DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

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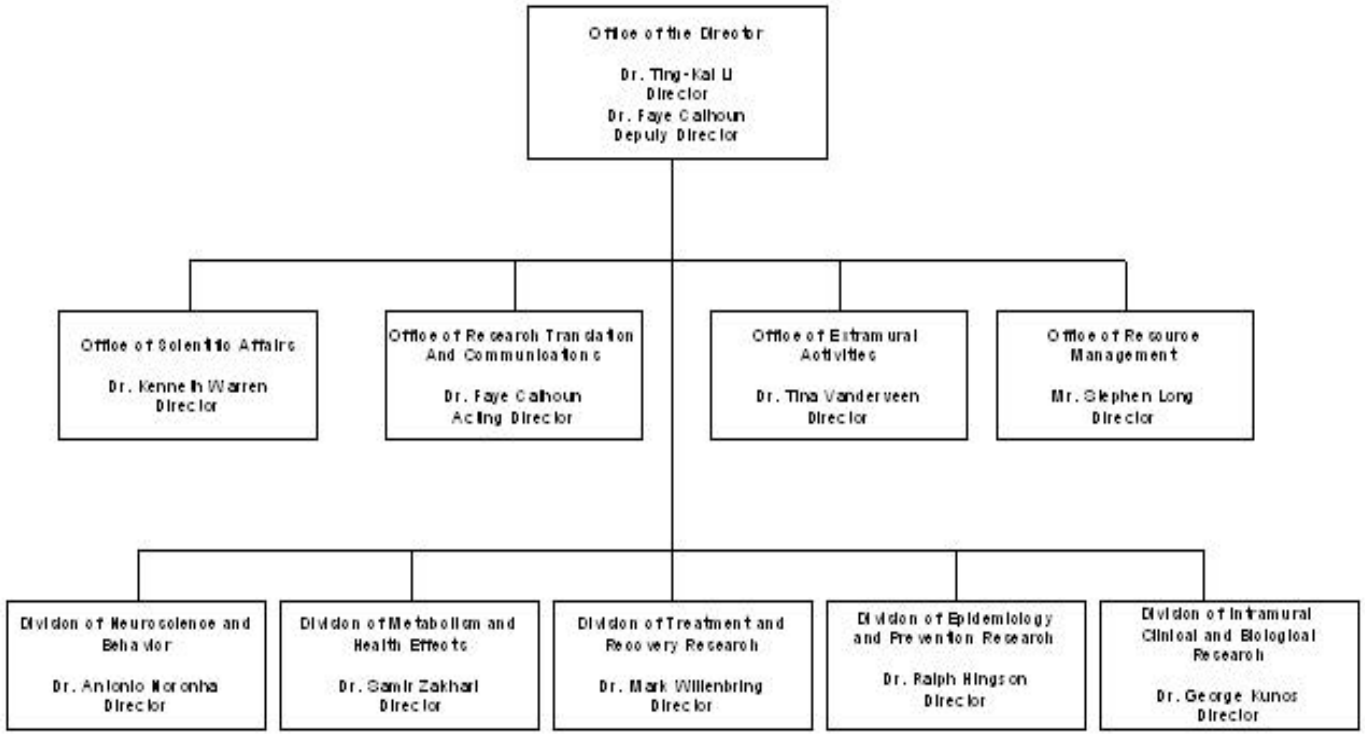
NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism



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, [$441,911,000] *$440,333,000.*

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Consolidated Appropriations Act, 2005]

National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$431,471,000	$441,911,000	$440,333,000
Enacted Rescissions	(2,802,000)	(3,634,000)	0
Subtotal, Adjusted Appropriation	428,669,000	438,277,000	440,333,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	(1,411,000)	0	0
Comparative transfer to NIBIB for Radiology Program	(28,000)	0	0
Comparative transfer to Buildings and Facilities	(216,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	1,411,000	0	0
Subtotal, adjusted budget authority	428,425,000	438,277,000	440,333,000
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	428,425,000	438,277,000	440,333,000
Unobligated balance lapsing	(35,000)	0	0
Total obligations	428,390,000	438,277,000	440,333,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $3,282,000 FY 2005 -$3,282,000 FY 2006 - $3,282,000
Excludes $4,478 in FY 2004 and $4,785 in FY 2005 for royalties.

Justification

National Institute on Alcohol Abuse and Alcoholism

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

Budget Authority:

FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
252	$428,425,000	233	$438,277,000	233	$440,333,000	0	$2,056,000

This document provides justification for the Fiscal Year 2006 activities of the National Institute on Alcohol Abuse and Alcoholism, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2006 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

Excessive alcohol consumption is the number-three cause of preventable death in the United States, the Centers for Disease Control and Prevention reported in 2004 (see Figure 1). The World Health Organization also ranked alcohol third among preventable risk factors for premature death in developed nations, in its 2002 report.

Put another way, leading epidemiologists from two eminent organizations, independently of each other and of the National Institutes of Health, have issued a wake-up call to the Nation and to the world: the amount of morbidity and mortality resulting from alcohol misuse is huge.

Why is excessive drinking such a big risk factor for death and disability? Is it the result of sheer numbers; that is, because so many people drink excessively, for whatever reason – because they simply like the way alcohol makes them feel, or because they seek relief from difficult emotions, or because they think that heavy drinking is expected of them in various situations?

Why Alcohol Ranks In the Top Three

The reasons listed above are just some of the factors that contribute to alcohol's high ranking. Much of the answer has to do with alcohol itself, with what it does in our bodies at the biological and chemical levels. Drinking too much, too fast, causes death and disability because it impairs judgment and motor coordination in the occasional drinker, raising the risk of injury. Drinking

too much, too often, not only puts people at risk of injury, but also can lead to adaptations, in the brain, that underlie addiction. When people become chronic, heavy drinkers, their cells, tissues, and organs also get high levels of exposure to this registered toxin and carcinogen.

Actual Causes of Death,[1] United States - 2000

Actual Cause	No. (%) in 2000
Tobacco	435, 000 (18.1)
Poor diet and physical inactivity	400,000 (16.6)
Alcohol consumption	**85, 000 (3.5)**
Microbial agents	75,000 (3.1)
Toxic agents	55, 000 (2.3)
Motor vehicle	43, 000 (1.8)
Firearms	29, 000 (1.2)
Sexual behavior	20, 000 (0.8)
Illicit drug use	17,000 (0.7)
Total	1,159,000 (48.2)

[1]Actual Causes of Death are the major external (nongenetic) modifiable factors that contribute to death in the United States

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

Figure 1. Alcohol appears third in the Centers for Disease Control and Prevention's list of preventable causes of death in the United States.

The answer also has to do with social and legal issues – issues of availability and social acceptance of various alcohol-related behaviors. And it has to do with alcohol's uniqueness in the degree to which new research findings about a disease of this magnitude aren't incorporated in clinical practice.

At the biological level, alcohol interacts with several of the brain's neurotransmitter systems, either directly or indirectly. These are the chemical and electrical communication systems that enable nerve cells to transmit crucial "messages" to each other, ensuring proper brain function. Alcohol's chemical nature is such that its biological interactions in the brain (and other organs) are uniquely widespread among substances of abuse.

The biologically active proteins of which these neurotransmitter systems are made are essential regulators of brain-cell function. Underlying the proteins are the genes that produce them. Genes account for about half of the risk of alcoholism, and here is one of the ways in which they raise our risk of alcoholism or protect us from it: variations in genes result in variations in the proteins they produce, including proteins in neurotransmitter systems. In turn, variations in these highly interactive proteins can translate into variations in cell and organ function and behavior,

including alcohol-related behavior.
Some people don't become alcoholic simply because they don't like what alcohol does to them, so they avoid it. It might very quickly make them feel incapacitated, for example. This has a protective effect against alcoholism. Others have the capacity to drink a lot (if they choose to, that is; environmental influences comprise the other half of the risk of alcoholism). The genetic/biological variations described above play a major role in these scenarios – variations in how alcohol makes us feel – and are major contributors to whether or not people are at risk of alcoholism.

Variations in alcohol metabolism also play a major role, and here, too, genes and proteins are involved. Some variations result in differences in how well people metabolize alcohol. For example, certain variations can result in physical discomfort. People who experience unpleasant sensations in response to alcohol may choose to avoid it.

When people do have the capacity to drink a lot, and their environment or other factors also promote drinking, they are at risk. If they drink as heavily as their capacity permits, they risk immediate causes of death or disability resulting from impaired judgment and motor coordination – factors that lead to injury or violence, for example. On a longer-term basis, they risk organ damage and adaptations in brain cells that could lead to alcohol dependence.

What Can We Do About It?

We are directing our efforts toward research that could have the largest impact on morbidity and mortality rates from excessive alcohol consumption. Our research is designed to:

- Address populations at highest risk. Studies show that, by far, youth have the highest prevalence of alcoholism and that most cases appear by age 25 (see Figure 2). Developing strategies to prevent underage drinking is crucial. Adolescent brains are still developing, and adding alcohol to the biological mix during this period of physiological transition might result in long-term consequences. Some animal studies suggest that alcohol misuse during adolescence could result in long-term cognitive deficits.

