVITIES

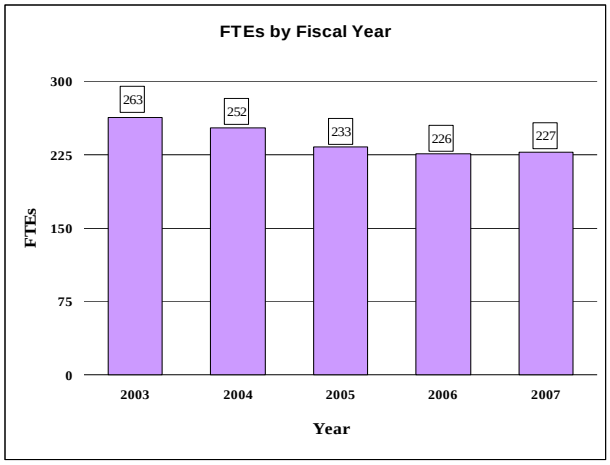
NIAAA currently devotes more than $27 million dollars to alcohol and HIV/AIDS research, primarily in the areas of epidemiology and natural history, etiology and pathogenesis, and behavioral prevention and treatment. Funding mechanisms include investigator-initiated R01's, training and career development grants, and large-scale collaborative programs. These include a Center for understanding the role of alcohol in the immunology of AIDS (for example, studies of viral replication, which research suggests is enhanced by alcohol, and disease progression) and a large-scale clinical cohort study among veterans, which will enable us to understand the medical consequences of co-occurring disorders and to test advanced treatment and patient-management practices.

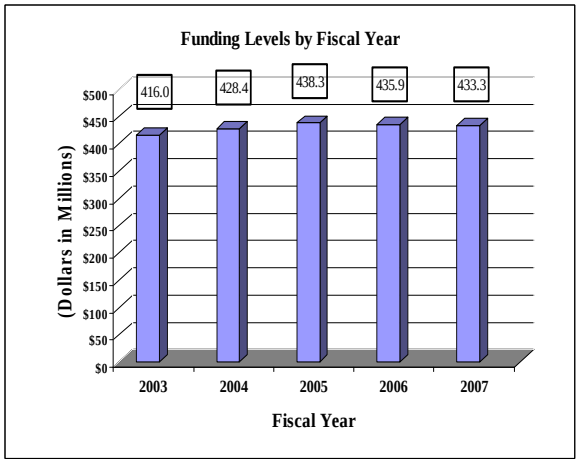
Topics of studies include adherence to medication regimens, neurological disease manifestations and brain imaging, mitochondrial oxidative stress in liver functioning, mechanisms of behavior change, and efficacy of multi-level interventions in high-risk communities, to identify a few. New directions in our research include (1) a focus on the role of nutrition and nutritional supplements in HIV-positive pregnant women who drink and (2) developing comprehensive, integrated behavioral and biomedical prevention strategies.

## Budget Policy

The Fiscal Year 2007 budget request for the NIAAA is $433,318,000, a decrease of $2,612,000 and 0.6 percent over the FY 2006 Appropriation. Included in the FY 2007 request is NIAAA's support for the trans-NIH Roadmap initiatives, estimated at 1.2% of the FY 2007 budget request. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIAAA are shown in the graphs below. Note that as the result of several administrative restructurings in recent years, FTE data is non-comparable.




NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $326,000 in FY 2007. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NIAAA has committed to a programmatic increase for an award, such increases will be provided.

NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIAAA, $270 thousand will be used to support three awards for the new K/R "Pathway to Independence" program.

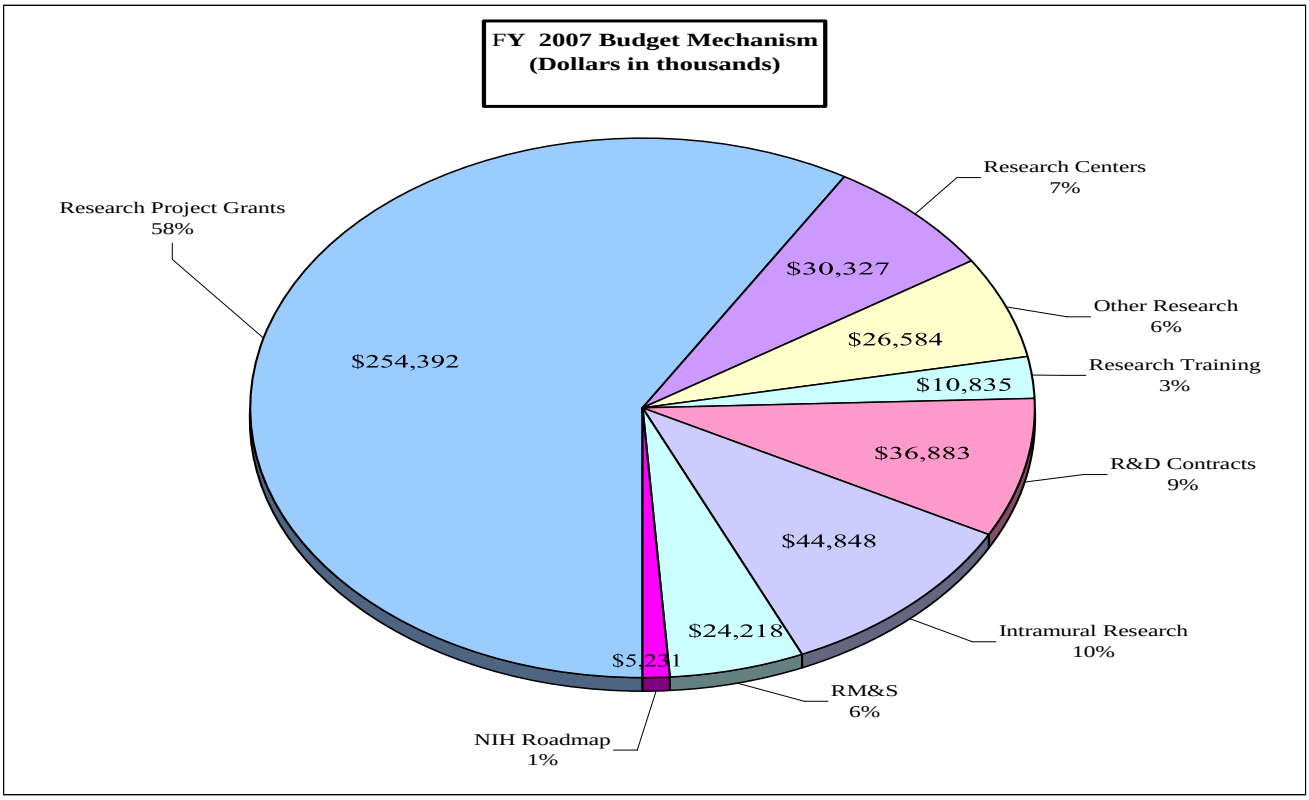
NIAAA will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes $704 thousand to support this project.