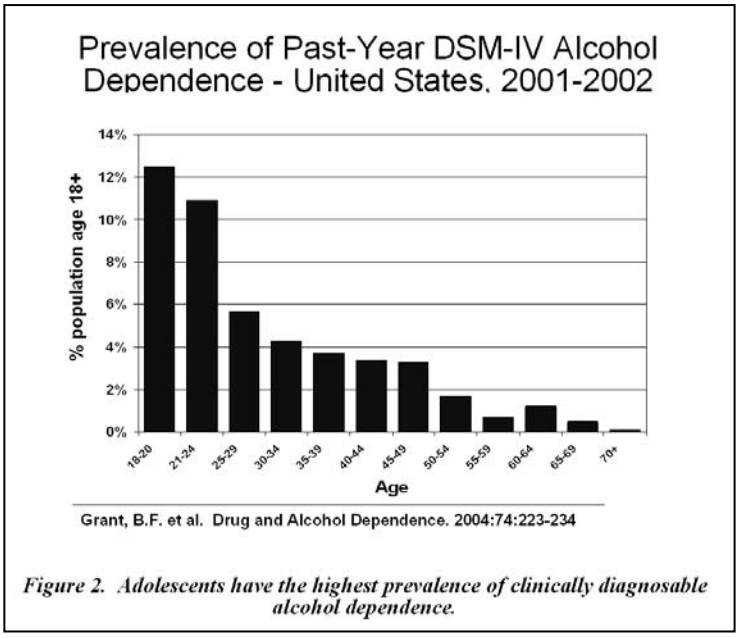


Figure 2. Adolescents have the highest prevalence of clinically diagnosable alcohol dependence.

- Identify the genes, proteins, and pathways involved in alcohol's behavioral and physical effects; identify molecular targets for medication development. Developing medications with a higher overall success rate is a top priority in alcohol research. Because the success of a given medication for alcoholism can either succeed or fail in people of similar demographics, the overall success rate of treatment is modest. This variability is due, in part, to the gene variations (and thus protein variations) they've inherited. Identifying these variations and developing medications that are responsive to them is a top priority.

- Identify environmental factors that contribute to (or protect against) alcohol misuse, and how these factors also interact with genetic/biological influences to increase (or protect against) the risk. Teasing apart these factors, so that we will know when they are acting singly or in combination, will help us develop more targeted treatments.

- Identify variations in alcohol metabolism that promote alcoholism or protect people from it. We also need to clarify the role that alcohol metabolism plays in alcohol's toxic effects on virtually any of the body's tissues and organs. Medical consequences of alcohol misuse, such as liver disease, contribute to alcohol's high-ranking rate of morbidity and mortality in the U.S. Understanding these effects at the molecular level will help us develop targeted pharmaceuticals for prevention and treatment.

- Develop strategies to ensure that findings from alcohol research are incorporated in clinical practice. Despite the magnitude of alcohol-related death and disability, and despite dissemination efforts, new findings from alcohol research meet largely with immobility on the part of the medical community.

Promising new medications are available for the treatment of alcoholism, but physicians generally do not regularly screen their patients for alcohol problems. Meanwhile, research supports the effectiveness of brief interventions in the clinical setting. With other diseases that result in morbidity and mortality of the magnitude generated by alcohol misuse, the medical community tends to be much more responsive to research findings. Alcohol's ambiguous social and legal status, as well as the fact that it appears, paradoxically, to offer some protection against certain chronic diseases, when used in moderation, are probable factors.

To address this need, NIAAA is establishing intramural clinical/research internships in alcohol abuse and alcoholism, as well as other training programs, for psychiatry and neurology residents. In this way, the Institute will help ingrain current alcoholism treatments into the armamentarium of the next generation of practitioners. This next generation of physicians will have the mindset that findings on alcohol diagnosis and treatment continue to emerge and should be incorporated in clinical practice.

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STORY OF DISCOVERY

Markers and Meds for Alcoholism: What Do Genes and Proteins Have to Do With It?

Studies show that about 50 percent of the risk of alcoholism is genetic. The other half of the risk comes from environmental influences. But *how* do genes put people at more or less risk of alcoholism? What do genes do in the body, in our cells, that leads to this common, life-altering disease? And how will knowing the answers to these questions help doctors prevent and treat it?

Scientists have built on two different approaches over the years – one is molecular/cell biology; the other is genetic epidemiology – to independently strengthen evidence for one of the mechanisms through which genes appear to contribute to alcoholism. It has to do with one of the major neurotransmitter systems in the brain – gamma-aminobutyric acid (GABA) – and its receptors on brain cells. Recent findings in this area are pointing the way to a potential genetic marker for risk of alcoholism, a key to early intervention. Along the way, potential targets for new medications, a major clinical need, are being revealed.

The Molecular Side: How Neurotransmitters Fit Into the Picture

Neurotransmitters carry messages from one brain cell to the next. They bind to receptors (proteins) in the membranes of the cells and regulate the electrical signals the cells use to process information. They also initiate changes in biochemical pathways in the cells. Some neurotransmitters, such as GABA, inhibit the electrical impulses that act as signals to brain cells. Other neurotransmitters promote them. These systems control how cells communicate as they carry out crucial brain functions. Substances that act on these systems can cause changes in them that translate into altered thought processes and behavior.

Since GABA was discovered in crayfish, in the 1960s, studies have revealed its pharmacological importance. Scientists found that drugs with anticonvulsant and sedative-hypnotic properties, such as barbiturates and benzodiazepines, act within molecular sites in GABA receptors. These medications work by slowing down impulse transmission through GABA, even more than GABA usually does.

Alcohol has sedating properties, and in the 1980s, scientists found that it, too, acts on the GABA system. They found that short-term alcohol exposure increases GABA's actions in animal brain cells, in specific brain areas. Later studies found that *chronic* alcohol exposure – a key concept, since alcoholism involves chronic exposure of brain cells to alcohol – has the opposite effect; it makes the GABA system less effective and, when alcohol is withdrawn, cells trigger electrical impulses more readily than is normal. Questions emerged: Is this gradual change in the GABA system one of the reasons alcoholics need to keep drinking and to drink ever-larger amounts? Is heavier drinking the brain's effort to recapture alcohol's initial boost of GABA's suppressive ("calming") effects on impulse transmission?

In the early 1990s, researchers began to focus more closely on GABA's receptors and their role in mediating alcohol's actions. They began to identify subunits that comprise the protein of which GABA receptors are made. The scientists then tested these subunits to see if they were sensitive to alcohol. One kind of GABA receptor ($GABA_A$) was a central focus. At the same time, imaging techniques showed that $GABA_A$ receptor activity is disrupted in people with a family history of alcoholism, suggesting a genetic link between the $GABA_A$ receptor and alcoholism.

Through these and many other studies, the overall picture emerging from molecular studies is that $GABA_A$ is one of alcohol's routes of action on brain cells and behavior. Today, we know that there are many sites of alcohol's action in the brain's neurochemistry. $GABA_A$ is considered an important one, and genetic studies are adding weight to the evidence.

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The Genetic Side: How Genes and Proteins Fit Into the Picture

Throughout life, genes turn on and off to produce proteins at the right time, when the proteins – like GABA receptors – are needed for critical cell functions. Everyone inherits the same genes that produce the same proteins, but variations people inherit may predispose them to certain diseases, like alcoholism. The key is finding out which gene variants lead to which alcohol-related traits. It's complex, because specific collections of genes on different chromosomes appear to influence different alcohol-related traits.

In the late 1980s, researchers from the Collaborative Study on the Genetics of Alcoholism (COGA) joined the effort to find out what makes some people become alcoholic, but others not, and began a concerted search for the contributory genes. By the 1990s, statistical studies from this NIAAA-funded project suggested that chromosome 4, among others chromosomes, were hot spots; that is, they were linked to alcohol-related behavioral traits. (Chromosomes are strands of DNA divided into segments that carry blueprints – "encode" – for specific proteins and regulate their production; each such segment is a gene.)

COGA researchers then compared variations in specific regions of DNA in groups of people with and without certain alcohol-related traits and linked them to genes on chromosome 4 encoding some of the subunits that comprise the $GABA_A$ receptor. Other researchers, from the NIAAA intramural program, independently found similar evidence.

Meanwhile, animal studies were enabling alcohol researchers to eliminate or enhance genes for subunits of the $GABA_A$ receptor. Scientists could then observe whether these changes resulted in physical and behavioral changes. These studies, too, linked specific $GABA_A$ subunits to alcohol-related traits.

Recent techniques have enabled scientists to quickly and cost-effectively find variations in thousands of genes and their effects on alcohol-related traits simultaneously. They're looking at collections of variations in individual building blocks of DNA – "bases" – for variations that occur with higher-than-usual frequency in specific populations. These "single nucleotide polymorphisms" (SNPs) can help identify which combinations of $GABA_A$ subunits affect which alcohol-related traits.