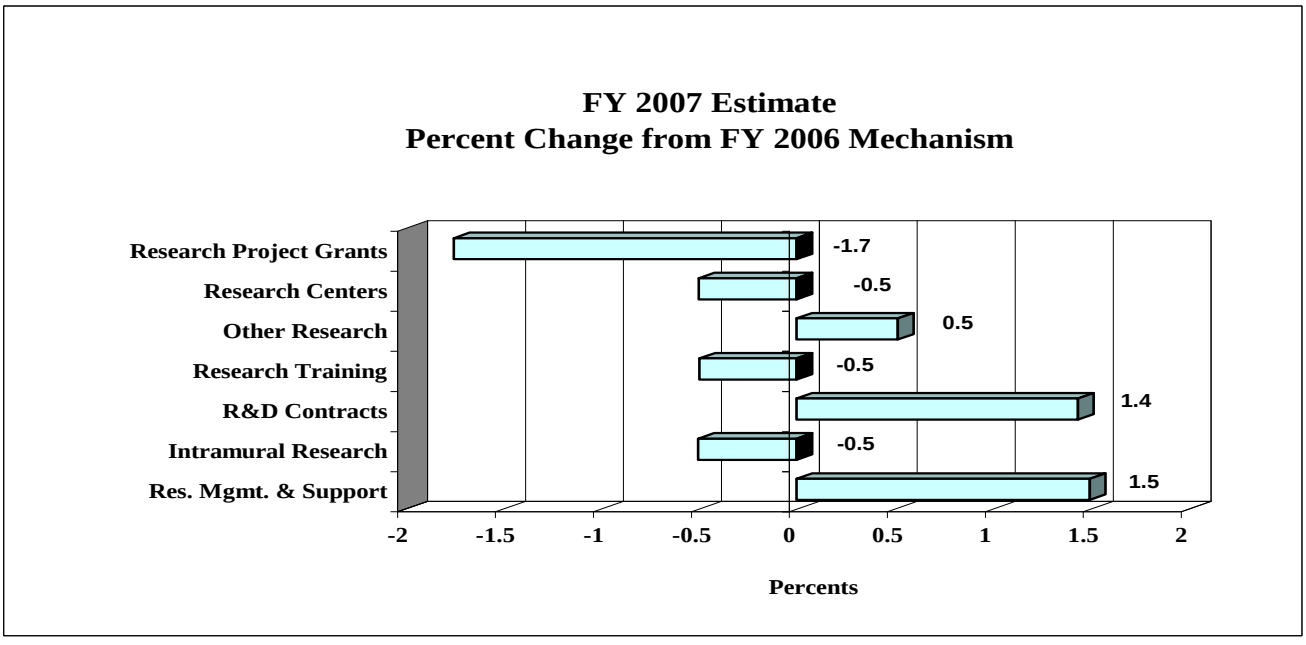
In the FY 2007 request, stipend levels for trainees supported through the Ruth L. Kirschstein National Research Service Awards will remain at the FY 2006 levels.

The FY 2007 request includes funding for 18 research centers, 125 other research grants, including 90 career awards, and 25 R&D contracts. Intramural Research decreases by 0.5 percent. Research Management and Support increases by 1.5 percent.

The FY 2007 request includes mandatory increases for pay and inflationary costs. These costs will be offset with programmatic savings achieved in travel, equipment, and supplies.

The mechanism distribution by dollars and percent change are displayed below:



**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

Budget Mechanism - Total

| MECHANISM | FY 2005 Actual | | FY 2006 Appropriation | | FY 2007 Estimate | |
|---|---|---|---|---|---|---|
| Research Grants: | No. | Amount | No. | Amount | No. | Amount |
| Research Projects: | | | | | | |
| Noncompeting | 524 | $188,156,000 | 543 | $190,855,000 | 526 | $191,919,000 |
| Administrative supplements | (29) | 1,737,000 | (28) | 1,668,000 | (26) | 1,500,000 |
| Competing: | | | | | | |
| Renewal | 52 | 22,191,000 | 47 | 20,001,000 | 42 | 18,205,000 |
| New | 150 | 43,450,000 | 135 | 39,162,000 | 123 | 35,644,000 |
| Supplements | 1 | 229,000 | 0 | 0 | 0 | 0 |
| Subtotal, competing | 203 | 65,870,000 | 182 | 59,163,000 | 165 | 53,849,000 |
| Subtotal, RPGs | 727 | 255,763,000 | 725 | 251,686,000 | 691 | 247,268,000 |
| SBIR/STTR | 20 | 8,770,000 | 17 | 7,237,000 | 17 | 7,124,000 |
| Subtotal, RPGs | 747 | 264,533,000 | 742 | 258,923,000 | 708 | 254,392,000 |
| Research Centers: | | | | | | |
| Specialized/comprehensive | 18 | 30,201,000 | 18 | 30,479,000 | 18 | 30,327,000 |
| Clinical research | 0 | 0 | 0 | 0 | 0 | 0 |
| Biotechnology | 0 | 0 | 0 | 0 | 0 | 0 |
| Comparative medicine | 0 | 0 | 0 | 0 | 0 | 0 |
| Research Centers in Minority Institutions | 0 | 0 | 0 | 0 | 0 | 0 |
| Subtotal, Centers | 18 | 30,201,000 | 18 | 30,479,000 | 18 | 30,327,000 |
| Other Research: | | | | | | |
| Research careers | 88 | 11,870,000 | 87 | 11,739,000 | 90 | 11,950,000 |
| Cancer education | 0 | 0 | 0 | 0 | 0 | 0 |
| Cooperative clinical research | 1 | 6,030,000 | 1 | 6,145,000 | 1 | 6,114,000 |
| Biomedical research support | 0 | 0 | 0 | 0 | 0 | 0 |
| Minority biomedical research support | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 37 | 8,836,000 | 34 | 8,563,000 | 34 | 8,520,000 |
| Subtotal, Other Research | 126 | 26,736,000 | 122 | 26,447,000 | 125 | 26,584,000 |
| Total Research Grants | 891 | 321,470,000 | 882 | 315,849,000 | 851 | 311,303,000 |
| Research Training: | FTTPs | | FTTPs | | FTTPs | |
| Individual awards | 68 | 2,495,000 | 67 | 2,490,000 | 67 | 2,478,000 |
| Institutional awards | 181 | 7,236,000 | 200 | 8,399,000 | 200 | 8,357,000 |
| Total, Training | 249 | 9,731,000 | 267 | 10,889,000 | 267 | 10,835,000 |
| Research & development contracts | 23 | 35,216,000 | 25 | 36,361,000 | 25 | 36,883,000 |
| (SBIR/STTR) | (4) | (1,366,000) | (9) | (2,625,000) | (9) | (2,625,000) |
| | FTEs | | FTEs | | FTEs | |
| Intramural research | 117 | 45,346,000 | 110 | 45,074,000 | 111 | 44,848,000 |
| Research management and support | 116 | 23,743,000 | 116 | 23,861,000 | 116 | 24,218,000 |
| Cancer prevention & control | 0 | 0 | 0 | 0 | 0 | 0 |
| Construction | | 0 | | 0 | | 0 |
| Buildings and Facilities | | 0 | | 0 | | 0 |
| NIH Roadmap for Medical Research | 0 | 2,771,000 | 0 | 3,896,000 | 0 | 5,231,000 |
| Total, NIAAA | 233 | 438,277,000 | 226 | 435,930,000 | 227 | 433,318,000 |
| (Clinical Trials) | | (51,479,000) | | (50,964,000) | | (50,506,000) |

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Budget Authority by Activity**
**(dollars in thousands)**

| ACTIVITY | FY 2005 Actual FTEs | FY 2005 Actual Amount | FY 2006 Appropriation FTEs | FY 2006 Appropriation Amount | FY 2007 Estimate FTEs | FY 2007 Estimate Amount | Change FTEs | Change Amount |
|---|---|---|---|---|---|---|---|---|
| Extramural Research: | | | | | | | | |
| Alcohol Biomedical and Behavioral Research | | $366,417 | | $363,099 | | $359,021 | | ($4,078) |
| Subtotal, Extramural research | | 366,417 | | 363,099 | | 359,021 | | (4,078) |
| Intramural research | 117 | 45,346 | 110 | 45,074 | 111 | 44,848 | 1 | (226) |
| Res. management & support | 116 | 23,743 | 116 | 23,861 | 116 | 24,218 | 0 | 357 |
| NIH Roadmap for Medical Research | 0 | 2,771 | 0 | 3,896 | 0 | 5,231 | 0 | 1,335 |
| Total | 233 | 438,277 | 226 | 435,930 | 227 | 433,318 | 1 | (2,612) |

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Summary of Changes**

| | | | | |
|---|---|---|---|---|
| FY 2006 Estimate | | | | $435,930,000 |
| FY 2007 Estimated Budget Authority | | | | 433,318,000 |
| Net change | | | | (2,612,000) |
| | FY 2006 Appropriation | | Change from Base | |
| CHANGES | FTEs | Budget Authority | FTEs | Budget Authority |
| A. Built-in: | | | | |
| 1. Intramural research: | | | | |
| a. Within grade increase | | $15,846,000 | | $221,000 |
| b. Annualization of January 2006 pay increase | | 15,846,000 | | 123,000 |
| c. January 2007 pay increase | | 15,846,000 | | 261,000 |
| d. One less day of pay | | 15,846,000 | | 0 |
| e. Payment for centrally furnished services | | 7,735,000 | | 116,000 |
| f. Increased cost of laboratory supplies, materials, and other expenses | | 21,493,000 | | 460,000 |
| Subtotal | | | | 1,181,000 |
| 2. Research Management and Support: | | | | |
| a. Within grade increase | | 14,775,000 | | 263,000 |
| b. Annualization of January 2006 pay increase | | 14,775,000 | | 115,000 |
| c. January 2007 pay increase | | 14,775,000 | | 244,000 |
| d. One less day of pay | | 14,775,000 | | 0 |
| e. Payment for centrally furnished services | | 2,774,000 | | 42,000 |
| f. Increased cost of laboratory supplies, materials, and other expenses | | 6,312,000 | | 127,000 |
| Subtotal | | | | 791,000 |
| Subtotal, Built-in | | | | 1,972,000 |