This technique recently enabled COGA investigators to make an important discovery. Previously, they had shown that people at risk of alcoholism differ from other people in one of their brainwaves (the beta wave). They went on to find a strong link between the alcoholism-predicting beta wave and a cluster of $GABA_A$-encoding genes on chromosome 4. Now, COGA researchers have shown that the human gene for a *subunit* of the $GABA_A$ receptor (the $\alpha 2$ subunit) is associated not only with the beta brainwave, but also with alcohol dependence. These are the kinds of studies that lead to genetic screening tools for risk of diseases like alcoholism and, potentially, to molecular points for pharmaceutical interventions.

As widespread as alcohol's actions are in the brain, it's likely that multiple genes will be linked to a variety of components of cell communication associated with alcohol-related traits. It's already happening. For example, COGA researchers also have found a link to alcoholism in another gene for a $GABA_A$ receptor subunit, on chromosome 15 – another potential trait marker.

Involvement by other neurotransmitter systems also is well documented. One of them, the cannabinoid system, was the focus of last year's Story of Discovery and is the molecular target of a medication being tested in a NIAAA clinical trial. As scientists learn how these various biological systems are involved in alcohol-related pathology, opportunities for medication development and biological markers of risk are emerging.

Selected Science Advances

Why Teens Fall for the Quick Fix

Background: Most cases of alcoholism appear in young people by the age of 25, making youth the age of greatest risk. Understanding the biological and behavioral mechanisms that underlie the development of alcoholism, and how they are linked, is crucial to understanding how to prevent and treat it.

Behaviors have biological underpinnings in the brain; for example, specific areas of the brain underlie the pursuit of rewards and the gratification of achieving them – our motivation to pursue the food and water that sustain us, for example. It is an ancient mechanism that has ensured our survival. Within these areas of the brain are the nerve cells that comprise them, and, within and around the cells, hundreds of synchronized biochemical reactions regulate cell functions that influence these behaviors.

The same "reward" area of the brain is thought also to underlie, in part, the pursuit and gratification involved in alcohol and other substance abuse. Scientists are identifying various components of this reward system, at the anatomical and physiological levels, and how they affect behavior.

In youth, some parts of the brain are still developing. In this comparison of adolescents and adults, scientists compared activity in areas of the brain known to be involved in this ancient pursuit-and-gratification scenario. They used magnetic resonance imaging to observe brain activity when adolescents and adults (1) anticipated a small cash reward and (2) actually received the cash.

Finding: During anticipation, a specific network of nerve cells known to underlie motivation is underactive in adolescents, compared with that in adults. (This "ventral striatal" neural circuit is part of the brain's reward area.) However, brain activity was similar in adolescents and adults when they actually received their cash rewards.

Implications: This study helps define the biology that underlies reward-related behavior in youth, the group at greatest risk of alcoholism. It shows us that adolescents appear not to have yet fully developed the molecular machinery required to sustain motivation – to work toward rewards. This could explain what every parent knows: that teens often won't do what it takes to achieve delayed rewards, but readily succumb to quick fixes – such as the immediacy of perceived social rewards and pleasurable sensations of alcohol. More important, the findings point to a circuit in the brain that, in future research, could reveal opportunities for interventions specific to this most vulnerable age group.

Less Response to Alcohol Means Higher Risk; Trait Linked to Gene

Background: Alcoholism has its roots in the brain, where an immense array of biochemical pathways act as intermediaries of alcohol's actions in nerve cells. Included in these pathways are genes that produce proteins, molecules that regulate every step of the brain's biochemistry. An inherited variation in a gene means a variation in the protein it produces, and thus can mean a variation in the pathways the protein regulates. Researchers have evidence that gene variants account for about half of the risk of alcoholism.

Scientists are defining how alcohol-related behaviors are linked to these many variants in genes, proteins, and pathways. In this study, researchers examined behaviors related to initial level of response to alcohol, because people and animals with a low initial response have been shown to be at greater risk of alcoholism. However, after a long period of frequent, heavy exposure to alcohol, the initial response to subsequent exposures begins to change as brain cells adapt to it. These brain changes underlie tolerance, a key factor in development of alcoholism.

In this study, scientists studied tolerance in a model that seems anything but elegant, but whose name is *C. elegans* – a worm that really does provide an elegant model for the study of alcohol-related genetics. Biological pathways that regulate a host of diseases are found across species, and some pathways that regulate development of tolerance to alcohol are among them. We can observe response to alcohol in *C. elegans*, then conduct experiments that would be impossible in humans to track down the genes linked to the response. The simplicity of the *C. elegans* genome, and the fact that we can manipulate it, enables us to do this. The results give us important clues about which genes to look for in the more complex human genome.

The findings from this study involve a fragment of biologically active brain protein, the neuropeptide NPR-1, that serves functions in *C. elegans* that the neuropeptide NPY serves in humans. NPY has been the subject of intensive studies by alcohol researchers, who have shown that it influences how much alcohol humans and animals drink. They've found that variations in human genes for NPY are associated with differences in alcohol consumption. Each of these variations, single nucleotide polymorphisms or "SNPs," consists of an altered sequence of the compounds that comprise a single building block of DNA in a given gene.

Researchers compared two groups of *C. elegans* with different initial responses (tolerance) to the same concentrations of alcohol, then used SNPs as markers as they searched for the genes that played a part in the response.

Finding: Scientists mapped *C. elegans'* tolerance to alcohol to the gene for NPR-1. They found that one variant of the gene was associated with faster adaptation – tolerance – to alcohol.

Implications: Faster development of tolerance to alcohol's effects translates into ability to drink more, raising the risk of alcoholism. This study points to the gene for NPY as having a role in development of tolerance, thanks to the powerful model provided by *C. elegans*. In turn, this raises the possibility that NPY could be a pharmaceutical target or that variations in the gene for NPY could serve as markers of risk.

The Right Treatment?

Background: To treat substance-use disorders and mood and anxiety disorders effectively, clinicians first have to know what they're dealing with. An ongoing obstacle has been that substance abuse can induce mood and anxiety disorders, clouding the picture. But many people have (1) a mood or anxiety disorder *and* (2) a substance-use disorder, each of which developed *independently* of one another. In other words, the mood or anxiety disorder wasn't induced by the effects of intoxication or withdrawal; it is "independent."

When mood or anxiety disorders are induced by intoxication or withdrawal, they generally resolve when the substance abuse stops. But if the mood or anxiety disorder isn't substance-induced, it must be treated in and of itself. The conventional thinking has been that the majority of mood and anxiety disorders co-occurring with substance-use disorders are substance-induced. But making a science-based distinction is important for effective treatment, which could have a large impact. The 10 mental health disorders most costly to six major U.S. employers include alcoholism and mood/anxiety disorders, a 2003 article in the Journal of Occupational and Environmental Medicine (vol. 45, issue 1) revealed.

In the new study, NIAAA scientists surveyed more than 43,000 people 18 years and older, as part of the National Epidemiologic Survey on Alcohol and Related Conditions. They examined the prevalence of mood and anxiety disorders that co-occur with substance-use disorders, but that developed independently of them (i.e., mood or anxiety disorders that were present before substance use began or lasted more than a month after substance cessation or withdrawal.)

This was the first epidemiologic study of its scope to use recent American Psychiatric Association diagnostic criteria that make the distinction between substance-induced mood or anxiety disorders and those that develop independently. The study sample was nationally representative and included important groups not usually included in surveys of the general population. The study also corrected previous under-representation of Hispanics and Blacks.

Finding: Mood or anxiety disorders that develop independently of substance intoxication and/or withdrawal are among the most prevalent psychiatric disorders in the U.S. Less than 1 percent of mood or anxiety disorders are substance-induced. Among people seeking treatment for a mood or anxiety disorder that developed independently of an alcohol- or drug-use disorder, almost 18 percent have an alcohol-use disorder; nearly 8 percent have a drug-use disorder. Among people seeking treatment for an alcohol-use disorder, almost 41 percent and almost 33 percent have a mood or anxiety disorder, respectively, that developed independently of intoxication or withdrawal. (Rates of independently occurring mood or anxiety disorders among people seeking treatment for a drug-use disorder are about 60 percent and 43 percent, respectively.)

Implications: These results call for clinicians to recognize the high prevalence of patients in whom independent mood and anxiety disorders co-occur with substance abuse. In these patients, mood and anxiety disorders must receive appropriate treatment separate from substance-abuse treatment. Given the widespread co-occurrence of these disorders, the new findings have major clinical, social, and financial implications.

A "Shuttle" for Neurotransmitter Adenosine Implicated in Alcohol's Effects

Background: It might seem counterintuitive, but people who appear to handle alcohol better than others – who are less sensitive to its sedating properties and its effects on coordination, for example – tend to be at higher risk of alcoholism. They're able to drink more, and heavy drinking leads to adaptations in brain cells that lead to this destructive disease.