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Summary of Changes--continued**

| CHANGES | 2006 Current Estimate Base | | Change from Base | |
|---|---|---|---|---|
| | No. | Amount | No. | Amount |
| B. Program: | | | | |
| 1. Research project grants: | | | | |
| a. Noncompeting | 543 | $192,523,000 | (17) | $896,000 |
| b. Competing | 182 | 59,163,000 | (17) | (5,314,000) |
| c. SBIR/STTR | 17 | 7,237,000 | 0 | (113,000) |
| Total | 742 | 258,923,000 | (34) | (4,531,000) |
| 2. Research centers | 18 | 30,479,000 | 0 | (152,000) |
| 3. Other research | 122 | 26,447,000 | 3 | 137,000 |
| 4. Research training | 267 | 10,889,000 | 0 | (54,000) |
| 5. Research and development contracts | 25 | 36,361,000 | 25 | 522,000 |
| Subtotal, extramural | | | | (4,078,000) |
| | FTEs | | FTEs | |
| 6. Intramural research | 110 | 45,074,000 | 1 | (1,407,000) |
| 7. Research management and support | 116 | 23,861,000 | 0 | (434,000) |
| 8. Cancer control and prevention | 0 | 0 | 0 | 0 |
| 9. Construction | | 0 | | 0 |
| 10. Buildings and Facilities | | 0 | | 0 |
| 11. NIH Roadmap for Medical Research | 0 | 3,896,000 | 0 | 1,335,000 |
| Subtotal, program | | 435,930,000 | | (4,584,000) |
| Total changes | 226 | | 1 | (2,612,000) |

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Budget Authority by Object**

| | FY 2006 Appropriation | FY 2007 Estimate | Increase or Decrease |
|---|---|---|---|
| Total compensable workyears: | | | |
| Full-time employment | 226 | 227 | 1 |
| Full-time equivalent of overtime & holiday hours | 1 | 1 | 0 |
| Average ES salary | $156,776 | $159,911 | $3,135 |
| Average GM/GS grade | 12.4 | 12.4 | 0.0 |
| Average GM/GS salary | $88,299 | $90,065 | $1,766 |
| Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207) | $80,886 | $82,504 | $1,618 |
| Average salary of ungraded positions | 108,879 | 111,057 | 2,178 |

| OBJECT CLASSES | FY 2006 Appropriation | FY 2007 Estimate | Increase or Decrease |
|---|---|---|---|
| Personnel Compensation: | | | |
| 11.1 Full-Time Permanent | $14,958,000 | $15,632,000 | $674,000 |
| 11.3 Other than Full-Time Permanent | 5,926,000 | 6,219,000 | 293,000 |
| 11.5 Other Personnel Compensation | 459,000 | 481,000 | 22,000 |
| 11.7 Military Personnel | 410,000 | 430,000 | 20,000 |
| 11.8 Special Personnel Services Payments | 2,917,000 | 3,040,000 | 123,000 |
| **Total, Personnel Compensation** | 24,670,000 | 25,802,000 | 1,132,000 |
| 12.0 Personnel Benefits | 5,585,000 | 5,847,000 | 262,000 |
| 12.2 Military Personnel Benefits | 366,000 | 384,000 | 18,000 |
| 13.0 Benefits for Former Personnel | 0 | 0 | 0 |
| **Subtotal, Pay Costs** | **30,621,000** | **32,033,000** | **1,412,000** |
| 21.0 Travel & Transportation of Persons | 801,000 | 756,000 | (45,000) |
| 22.0 Transportation of Things | 243,000 | 226,000 | (17,000) |
| 23.1 Rental Payments to GSA | 1,000 | 1,000 | 0 |
| 23.2 Rental Payments to Others | 10,000 | 9,000 | (1,000) |
| 23.3 Communications, Utilities & Miscellaneous Charges | 1,284,000 | 1,194,000 | (90,000) |
| 24.0 Printing & Reproduction | 208,000 | 200,000 | (8,000) |
| 25.1 Consulting Services | 406,000 | 381,000 | (25,000) |
| 25.2 Other Services | 2,568,000 | 2,399,000 | (169,000) |
| 25.3 Purchase of Goods & Services from Government Accounts | 43,286,000 | 43,142,000 | (144,000) |
| 25.4 Operation & Maintenance of Facilities | 167,000 | 159,000 | (8,000) |
| 25.5 Research & Development Contracts | 17,284,000 | 17,619,000 | 335,000 |
| 25.6 Medical Care | 1,193,000 | 1,106,000 | (87,000) |
| 25.7 Operation & Maintenance of Equipment | 594,000 | 555,000 | (39,000) |
| 25.8 Subsistence & Support of Persons | 0 | 0 | 0 |
| **25.0 Subtotal, Other Contractual Services** | **65,498,000** | **65,361,000** | **(137,000)** |
| 26.0 Supplies & Materials | 2,985,000 | 2,774,000 | (211,000) |
| 31.0 Equipment | 3,645,000 | 3,395,000 | (250,000) |
| 32.0 Land and Structures | 0 | 0 | 0 |
| 33.0 Investments & Loans | 0 | 0 | 0 |
| 41.0 Grants, Subsidies & Contributions | 326,738,000 | 322,138,000 | (4,600,000) |
| 42.0 Insurance Claims & Indemnities | 0 | 0 | 0 |
| 43.0 Interest & Dividends | 0 | 0 | 0 |
| 44.0 Refunds | 0 | 0 | 0 |
| **Subtotal, Non-Pay Costs** | **401,413,000** | **396,054,000** | **(5,359,000)** |
| **NIH Roadmap for Medical Research** | **3,896,000** | **5,231,000** | **1,335,000** |
| **Total Budget Authority by Object** | **435,930,000** | **433,318,000** | **(2,612,000)** |