What happens in the nerve cells of the brain that influences how sensitive people are to alcohol and how much they drink? A number of neurotransmitter systems act as intermediaries of alcohol's actions in the brain, and differences in them can cause differences in behaviors. The adenosine system is one of them. It regulates communication among nerve cells by intermittently suppressing them. A recent article in Nature Neuroscience makes a compelling case for specific parts of the adenosine system as important players.

The A_1 receptor for the neurotransmitter adenosine is in the membrane surrounding nerve cells, and when adenosine binds to it, the receptor becomes active. This results in signals in nerve cells that initiate certain functions, including functions that lead to sedation and to coordination problems. It was this similarity to alcohol's effects on behavior that suggested to scientists that the adenosine system might be one of the targets of alcohol's actions.

In this mouse study, scientists focused on the ENT-1 transporter, a molecule that keeps adenosine from further binding with A_1 receptors. Earlier studies, in cultured cells, showed that alcohol changes ENT-1 activity in ways that diminish the signaling in nerve cells that results from A_1 receptor activation. Chronic alcohol exposure results in a drop in ENT-1 production.

By genetically eliminating the ENT-1 transporter, scientists in this study created a scenario similar to chronic alcohol exposure (i.e., diminished A_1-related signaling). Then, in the same mice, researchers pharmaceutically restored the A_1 receptor activity they had diminished when they eliminated the ENT-1 transporter. They asked how manipulating different components of the adenosine system affected the amount of alcohol mice drank and their response to alcohol.

Finding: For the first time, scientists drew direct links between the ENT-1 adenosine transporter and alcohol's behavioral outcomes in living animals. Compared with normal mice, animals lacking the transporter drank twice as much alcohol. Even when both groups had the same blood-alcohol level, the ENT-1-deficient mice were less sedated and had fewer coordination problems. However, injecting ENT-1-deficient mice with a compound that independently stimulated A_1 receptor signaling reduced their alcohol consumption and preference.

Implications: We knew that alcohol's initial boost of A_1-related signaling diminishes when alcohol exposure becomes chronic, a potential explanation of how tolerance to alcohol, a hallmark of alcoholism, develops. Scientists are zeroing in on parts of the adenosine system, such as the ENT-1 transporter, that play a role in preference for alcohol, amount consumed, and sensitivity to its effects – a predictor of risk. Would manipulating specific components of the adenosine system with new medications – for example, those that stimulated the A_1 receptor – reduce drinking in people with alcoholism?

Valproate Shows Promise in Reducing Heavy Drinking By Bipolar Alcoholics

Background: Mental disorders and substance-use disorders often occur in the same person, complicating treatment. Studies consistently report that people with one condition, bipolar disorder (in which mania alternates with depression) have a higher rate of substance-use disorders than does the general population. More than 2 million American adults have bipolar disorder, according to the National Institute of Mental Health, and about 61 percent of them have a substance-use disorder. Compared with the general population, they are 10 times more likely to be alcohol dependent and 8 times more likely to abuse other substances. Among all other psychiatric disorders, bipolar disorder has the second highest rate of co-occurring alcohol or substance abuse.

Lithium is the traditional medication of choice for bipolar patients. However, when lithium was tested in depressed alcoholics, it didn't reduce their drinking. Valproate, an anti-seizure drug that has shown promise for treatment of alcoholics *without* a co-occurring psychiatric disorder, also appears to reduce mania in bipolar patients who aren't alcoholic.

In this study, researchers asked how valproate would affect patients who had both bipolar disorder and alcoholism. They compared patients who were demographically and clinically similar, more than one-fourth of whom were female and one-fourth of whom were African-American. For 6 months, all of the patients continued their lithium and psychosocial treatments, but also were given either valproate or a placebo. Neither the patients nor the clinicians knew which treatment was given until the end of the study.

Finding: Fewer of the alcoholic bipolar patients who took valproate in this study had heavy-drinking days, compared with those on placebo (44 vs. 68 percent, respectively). Valproate patients also took longer to relapse into heavy drinking than did placebo patients (93 days vs. 62 days). No serious side effects were reported among patients on valproate, while the placebo group had significantly worse scores on a liver-function test.

Implications: In patients with bipolar disorder, alcoholism increases suicide risk, medical complications, impulsivity, violence, and costs for services, and decreases cognitive function and compliance with treatment. The finding described here offers clinicians a way of helping some bipolar patients with alcoholism to reduce heavy drinking.

New or Expanded Initiatives in Alcohol Research

Preventing Underage Drinking and Reducing its Adverse Consequences - Recent analyses show that youth have the highest prevalence of clinically diagnosable alcohol dependence of any other age group. Our goals are to understand the factors that contribute to the high prevalence of alcohol addiction in this age group and to use this knowledge to develop more effective prevention and treatment interventions.

We now know that the brain continues to develop into young adulthood, raising the possibility that adolescent brains respond differently to alcohol exposure than do adult brains and that alcohol may alter brain development in adolescents. We are examining whether these possibilities have scientific support and whether any alcohol-induced changes that occur have lasting consequences, in terms of both cognition and addiction. Also, we are examining how biological factors interact with the social environment of adolescents to promote alcohol dependence in this vulnerable age group. The overarching question is: what are the best interventions to protect our youth?

Rural youth have higher rates of some alcohol-related risk factors than do youth in other areas, and one of our initiatives focuses on them. Academic health centers in rural regions will conduct this research, because they have the centralized capacity (and networks) to address the many facets of alcohol misuse by youth, from medical care and research to social services. In addition to yielding vital data, this strategy will test whether or not existing health systems can adequately address alcohol-related problems of youth.

In a separate project, we are partnering with the U.S. Department of Justice's Office of Juvenile Justice and Delinquency Prevention (OJJDP) in a program called Enforcing Underage Drinking Laws. Our goal is to understand how to more effectively reduce availability and consumption of alcohol among rural and small-town youth under the age of 21 through enforcement of underage drinking laws. OJJDP is funding communities to implement different approaches to enforcing the laws, and NIAAA is providing the research base for this work. NIAAA also has formed a partnership to address underage drinking with the U.S. Department of Agriculture program that includes 4-H Clubs.

Medication Development for Alcoholism – Developing widely effective medications for alcoholism is one of the most pressing needs in alcoholism treatment. Alcohol acts on several of the brain's neurotransmitter systems, each of which may contain potential targets for medication development. Genetic variations within these systems may result in variations in how well (or how poorly) individuals respond to various medications.

Accordingly, our goal is to develop medications that will act on a range of molecular sites in different neurotransmitter systems. We currently are developing three kinds of medications aimed at three distinct brain circuits. These agents act on systems that involve (1) corticotropin-releasing factor, part of a neurotransmitter system involved in the response to stress; (2) a receptor in the endocannabinoid neurotransmitter system, among whose roles in the brain is

regulation of appetitive behavior and which has been shown to influence propensity for alcohol; or (3) the neuropeptide NPY, which appears to be involved in appetitive behavior and anxiety, both of which have implications for levels of alcohol consumption.

In addition, basic research is yielding sites in the glutamate and the gamma-aminobutyric acid neurotransmitter systems that hold potential as targets for novel medications. Combinations of sites in more than one neurotransmitter system also are being considered.

Several medications approved by the Food and Drug Administration for treatment of other diseases appear to have promise for treating alcoholism and are being tested for that purpose.

Alcohol metabolism – Critical questions about alcohol metabolism remain to be answered. The overarching question is: how do variations in alcohol metabolism, from person to person or population to population, contribute to alcoholism and diseases related to alcohol's toxic effects on organs – or protection from these conditions? For example, we need to know more about the formation of toxic products of alcohol metabolism and physiological and pathological responses to these compounds. This information is necessary for identifying biomarkers of risk and disease, and can reveal potential molecular points for intervention.

An example of potential toxic effects related to alcohol metabolism is that the alcohol metabolite acetaldehyde is implicated in upper gastrointestinal tract cancer. The metabolite acetate, the end product of alcohol metabolism, can enter the blood circulation of the brain, unlike many other potentially toxic compounds that are filtered out. Evidence suggests that acetate, too, should be explored further for its potential for detrimental effects on organs and behavior.

Alcohol metabolism results in increased generation of highly reactive molecules called "free radicals" and reduces the ability of naturally occurring antioxidants to neutralize them. Free radicals can damage almost any critical component of cells, including DNA, proteins, and fatty compounds in the protective membranes around cells. New compounds that result from free-radical activity (protein adducts) alter cell function, damage organs (including the brain), and alter behavior.

On the other hand, free radicals perform some necessary intermediate steps in important biochemical reactions in cells, and the body repairs most of the damage that free radicals generate. It's a balancing act, and alcohol appears to tip the balance. Meanwhile, some studies suggest that increasing levels of naturally occurring antioxidants may limit tissue damage caused by excessive alcohol exposure. Studies of damage to liver tissue and animal fetal tissue, for example, are underway.