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Salaries and Expenses**

| OBJECT CLASSES | FY 2006 Appropriation | FY 2007 Estimate | Increase or Decrease | Percent Change |
|---|---|---|---|---|
| **Personnel Compensation:** | | | | |
| Full-Time Permanent (11.1) | $14,958,000 | $15,632,000 | $674,000 | 4.5 |
| Other Than Full-Time Permanent (11.3) | 5,926,000 | 6,219,000 | 293,000 | |
| Other Personnel Compensation (11.5) | 459,000 | 481,000 | 22,000 | 4.8 |
| Military Personnel (11.7) | 410,000 | 430,000 | 20,000 | 4.9 |
| Special Personnel Services Payments (11.8) | 2,917,000 | 3,040,000 | 123,000 | 4.2 |
| **Total Personnel Compensation (11.9)** | **24,670,000** | **25,802,000** | **1,132,000** | **4.6** |
| Civilian Personnel Benefits (12.1) | 5,585,000 | 5,847,000 | 262,000 | 4.7 |
| Military Personnel Benefits (12.2) | 366,000 | 384,000 | | |
| Benefits to Former Personnel (13.0) | 0 | 0 | 0 | 0.0 |
| **Subtotal, Pay Costs** | **30,621,000** | **32,033,000** | **1,412,000** | **4.6** |
| Travel (21.0) | 801,000 | 756,000 | (45,000) | -5.6 |
| Transportation of Things (22.0) | 243,000 | 226,000 | (17,000) | -7.0 |
| Rental Payments to Others (23.2) | 10,000 | 9,000 | (1,000) | -10.0 |
| Communications, Utilities and Miscellaneous Charges (23.3) | 1,284,000 | 1,194,000 | (90,000) | -7.0 |
| Printing and Reproduction (24.0) | 208,000 | 200,000 | (8,000) | -3.8 |
| **Other Contractual Services:** | | | | |
| Advisory and Assistance Services (25.1) | 288,000 | 272,000 | (16,000) | -5.6 |
| Other Services (25.2) | 2,568,000 | 2,399,000 | (169,000) | -6.6 |
| Purchases from Govt. Accounts (25.3) | 14,975,000 | 14,511,000 | (464,000) | -3.1 |
| Operation & Maintenance of Facilities (25.4) | 167,000 | 159,000 | (8,000) | -4.8 |
| Operation & Maintenance of Equipment (25.7) | 594,000 | 555,000 | (39,000) | -6.6 |
| Subsistence & Support of Persons (25.8) | 0 | 0 | 0 | 0.0 |
| **Subtotal Other Contractual Services** | **18,592,000** | **17,896,000** | **(696,000)** | **-3.7** |
| Supplies and Materials (26.0) | 2,985,000 | 2,774,000 | (211,000) | -7.1 |
| **Subtotal, Non-Pay Costs** | 24,123,000 | 23,055,000 | (1,068,000) | -4.4 |
| **Total, Administrative Costs** | **54,744,000** | **55,088,000** | **344,000** | **0.6** |

## NATIONAL INSTITUTES OF HEALTH

### National Institute on Alcohol Abuse and Alcoholism

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2006 House Appropriations Committee Report Language (H.R. 109-143)

Item

***Alcohol, obesity, and liver disease –*** The relationship among the use of alcohol, the occurrence of obesity, and the presence of liver diseases has become increasingly worrisome for clinicians. While alcohol's negative impact on weight and liver wellness is long established, the current epidemic of obesity and its consequent increase in liver disease creates a new focus for research. The Committee encourages NIAAA to focus greater attention to this relationship with special emphasis on the differentiation of impact of alcohol consumption on the liver for specific populations, such as women, minorities, the elderly, and others. (p. 90)

Action Taken or to Be Taken

Obesity is an added risk factor for the development of alcoholic liver disease (ALD), especially in such conditions as fatty liver, fibrosis, and cirrhosis, and it constitutes a major area of research at NIAAA. Alcohol increases fat synthesis by the liver in ways that promote damage to this vital organ.

NIAAA contributed to the NIH *Action Plan for Liver Disease Research* submitted to Congress in March 2005, in which sixteen areas of liver research were highlighted. Eight of these highlighted areas are actively pursued by NIAAA. In 2004, we assembled a multidisciplinary team to highlight research gaps and opportunities in the area of alcohol metabolism, obesity, and liver damage. The team's findings were presented to the NIAAA Extramural Advisory Board and to the National Advisory Council on Alcohol Abuse and Alcoholism in 2005. In response to their recommendations, we included these areas of research in a Request for Applications (RFA) for the study of alcohol metabolism and tissue injury, including the liver. In this RFA, investigators are encouraged to examine how alcohol consumption induces liver damage, especially in the presence of other risk factors such as obesity. Investigators are also encouraged to study how gender differences impact vulnerability to liver damage and how hormones may contribute to the process.

These issues were also highlighted at a NIAAA-organized workshop (*Mechanisms of Alcohol-Induced Hepatic Fibrosis*) at the 2005 meeting of the Research Society on Alcoholism, an important venue for stimulating research and sharing information among investigators. To stimulate research on other factors that influence alcohol-induced liver injury, such as the hepatitis C virus, NIAAA also organized a symposium for clinicians and basic researchers, in conjunction with the annual meeting of the American Association for the Study of Liver Diseases, in November 2005. In addition, NIAAA organized a workshop, *Role of Betaine in the Treatment of ALD*, to encourage studies on the role of nutrition and obesity in liver damage. In a paper published in *Hepatology*, a premier journal for liver research, NIAAA staff highlighted the

need to study special populations that are more vulnerable to ALD, such as women, African Americans, Hispanics, obese and diabetic individuals, patients with hemochromatosis, and Asians with variations in alcohol-metabolizing enzymes.

Item

***Translation –*** The Committee is interested in ensuring that current research on the health effects of alcohol and alcoholism is more effectively communicated and disseminated within the alcohol-abuse treatment community. The Committee recommends that NIAAA jointly work with related alcohol research organizations on a plan to broaden the reach and timely communication of funded alcohol and alcoholism research to the treatment community. (p. 90)

Action Taken or to Be Taken

An essential part of NIAAA's portfolio is research on the health effects of alcohol use and the development of new and improved treatments for alcoholism and alcohol use disorders. NIAAA has been working diligently with professional societies including the Research Society on Alcoholism, the American Society on Addiction Medicine (ASAM), the American Psychological Association (APA), and the American Psychiatric Association, as well as other Federal Agencies, to translate and transfer research-based information for application in real-world treatment and prevention settings. NIAAA will build on these efforts, a few of which are highlighted below.