Among the questions we seek to answer are: Can adducts serve as biomarkers of risk and of the courses of alcohol-related diseases themselves? Can adduct formation be safely modulated to mitigate damage to proteins and cells?

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NIH Roadmap Initiative Accelerates Alcohol Research

The deciphering of the human genome, and those of other animals, offers unprecedented opportunities. However, the physiological and behavioral impact of genes actually occurs through the actions of the many thousands of proteins encoded by a given genome – its "proteome." The field of proteomics needs tools that will enable researchers to determine, in real time, the amounts, locations, and interactions of large numbers of specific proteins.

The NIH Roadmap initiative on National Technology Centers for Networks and Pathways responds to that need. Through the initiative, Centers are working cooperatively to develop technologies that can be used to characterize the complex biochemical pathways and molecular interactions in which proteins engage – pathways and interactions that result in physiological and behavioral outcomes, including disease.

This initiative is particularly relevant to alcohol research. A major goal of alcohol research is to understand more completely the proteins and pathways involved in alcohol metabolism, individual differences in which may either promote or protect people from development of the disease. Another goal is to identify biomarkers of risk, based on these pathways, for alcohol abuse and dependence. The initiative will develop tools that can be used by alcohol researchers in their work to identify biomarkers of alcohol-related risk and disease.

The search for more widely effective medications for alcohol-use disorders also will benefit from the initiative. It will provide a better understanding of the functions of proteins in the dynamic systems that constitute the biological pathways involved in various facets of pathological alcohol consumption, such as craving for alcohol.

Other Areas of Interest in Alcohol Research

Imaging – Alcohol has effects at multiple levels, from the cellular to the behavioral, and new imaging techniques are enabling scientists to approach these areas from an integrated perspective – for example, to relate changes in nerve cells to function in specific areas of the brain responding to alcohol exposure. New or recently improved technologies are enabling scientists to observe responses of living cells to experimental manipulations, in real time. This ability is useful in several areas of alcohol research; for example, fMRI and diffusion tensor imaging (DTI) are being used to study the effects of alcohol on neural circuitry in specific brain regions. Knowing where in the brain alcohol has effects and how these effects translate into function and behavior is crucial. DTI also is being used to study degradation of white matter in the brain and will help track changes in structure and function that occur with abstinence from alcohol and relapse to drinking – clues as to where to probe more deeply at the molecular level, for potential points for intervention.

Improving Effectiveness of Treatment – Developing, evaluating, and improving effectiveness and cost-effectiveness of treatments is a central goal in alcohol research. We know that different types of current behavior therapies result in approximately equivalent outcomes. To advance beyond this state, we must further our understanding of the mechanisms that underlie how and why alcohol-related behaviors change. Because neurobiological, psychological, and social factors are important determinants of change, this initiative includes multiple levels of research. We need to develop an integrated understanding of the complex interactions among these factors to improve the effectiveness of behavior-change strategies.

Another crucial element in improving the effectiveness of treatment is to increase the willingness of clinicians and insurers to address alcohol-use disorders and to implement new findings. The effectiveness of current strategies to implement change in this regard isn't clear, and simply disseminating research findings doesn't appear to translate into changes in treatment. We need to develop and introduce more effective approaches to ensuring that clinicians and insurers address alcohol-related problems and incorporate science-based findings in their decisions.

Biosensors – Several recent technological advances are enabling us to develop biosensors for alcohol under our DARPA-inspired Advanced Alcohol Research Program. The sensors, which will enable continuous measurement of alcohol levels, will be at or near the marketing stage within 3-to-5 years. They have significant implications not only for the clinical setting, but also for basic research.

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The NIH Neuroscience Blueprint

Overview -- The Blueprint is a framework to enhance cooperation among 15 NIH Institutes and Centers that support research on the nervous system. Over the past decade, driven by the science, the NIH neuroscience Institutes and Centers have increasingly joined forces through initiatives and working groups focused on specific disorders. The Blueprint builds on this foundation, making collaboration a day-to-day part of how the NIH does business in neuroscience. By pooling resources and expertise, the Blueprint can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community.

FY2005 -- For fiscal year 2005, the Blueprint participants are developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. These initiatives, with the participation of all Blueprint Institutes, include an inventory of neuroscience tools funded by the NIH and other government agencies, enhancement of training in the neurobiology of disease for basic neuroscientists, and expansion of ongoing gene expression database efforts.

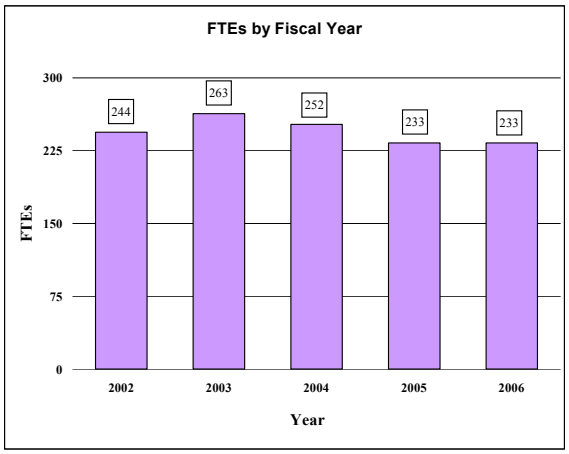
FY2006 -- Advances in the neurosciences and the emergence of powerful new technologies offer many opportunities for Blueprint activities that will enhance the effectiveness and efficiency of

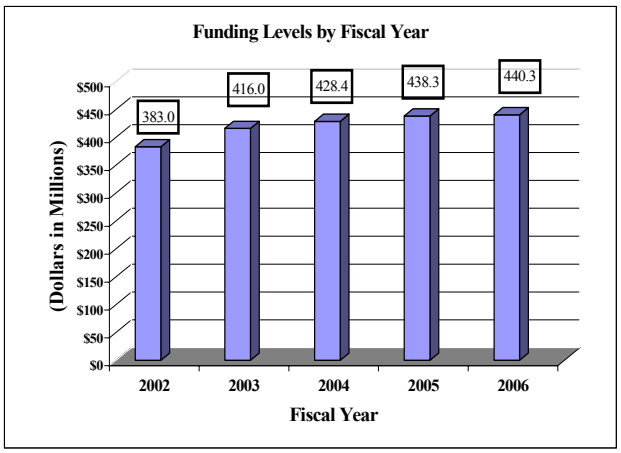
neuroscience research. Blueprint initiatives for fiscal year 2006 will include systematic development of genetically engineered mouse strains of critical importance to research on nervous system and its diseases and training in critical cross cutting areas such as neuroimaging and computational biology.

Budget Policy

The Fiscal Year 2006 budget request for the NIAAA is $440,333,000, an increase of $2,056,000 and 0.5 percent over the FY 2005 Final Conference Level. Also included in the FY 2006 request is NIAAA's support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the FY 2006 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. 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.





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 $61,393,000 in FY2006. While no inflationary increases are provided for direct, recurring costs in non-competing RPG's, where the NIAAA has committed to a programmatic increase in an award, such increases will be provided.

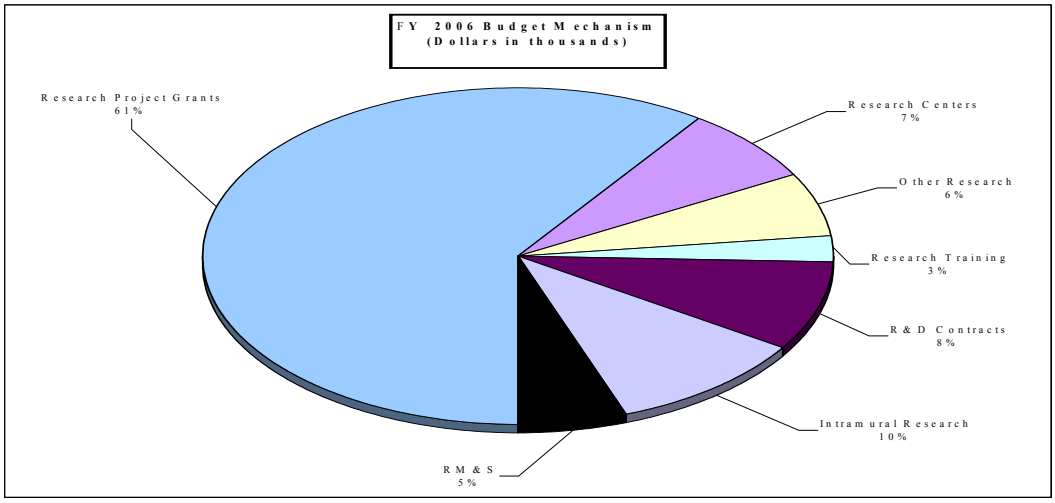
Advancement in medical research is dependent on attracting, training, and retaining the best and the brightest individuals to pursue careers in biomedical and behavioral research. In the FY2006 request, most stipend levels for individuals supported by the Ruth L. Kirschstein National Research Service Awards are maintained at the FY2005 levels. To help prevent the potential attrition of our next generation of highly trained post-doctoral trainees, stipend levels for post-docs with 1-2 years of experience are increased by 4.0%. This will bring these stipends closer to the goal NIH established for post-doc stipends in March, 2000. In addition, individual post-doctoral fellows will receive an increase of $500 in their institutional allowance for rising health benefit costs. The need for increased health benefits is particularly acute for these post-doctoral trainees, who, because of their age and stage of life are more likely to have family responsibilities. The increases in stipends and health insurance are financed within the FY2006 request by reducing the number of Full-Time Training Positions, because NIH believes that is