In July 2005, NIAAA released an updated guide for health care practitioners to help them identify, diagnose and treat patients with heavy drinking and alcohol use disorders. Entitled *Helping Patients Who Drink Too Much: A Clinician's Guide,* this guide is written for primary care and mental health clinicians, and was prepared with guidance from physicians, nurses, physician assistants, and clinical researchers. The methods of alcohol screening and brief intervention included in the guide have demonstrated their ability to reduce drinking and alcohol-related problems. Large-scale distribution, including a national mailing to physicians through the American Medical Association, is currently underway. The guide is available online at http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf and in a pocket version.

To augment its own efforts, NIAAA collaborates with other HHS agencies to foster the application of treatment and prevention practices that have been shown to be effective in research. For example, through an interagency science-to-service initiative led by the Substance Abuse and Mental Health Services Administration (SAMHSA), NIAAA has collaborated with the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH) in developing a research-based list of effective treatment and prevention practices to encourage their adoption on the front lines of clinical care. Plans are also being initiated to jointly fund NIAAA, NIDA, and NIMH research announcements in order to stimulate wider application of these best practices.

NIAAA also is working with several key professional organizations to encourage application of alcohol-research findings by their members. In 2005, the APA and NIAAA collaborated to present NIAAA-funded findings at the APA's annual conference, attended by 12,000 to 15,000 psychologists and researchers. In 2006, NIAAA plans to sponsor a series of presentations of

clinically-relevant alcohol-research findings at the annual meeting of the American Psychiatric Association, which is expected to attract approximately 10,000 to 12,000 psychiatrists and researchers. In 2006, NIAAA also will present a symposium, *Medications Development for Alcoholism: From the Bench to the Patient*, for members of the ASAM.

FY 2006 Senate Appropriations Committee Report Language (S.R. 109-103)

Item

***Alaska Substance Abuse*** – The Committee is aware of serious problems with alcohol and substance abuse, especially among its Alaska Native population, and the need for translating research into clinical applications for this population. The Committee urges NIAAA to sponsor a Research to Practice Forum with the Substance Abuse and Mental Health Services Administration to focus on bridging the gap between researchers and practitioners and translating scientific research into clinical applications, and encourages NIAAA to support the implementation of any recommendations developed at the forum. (p. 139)

Action Taken or to Be Taken

The Institute is currently funding the only treatment study of alcoholism in a Native Alaskan population. Using a rural health model, the study is evaluating the efficacy of several pharmacological adjuncts in augmenting the existing alcoholism treatment for Alaskan Natives. The rural health model utilizes local Alaskan primary care providers and native peoples rather than specialized providers to deliver a medical management intervention in a remote rural setting. These medications are being evaluated alone and in combination in a double blind, placebo controlled study of alcohol dependent individuals of Alaskan heritage. The study will determine whether these medications can reduce the risk of alcohol relapse when used in conduction with alcohol counseling. Upon completion of this study the results and clinical implications of this research will be disseminated to local practitioners in a Research to Practice Forum. This project has the enthusiastic support of the Southern Alaska Regional Health Consortium (SEARCH), the native health care consortium which is the site for the study.

NIAAA, through its health disparities strategic plan, has made a clear commitment to expand community outreach efforts that increase access to research findings and the create appropriate alcohol and health materials, education for health professionals, and incorporate community input regarding alcohol research that will have direct applications to target communities including Alaskan Native and Native American populations. In addition, NIAAA has embarked on a series of important collaborative projects with the Substance Abuse and Mental Health Administration (SAMHSA) to build relationships between researchers and practitioners aimed at speeding the application of research findings to clinical settings. These projects have included efforts to better address underage drinking and co-occurring disorders across minority and non-minority populations and to broadly disseminate *The Practitioner's Guide for Screening and Addressing Alcohol Problems.* More recently, NIAAA has embarked on a new venture with SAMHSA, the National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH) to co-sponsor a number of specific science-to-service forums. This effort includes the upcoming forum to bridge the gap between science and service in the use of pharmacotherapies to treat severe mental illness and co-occurring substance use disorders and effective treatment for adolescents. We are also leading the effort with SAMHSA to find innovative strategies to

rapidly apply what we are learning from implementation science and outcome research, especially with adolescents. It is our clear intent to continue to sponsor or co-sponsor problem specific forums with SAMHSA and other NIH agencies to continue to promote the high-quality plans for improving the quality of prevention and treatment services to address all people, including Alaskan Native and Native American populations.

Item

***Alcohol Abuse by College Students –*** Colleges continue to struggle with the consequences of alcohol abuse by students. The Committee encourages NIAAA to continue its program of fast-track approval for research grants to be carried out collaboratively by scientists and college administrators who express an urgent need for intervention. The Committee understands that NIAAA is updating the 2001 report of the NIAAA Task Force on College Drinking, to incorporate new findings. The Committee further encourages NIAAA to provide this update to college presidents and other relevant organizations. (p. 139)

Action Taken or to be Taken

NIAAA is supporting 15 fast-track partnerships at universities throughout the country. Intervention strategies under study in these projects include: the protective influence of residential learning communities; peer-facilitated alcohol interventions; campus – community coalitions; peer-led motivational enhancement with freshman women; a freshman parent-student initiative; fraternity and sorority interventions; alcohol screening and interventions in college clinics; reducing high-risk drinking among first-year students; university assistance programs; interventions for freshman violators; social norms interventions; and reducing high-risk drinking among students celebrating their 21st birthdays. Depending on the success of the currently funded projects, NIAAA will consider supporting additional similarly structured projects.

NIAAA will be issuing a new College Bulletin to update aspects of the report of the Task Force on College Drinking. The bulletin will include updated statistics on college drinking and its consequences, NIAAA's newly developed definition of binge drinking (which incorporates a 2-hour time frame), a discussion of alcohol poisoning, information on freshman year drinking patterns, a section discussing new research on individual and environmental interventions for college students, and updates on NIAAA's "Rapid Response" grant program and Underage Drinking Initiative. The NIAAA will distribute the bulletin widely among college presidents and administrators.