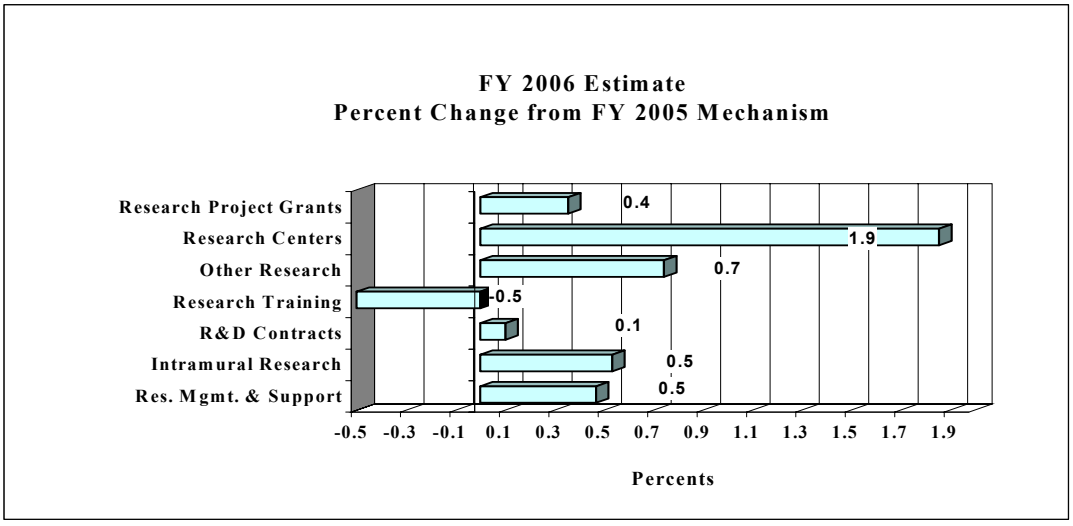
important to properly support and adequately compensate those who are participating in these training programs, so that the programs can continue to attract and retain the trainees most likely to pursue careers in biomedical, behavioral and clinical research.

The Fiscal Year 2006 request includes funding for 20 research centers, 132 other research grants, including 94 clinical career awards, and 34 R&D contracts. Intramural Research and Research Management and Support receive increases of 0.5 percent, the same as the NIH total increase.

NIAAA is participating in the NIH Neuroscience Blueprint. The FY2006 request includes $400,000 for a variety of Neuroscience Blueprint initiatives, including neuroscience cores, training initiatives, and the Neuromouse project.

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 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	535	$193,401,000	525	$188,629,000	556	$191,334,000
Administrative supplements	(40)	3,071,000	(40)	3,081,000	(35)	2,687,000
Competing:						
Renewal	51	18,536,000	56	20,889,000	54	20,424,000
New	152	37,182,000	165	41,904,000	162	40,969,000
Supplements	0	0	0	0	0	0
Subtotal, competing	203	55,718,000	221	62,793,000	216	61,393,000
Subtotal, RPGs	738	252,190,000	746	254,503,000	772	255,414,000
SBIR/STTR	28	8,749,000	29	7,408,000	29	7,430,000
Subtotal, RPGs	766	260,939,000	775	261,911,000	801	262,844,000
Research Centers:						
Specialized/comprehensive	18	29,804,000	18	31,598,000	19	32,081,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	179,000	0	278,000	1	387,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	18	29,983,000	18	31,876,000	20	32,468,000
Other Research:						
Research careers	76	9,874,000	93	11,268,000	94	11,440,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	13	9,489,000	1	6,030,000	1	6,030,000
Biomedical research support	0	8,000	0	10,000	0	12,000
Minority biomedical research support	0	0	0	0	0	0
Other	28	8,238,000	37	9,037,000	37	9,059,000
Subtotal, Other Research	117	27,609,000	131	26,345,000	132	26,541,000
Total Research Grants	901	318,531,000	924	320,132,000	953	321,853,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	56	1,948,000	56	1,978,000	55	1,978,000
Institutional awards	211	9,469,000	208	9,442,000	202	9,383,000
Total, Training	267	11,417,000	264	11,420,000	257	11,361,000
Research & development contracts	34	33,630,000	34	37,208,000	34	37,246,000
(SBIR/STTR)	(9)	(1,247,000)	(9)	(2,625,000)	(9)	(2,625,000)
	FTEs		FTEs		FTEs	
Intramural research	119	42,471,000	111	45,634,000	111	45,878,000
Research management and support	133	22,376,000	122	23,883,000	122	23,995,000
Cancer prevention & control		0		0		0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, N	252	428,425,000	233	438,277,000	233	440,333,000
(RoadMap Support)		(1,411,000)		(2,761,000)		(3,938,000)
(Clinical Trials)		(50,851,000)		(52,020,000)		(52,264,000)

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual FTEs	FY 2004 Actual Amount	FY 2005 Appropriation FTEs	FY 2005 Appropriation Amount	FY 2006 Estimate FTEs	FY 2006 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Alcohol Biomedical and Behavioral Research		$363,578		$368,760		$370,460		$1,700
Subtotal, Extramural research		363,578		368,760		370,460		1,700
Intramural research	119	42,471	111	45,634	111	45,878	0	244
Res. management & support	133	22,376	122	23,883	122	23,995	0	112
Total	252	428,425	233	438,277	233	440,333	0	2,056

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Summary of Changes

FY 2005 Estimate				$438,277,000
FY 2006 Estimated Budget Authority				440,333,000
Net change				2,056,000
	FY 2005 Appropriaton		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$14,416,000		$204,000
b. Annualization of January 2005 pay increase		14,416,000		133,000
c. January 2006 pay increase		14,416,000		249,000
d. One less day of pay		14,416,000		(56,000)
e. Payment for centrally furnished services		7,587,000		38,000
f. Increased cost of laboratory supplies, materials, and other expenses		23,631,000		445,000
Subtotal				1,013,000
2. Research Management and Support:				
a. Within grade increase		14,411,000		255,000
b. Annualization of January 2005 pay increase		14,411,000		133,000
c. January 2006 pay increase		14,411,000		249,000
d. One less day of pay		14,411,000		(56,000)
e. Payment for centrally furnished services		2,583,000		13,000
f. Increased cost of laboratory supplies, materials, and other expenses		6,889,000		125,000
Subtotal				719,000
Subtotal, Built-in				1,732,000

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Summary of Changes--continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	525	$191,710,000	31	$2,311,000
b. Competing	221	62,793,000	(5)	(1,400,000)
c. SBIR/STTR	29	7,408,000	0	22,000
Total	775	261,911,000	26	933,000
2. Research centers	18	31,876,000	2	592,000
3. Other research	131	26,345,000	1	196,000
4. Research training	264	11,420,000	(7)	(59,000)
5. Research and development contracts	34	37,208,000	34	38,000
Subtotal, extramural				1,700,000
	FTEs		FTEs	
6. Intramural research	111	45,634,000	0	(769,000)
7. Research management and support	122	23,883,000	0	(607,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Building and Facilities		0		0
Subtotal, program		438,277,000		324,000
Total changes	233		0	2,056,000

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	233	233	0
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$146,000	$147,000	$1,000
Average GM/GS grade	12.1	12.1	0.0
Average GM/GS salary	$82,139	$83,781	$1,642
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$80,528	$82,139	$1,611
Average salary of ungraded positions	90,108	91,910	1,802

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$14,820,000	$15,441,000	$621,000
11.3 Other than Full-Time Permanent	5,108,000	5,321,000	213,000
11.5 Other Personnel Compensation	411,000	428,000	17,000
11.7 Military Personnel	469,000	487,000	18,000
11.8 Special Personnel Services Payments	2,264,000	2,348,000	84,000
Total, Personnel Compensation	23,072,000	24,025,000	953,000
12.0 Personnel Benefits	5,186,000	5,404,000	218,000
12.1 Military Personnel Benefits	497,000	519,000	22,000
13.0 Benefits for Former Personnel	72,000	75,000	3,000
Subtotal, Pay Costs	**28,827,000**	**30,023,000**	**1,196,000**
21.0 Travel & Transportation of Persons	870,000	853,000	(17,000)
22.0 Transportation of Things	257,000	252,000	(5,000)
23.1 Rental Payments to GSA	241,000	241,000	0
23.2 Rental Payments to Others	220,000	220,000	0
23.3 Communications, Utilities & Miscellaneous Charges	1,102,000	1,093,000	(9,000)
24.0 Printing & Reproduction	103,000	99,000	(4,000)
25.1 Consulting Services	424,000	416,000	(8,000)
25.2 Other Services	2,089,000	2,075,000	(14,000)
25.3 Purchase of Goods & Services from Government Accounts	42,526,000	41,923,000	(603,000)
25.4 Operation & Maintenance of Facilities	2,149,000	2,134,000	(15,000)
25.5 Research & Development Contracts	18,982,000	18,925,000	(57,000)
25.6 Medical Care	1,583,000	1,578,000	(5,000)
25.7 Operation & Maintenance of Equipment	656,000	651,000	(5,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**68,409,000**	**67,702,000**	**(707,000)**
26.0 Supplies & Materials	3,139,000	3,125,000	(14,000)
31.0 Equipment	3,557,000	3,511,000	(46,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	331,552,000	333,214,000	1,662,000
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	**409,450,000**	**410,310,000**	**860,000**
Total Budget Authority by Object	**438,277,000**	**440,333,000**	**2,056,000**