Item

***Alcohol Dependence as a Developmental Disorder –*** Epidemiology studies show that alcohol is the drug of choice for youth and that it is associated with a host of consequences in this age group, including death and increased risk of harm and other negative outcomes. The Committee is aware of more recent data showing that 18- to 24-year-olds have the highest prevalence of alcohol dependence of any age group. These and other data make it clear to the Committee that alcohol has become entrenched in the developmental processes of adolescence, and that the developmental changes of adolescence appear to make this age group particularly vulnerable to alcohol's effects. The Committee urges NIAAA to continue its youth initiative, to work toward understanding how to extricate alcohol from adolescent development and how to change adolescents' behaviors toward alcohol. The Committee recognizes the importance of including

scientists from several disciplines, from behavior to genetics, to reflect the many factors that contribute to underage drinking, and encourages NIAAA to continue guiding the research through its team approach. (p. 139)

Action Taken or to Be Taken

NIAAA has embarked upon a broad, multi-faceted, multi-disciplinary initiative to address underage drinking in a developmental framework. This initiative, led by NIAAA's Team on Underage Drinking, involves research, outreach and collaboration with other government entities. To inform this initiative, NIAAA convened an expert advisory group comprised of developmental scientists, biological scientists, geneticists, behavioral scientists, and policy and communications specialists. At a series of meetings, this group delineated key considerations in the area of underage drinking and developed recommendations for future studies. In October 2005, NIAAA published an issue of *Alcohol, Research and Health* entitled "Alcohol and Development in Youth: A Multidisciplinary Overview." This volume, which summarizes the current state of the science, has already been widely distributed and is also available on NIAAA's website in electronic form. It will help inform the Surgeon General's Call to Action on Underage Drinking, for which NIAAA and SAMHSA have been designated by the Surgeon General as principal partners.

NIAAA is planning to release a second publication specifically addressing the development of drinking behavior and alcohol-related problems in the context of overall child and adolescent development. NIAAA has also commissioned comprehensive reviews of the underage drinking prevention and treatment literature to synthesize the science to date, identify the most successful interventions thus far, and provide guidance for improved and expanded intervention efforts in the future. NIAAA will convene a feasibility/consensus conference in 2006 where experts will discuss recommendations for diagnosing alcohol use disorders in adolescents, screening instruments for use with adolescents, and expanding screening and brief intervention in underage populations. An initiative to expand research on alcohol and the developing brain will be implemented in 2007. In preparation for this, a collaboration to add the collection of drinking information to an ongoing NIMH longitudinal imaging study of the developing brain is being explored. The *Leadership to Keep Children Alcohol Free* continues to focus on the prevention of alcohol use by 9 to 15 year olds. The expert advisory group convened by the NIAAA's Team on Underage Drinking included two *Leadership* Governors' spouses.

Item

***Alcohol, obesity, and liver disease –*** The relationship among the use of alcohol, the occurrence of obesity, and the presence of liver diseases has become increasingly worrisome for clinicians. While alcohol's negative impact on weight and liver wellness is long established, the current epidemic of obesity and its consequent increase in liver disease creates a new focus for research. The Committee encourages NIAAA to focus greater attention to this relationship with special emphasis on the differentiation of impact of alcohol consumption on the liver for specific populations, such as women, minorities, the elderly, and others. (p. 139/140)

Action Taken or to Be Taken

Please refer to page 25 of this document for NIAAA's response regarding alcohol, obesity, and liver disease.

Item

***Brain Development –*** The Committee is aware of recent evidence that the human brain continues to develop for a longer period than previously thought, and that NIAAA has found physical differences in how adult brains and adolescent brains respond to certain stimuli. Biochemical and physiological events in the brain translate into behaviors. NIAAA is urged to continue research that will reveal biological links between adolescent brain changes, alcohol-related behaviors, and capacity for alcohol, and research that will reveal alcohol's short- and long-term impact on developmental changes in the adolescent brain. (p. 140)

Action Taken or To Be Taken

NIAAA currently supports sixteen grants on the brain mechanisms associated with adolescent drinking which cover the following research areas: 1) brain mechanisms and risk factors for alcoholism during late childhood through adolescence; 2) the interaction of genetic, neurobiological, environmental, and social factors (e.g., stress, peer influences) in the development of adolescent alcohol abuse; 3) the acute and long-term effects of heavy drinking during adolescence on cognitive/brain functioning; and 4) the contribution of early alcohol exposure to excessive drinking and abnormal cognitive and social functioning during subsequent developmental stages.

Despite advances in our knowledge of how the adolescent brain responds to alcohol, many questions remain unanswered. For example, we know that adolescents are less sensitive to the aversive effects, but more sensitive to the cognitive impairing effects of alcohol. Yet, we do not understand the underlying mechanisms for these phenomena. The role of puberty and associated life stressors, affective states, and social factors in the onset and continuation of adolescent drinking has not been delineated, nor do we fully understand the consequences of early heavy drinking on behavioral, physiological, or brain maturational processes.

To more clearly define the effects of heavy drinking on the adolescent brain, NIAAA collaborated with the National Institute on Drug Abuse (NIDA) on a Request for Applications (RFA) entitled, "*Consequences of Drug and Alcohol Exposure on Brain and Behavioral Development.*" This year, two new applications will be funded under this initiative to look at neural risk factors and consequences of heavy drinking on brain function in adolescents using neuroimaging and neurobehavioral techniques. NIAAA is also involved in a joint RFA on social neuroscience with NIDA and the National Institute on Aging at NIH, and the Institute of Neurosciences, Mental Health and Addiction in Canada. The purpose of this initiative is to stimulate research on the brain mechanisms underlying social behaviors, including social decision making, interpersonal/peer relationships, self-regulation, and emotional regulation as they relate to the development of adolescent alcohol abuse and dependence. These initiatives are part of our continuing research efforts to understand the relationship between adolescent brain changes and the propensity for teenagers to drink excessively at this stage of development, and its impact on subsequent brain development.

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Authorizing Legislation**

| | PHS Act/ Other Citation | U.S. Code Citation | 2006 Amount Authorized | FY 2006 Appropriation | 2007 Amount Authorized | FY 2007 Budget Estimate |
|---|---|---|---|---|---|---|
| Research and Investigation | Section 301 | 42§241 | Indefinite | $425,041,000 | Indefinite | $422,483,000 |
| Abuse and Alcoholism | Section 41B | 42§285b | Indefinite | | Indefinite | |
| National Research Service Awards | Section 487(d) | 42§288 | a/ | 10,889,000 | | 10,835,000 |
| Total, Budget Authority | | | | 435,930,000 | | 433,318,000 |

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Appropriations History**

| Fiscal Year | Budget Estimate to Congress | House Allowance | Senate Allowance | Appropriation 1/ |
|---|---|---|---|---|
| 1998 | 208,112,000 2/ | 226,205,000 | 228,585,000 | 227,175,000 |
| 1999 | 229,551,000 2/ 3/ | 248,778,000 | 259,747,000 | 259,747,000 |
| Rescission | 0 | 0 | 0 | (172,000) |
| 2000 | 248,916,000 2/ | 265,497,000 | 265,497,000 | 29,393,500 |
| Rescission | | | | (1,566,000) |
| 2001 | 308,661,000 2/ | 349,216,000 | 336,848,000 | 340,678,000 |
| Rescission | | | | (154,000) |
| 2002 | 381,966,000 | 379,026,000 | 390,761,000 | 384,238,000 |
| Rescission | | | | (623,000) |
| 2003 | 416,773,000 | 401,933,000 | 418,773,000 | 418,773,000 |
| Rescission | | | | (2,722,000) |
| 2004 | 430,121,000 | 430,121,000 | 431,521,000 | 431,471,000 |
| Rescission | | | | (2,802,000) |
| 2005 | 441,911,000 | 441,911,000 | 444,900,000 | 441,911,000 |
| Rescission | | | | (3,634,000) |
| 2006 | 440,333,000 | 440,333,000 | 452,271,000 | 440,333,000 |
| Rescission | | | | (4,403,000) |
| 2007 | 433,318,000 | | | |

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research
3/ Reflects a decrease of $692,000 for the budget amendment for Bioterrorism

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Detail of Full-Time Equivalent Employment (FTEs)**

| OFFICE/DIVISION | FY 2005 Actual | FY 2006 Appropriation | FY 2007 Estimate |
|---|---|---|---|
| Office of the Director | 11 | 11 | 11 |
| Office of Extramural Activities | 12 | 12 | 12 |
| Office of Scientific Affairs | 10 | 10 | 10 |
| Office of Research Translation and Communications | 14 | 14 | 14 |
| Office of Resource Management | 31 | 29 | 29 |
| Division of Epidemiology and Prevention Research | 10 | 12 | 12 |
| Division of Metabolism and Health Effects | 9 | 9 | 9 |
| Division of Neuroscience and Behavior | 10 | 10 | 10 |
| Division of Treatment and Recovery Research | 9 | 9 | 9 |
| Division of Intramural Clinical and Biological Research | 117 | 110 | 111 |
| Total | 233 | 226 | 227 |
| Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research | | | |
| FTEs supported by funds from Cooperative Research and Development Agreements | (0) | (0) | (0) |

| FISCAL YEAR | Average GM/GS Grade |
|---|---|
| 2003 | 11.6 |
| 2004 | 11.7 |
| 2005 | 12.4 |
| 2006 | 12.4 |
| 2007 | 12.4 |

**NATIONAL INSTITUTES OF HEALTH**
**National Institute on Alcohol Abuse and Alcoholism**

**Detail of Positions**

| GRADE | FY 2005 Actual | FY 2006 Appropriation | FY 2007 Estimate |
|---|---|---|---|
| Total - ES Positions | 3 | 3 | 3 |
| Total - ES Salary | $461,105 | $470,327 | $479,733 |
| GM/GS-15 | 21 | 20 | 20 |
| GM/GS-14 | 42 | 40 | 40 |
| GM/GS-13 | 39 | 37 | 38 |
| GS-12 | 28 | 26 | 26 |
| GS-11 | 11 | 10 | 10 |
| GS-10 | 1 | 1 | 1 |
| GS-9 | 9 | 9 | 9 |
| GS-8 | 6 | 6 | 6 |
| GS-7 | 5 | 5 | 5 |
| GS-6 | 0 | 0 | 0 |
| GS-5 | 1 | 1 | 1 |
| GS-4 | 1 | 1 | 1 |
| GS-3 | 0 | 0 | 0 |
| GS-2 | 0 | 0 | 0 |
| GS-1 | 0 | 0 | 0 |
| Subtotal | 164 | 156 | 157 |
| Grades established by Act of July 1, 1944 (42 U.S.C. 207): | | | |
| Assistant Surgeon General | | | |
| Director Grade | 2 | 2 | 2 |
| Senior Grade | 4 | 4 | 4 |
| Full Grade | | | |
| Senior Assistant Grade | | | |
| Assistant Grade | | | |
| Subtotal | 6 | 6 | 6 |
| Ungraded | 76 | 76 | 76 |
| Total permanent positions | 174 | 167 | 168 |
| Total positions, end of year | 249 | 242 | 243 |
| Total full-time equivalent (FTE) employment,end of year | 233 | 226 | 227 |
| Average ES level | ES-5 | ES-5 | ES-5 |
| Average ES salary | $153,701 | $156,776 | $159,911 |
| Average GM/GS grade | 12.4 | 12.4 | 12.4 |
| Average GM/GS salary | $86,568 | $88,299 | $90,065 |

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research