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$14,820,000	$15,441,000	$621,000
Other Than Full-Time Permanent (11.3)	5,108,000	5,321,000	213,000
Other Personnel Compensation (11.5)	411,000	428,000	17,000
Military Personnel (11.7)	469,000	487,000	18,000
Special Personnel Services Payments (11.8)	2,264,000	2,348,000	84,000
Total Personnel Compensation (11.9)	**23,072,000**	**24,025,000**	**953,000**
Civilian Personnel Benefits (12.1)	5,186,000	5,404,000	218,000
Military Personnel Benefits (12.2)	497,000	519,000	
Benefits to Former Personnel (13.0)	72,000	75,000	3,000
Subtotal, Pay Costs	**28,827,000**	**30,023,000**	**1,196,000**
Travel (21.0)	870,000	853,000	(17,000)
Transportation of Things (22.0)	257,000	252,000	(5,000)
Rental Payments to Others (23.2)	220,000	220,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	1,102,000	1,093,000	(9,000)
Printing and Reproduction (24.0)	103,000	99,000	(4,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	424,000	416,000	(8,000)
Other Services (25.2)	2,089,000	2,075,000	(14,000)
Purchases from Govt. Accounts (25.3)	11,851,000	11,517,000	(334,000)
Operation & Maintenance of Facilities (25.4)	2,149,000	2,134,000	(15,000)
Operation & Maintenance of Equipment (25.7)	656,000	651,000	(5,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**17,169,000**	**16,793,000**	**(376,000)**
Supplies and Materials (26.0)	3,138,000	3,124,000	(14,000)
Subtotal, Non-Pay Costs	22,859,000	22,434,000	(425,000)
Total, Administrative Costs	**51,686,000**	**52,457,000**	**771,000**

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

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

FY 2005 House Appropriations Committee Report Language (H. Rpt. 108-636)

Item

Asian American and Pacific Islander (AAPI) populations. **–** The Committee suggests that NIAAA take further steps to meet the research needs of the rapidly growing AAPI populations in the fifty states and the six Pacific Island jurisdictions. NIAAA should consider creating an NIAAA Asian American and Pacific Islander Workgroup to develop an AAPI research agenda and implementation plan for alcohol and alcohol abuse issues**.** (p. 96)

Action Taken or to Be Taken

The NIAAA recognizes the research needs of the Asian American and Pacific Islander (AAPI) populations and has established a Cooperative Agreement with investigators at the University of Hawaii's John A. Burns School of Medicine. The aim of this cooperative agreement is to develop and sustain a program in alcohol research that focuses on Asian Americans and Pacific Islanders; on cultural perspectives necessary for accessing these groups and conducting research and developing programs specific to them.

In collaboration with the University of Texas, the project will include epidemiology- and intervention-research development and research training/mentoring of junior investigators at the University of Hawaii's John A. Burns School of Medicine. The epidemiology studies emanating from these efforts will describe the nature and scope of alcohol misuse among Asian Americans and Pacific Islanders – the first phase of our plan to encourage practical application of research findings with direct clinical utility for these populations. The interface between medicine and research provided by the junior investigators at the School of Medicine will help ensure that clinically applicable research findings on alcohol misuse are transferred to the clinical setting -- particularly as the careers of these junior investigators develop, as they become the next generation of researcher/clinicians. Pilot studies and training programs will include all of the ethnic groups in Hawaii.

Item

Nonalcoholic steatohepatitis (NASH).– The Committee notes that the mechanisms that cause NASH and the treatment protocols that are effective with regard to NASH also offer promise for treating alcoholic liver disease (ALD). The Committee encourages

additional research focused on NASH and ALD to address both these diseases as well as to further test the hypothesis that the mechanisms causing these diseases are similar**.** (p. 96)

Action Taken or to Be Taken

The NIAAA is working closely with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on an action plan for liver disease, which will be submitted in the next fiscal year. The plan includes collaborations between the two Institutes, including research on alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH). These two conditions have some similarities; for example, they exhibit similar cellular changes triggered by the same group of cellular chemicals (cytokines), and both respond to several of the same treatments. However, their clinical profiles have distinct differences. Their laboratory profiles also differ, suggesting potential differences in their pathways of pathology. Because differences in these pathways would be crucial to the development of effective treatments, research specific to ASH also is ongoing.

Item

Underage rural drinking. **–** The Committee understands that alcohol is the number one drug of choice among children and adolescents in this country. The Committee commends NIAAA for being one of the scientific leaders in developing prevention/intervention programs for young people with alcohol and risky behavior problems. It encourages NIAAA to continue to provide leadership in developing model longitudinal prevention/intervention community-based programs focusing on how individual families, school, and community networks can help reduce high-risk behavior among nine- to fifteen-year-olds in rural and small urban areas. The Committee encourages NIAAA to continue to utilize the expertise of academic health centers in this effort**.** (p. 96)

Action Taken or to Be Taken

The NIAAA is undertaking an initiative designed to develop model longitudinal, community-based prevention and intervention strategies. Academic health centers in rural areas are being encouraged to conduct this project, because (1) rural youth are a high-risk group and (2) these centers not only have existing research capacity, but also have extensive community ties and health-care and social-service networks in rural communities.

The centers will collect longitudinal data on their 9- to-15-year-old clients. Among the goals of the project are to identify the biological, behavioral, and environmental profiles of children who are at varying degrees of risk of alcohol problems; identify effective prevention and intervention strategies; and encourage rapid translation of findings into real-world interventions.

Studies show, for example, that children who are closely monitored by warm, supportive parents and that children who attend after-school programs are at lower risk of drinking than are others. These findings might appear to be intuitive; however, it is uncertain whether these children of responsible parents are responding strictly to their environmental influences or also are manifesting a genetic predisposition for responsible behavior.

Studies in this initiative will help investigators tease apart the influence of environment and genetics on adolescent drinking behaviors, so that we will better understand who can be helped by environmental (for example, family and school) preventive interventions, and who is less likely to respond, and how to maximize the effectiveness of such interventions. In the second phase of the initiative, grantees are being required to demonstrate expertise in coordinating delivery of interventions in schools and other community venues where youth congregate.

FY 2005 Senate Appropriations Committee Report Language (S. Rpt. 108-345)

Item

Alcohol Policy Information System – The Committee supports the Alcohol Policy Information System [APIS]. This clearinghouse provides users with access to the latest and most comprehensive information to develop and implement effective policies and practices to combat underage drinking and other alcohol problems. The Committee strongly encourages the NIAAA to increase funding in this area and to report on its efforts to maintain the APIS, and to develop a plan to increase public awareness and use of this information clearinghouse. (p. 145)

Action Taken or to Be Taken

The APIS project's detailed data on Federal and State alcohol laws enable researchers to compare the impact of various policies on alcohol-related problems among youth and others. This, in turn, provides science-based information for legislators and communities to use in setting alcohol policy. For example, APIS can provide information about the effect of closing state-based loopholes in underage drinking laws on underage drinking-and-driving fatalities. It can provide information about the effect of rescinding laws that allow insurers to withhold payments for emergency-department care rendered for alcohol-related injuries – a policy that may discourage emergency physicians from screening patients for alcohol problems. Whether rescinding these laws will increase screening and counseling and reduce alcohol-related emergency-department visits is not known. Currently, 8 million emergency-department visits are alcohol related, but only about 2 million are officially recorded as such.

The NIAAA plans to continue the APIS project, whose Worldwide Web address is http://www.alcoholpolicy.niaaa.nih.gov/. Consultants and NIAAA staff have recommended that we place greater emphasis on certain existing APIS components

designed to facilitate comparisons of policy status across jurisdictions or over time (comparisons that are essential to facilitate research on the effects of various policies). We plan to incorporate these recommendations in our renewal.

The APIS project in its current form offers unique information. It permits before-and-after comparisons of states that adopt specific alcohol-related policies with states that do not adopt such policies, to see whether the policies reduce alcohol-related mortality and health and social problems. The NIAAA plans to increase the utility of APIS further, by inviting other agencies to link their relevant data into the system, to broaden its scope. Alcohol policy information presented through APIS can be augmented by policy information on drugs, tobacco, and traffic safety collected by the National Institute on Drug Abuse, the Office of National Drug Control Policy, the Centers for Disease Control and Prevention, and the National Highway Traffic Safety Administration. This expansion will enable researchers to link information from a variety of public health policy areas to state and Federal data on mortality and morbidity and to data from surveys on health-risk behaviors. Researchers thus will have new opportunities to assess what combinations of public policies may optimally benefit the public's health. In addition, the expansion will broaden public awareness of, and access to, APIS.

Item

Alaska Alcohol and Substance Abuse – The Committee is aware of serious problems with alcohol and substance abuse in Alaska, especially among its Alaska Native population and of 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. 145)

Action Taken or to Be Taken

NIAAA, SAMHSA, and representatives of the State of Alaska met late in 2002 to discuss what kind of forum would be most helpful to alcohol-and drug-treatment providers and to the State. The NIAAA has discontinued funding for the forum and has refocused on other projects for translating research into practical applications. For example, we have formed partnerships with other organizations for the purpose of applying research findings on underage drinking, such as the Department of Agriculture's 4-H program and the Enforcing Underage Drinking Laws program of the Department of Justice's Office of Juvenile Justice and Delinquency Prevention.

Item

Co-occuring Substance Abuse Disorders – The Committee notes that the Report to Congress on the Prevention and Treatment of Co-occurring Substance Abuse Disorders and Mental Health Disorders found that a "significant lack of prevalence data on co-

occurring disorders exists." The Committee encourages NIMH, NIAAA, and NIDA to collaborate with States to develop more recent and accurate data on persons with co-occurring mental health and substance-use disorders – with an emphasis on individuals with mild to moderate mental health disorders.
(p. 145)

Action Taken or to Be Taken

The NIAAA has analyzed, and is continuing to analyze, results of a 2002 survey of more than 43,000 U.S. adults, in order to understand the associations between alcohol and drug use disorders and co-occurring psychiatric and medical conditions. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, at http://niaaa.census.gov/) provides the most reliable national prevalence estimates, to date, of alcohol and drug abuse and dependence, including nicotine dependence, and psychiatric comorbidities, including mental conditions that have not reached the level of clinical diagnosis. In addition, NESARC corrected the under-representation of Blacks and Hispanics that has occurred in previous comorbidity studies. The National Institute on Drug Abuse (NIDA) contributed funds to this NIAAA project. Numerous papers based on the NESARC data have been published or are in press, and the complete data set has been available on-line since June 2004 for analysis by the general scientific community, including NIDA and the National Institute of Mental Health.

The NIAAA also is collaborating with the National Institute of Mental Health and NIDA on testing treatment protocols for persons with co-occurring mental and addictive disorders. In addition, NIAAA and these other Institutes are cosponsoring a national conference on comorbidity, in Spring 2005. The NIAAA and other Institutes also have ongoing collaborations on health-services research; for example, joint grant solicitations for the study of how best to provide services for people with co-occurring mental and addictive disorders, and joint funding of specific grants.

Item

Drinking as a Developmental Disorder – The Committee understands that new NIAAA research has shown serious drinking problems previously associated with middle adulthood often begin to emerge during adolescence and young adulthood. The Committee encourages NIAAA to continue researching alcohol-related problems in a developmental context and recognizes that alcohol abuse and dependence are best characterized as developmental disorders that become manifest throughout the lifespan**.**
(p. 145)

Action Taken or to Be Taken

Prevalence of clinically diagnosable alcoholism is, by far, highest among youth. The NIAAA is increasing efforts to advance understanding of drinking problems in a developmental context and has formed a transdisciplinary team of internal and external experts on underage drinking. Team members include scientists, from a variety of fields,

with expertise in the biological, behavioral, and environmental processes involved in the transitions from childhood to adolescence and from adolescence to adulthood. They serve as a steering committee for our initiatives on underage drinking.

A report on the developmental basis of excessive alcohol use is underway and will be issued in about a year. As this process continues, we will plan and conduct new initiatives to address the specific gaps in our knowledge base that we identify.

Item

Knowledge Transfer – The Committee urges NIAAA to redouble its efforts to transfer new knowledge to communities and to primary care health providers who can apply it to prevention and treatment. Recognizing the developmental nature of alcohol-related problems, NIAAA should continue to focus intensively on the transition from childhood into adolescence, adolescence itself, and the transition from adolescence into young adulthood. The Committee looks forward to research findings that will reduce the risk to future generations of Americans and will spare countless additional parents from suffering the consequences of problem drinking in their children. (p. 145)

Action Taken or to Be Taken

The NIAAA is increasing efforts and employing new strategies to ensure that research findings with clinical applications are incorporated in practice. The transdisciplinary team we have established to address underage drinking includes, in addition to leading scientists, members who are well-versed and well-connected in the communications and policy arenas. For example, we have included two State governors' spouses, the law professor who chaired the Institute of Medicine's project on underage drinking, and representatives of local schools, and national organizations with an interest in prevention of alcohol-related problems of youth. These members are advising the team as to how to encourage practitioners and communities to adopt alcohol-related findings that are ready for clinical application.

In addition, NIAAA is encouraging incorporation of relevant research findings in the justice system through Enforcing Underage Drinking Laws, a program of the U.S. Department of Justice's Office of Juvenile Justice and Delinquency Prevention. We also have formed a partnership with the program of the U.S. Department of Agriculture under whose auspices 4-H Clubs fall. The partnership will allow NIAAA to share its research expertise on underage drinking, as well as findings that are ready for practical application, through 4-H staff, 4-H research faculty, and 4-H volunteers. The 4-H program will bring to the partnership expertise in positive youth development and will help inform (and will participate in) the NIAAA research agenda.

More than 60 current and former State governors' spouses have joined the Leadership to Keep Children Alcohol Free, a NIAAA-led collaborative project on prevention of underage drinking. The Governors' spouses are bringing current, science-based

information about alcohol use in early adolescence to the attention of policy makers and opinion leaders at the national level.

The NIAAA and the Substance Abuse and Mental Health Services Administration (SAMHSA) both serve on the Interagency Coordinating Committee on Prevention of Underage Drinking. This joint participation also is intended to increase the transfer of alcohol-related research findings to clinical practice.

Item

Nonalcoholic Steatohepatitis [NASH] **–** The Committee notes that the mechanisms that cause NASH and the treatment protocols that are effective with regard to NASH also offer promise for treating alcoholic liver disease [ALD]. The Committee urges additional research focused on NASH and ALD to address both these diseases as well as to further test the hypothesis that the mechanisms causing these diseases are similar and new research findings may address both diseases. (p. 145)

Action Taken or to Be Taken

The NIAAA is working closely with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on an action plan for liver disease, which will be submitted in the next fiscal year. The plan includes collaborations between the two Institutes, including research on alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH). These two conditions have some similarities; for example, they exhibit similar cellular changes triggered by the same group of cellular chemicals (cytokines), and both respond to several of the same treatments. However, their clinical profiles have distinct differences. Their laboratory profiles also differ, suggesting potential differences in their pathways of pathology. Because differences in these pathways would be crucial to the development of effective treatments, research specific to ASH also is ongoing.

Item

Using an Integrative Approach **–** The Committee encourages NIAAA to continue directing substantial effort and resources toward the achievement of a more fully integrated and comprehensive scientific understanding of the environmental, behavioral, biological, and genetic factors that promote the initiation, maintenance, and acceleration of alcohol use, and that influence the transition into harmful alcohol use, including abuse and dependence. (p. 145)

Action Taken or to Be Taken

To address underage drinking, the NIAAA has created an interdisciplinary team that is seeking to understand alcoholism from a developmental perspective. The prevalence of alcoholism is higher among youth than among any other age group. One of the team's major areas of focus is to understand how environmental, behavioral, biological, and genetic factors combine to influence the transition from youthful experimentation with alcohol or light drinking to alcohol abuse and dependence, and how to prevent risky

behaviors. Leading scientists from each of the relevant fields are on the team, as are communications and policy experts. Their integrated perspective is serving to provide guidance for researchers, both internal and external to NIH; accelerate the research; and ensure practical application of research findings.

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Institute on Alcohol Abuse and Alcoholism	Section 41B	42§285b	Indefinite	$426,857,000	Indefinite	$428,972,000
National Research Service Awards	Section 487(d)	42§288	a/	11,420,000	b/	11,361,000
Total, Budget Authority				438,277,000		440,333,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

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/
1997	$192,280,000 2/	$212,079,000	$195,891,000 2/	$211,870,000 3/
1998	208,112,000 2/	226,205,000	228,585,000	227,175,000
1999	229,551,000 2/4/	248,778,000	259,747,000	259,747,000
Rescission				(172,000)
2000	248,916,000 2/	265,497,000	265,497,000	293,935,000
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			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reduction of $134,000.
4/ 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 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	9	11	11
Office of Extramural Activities	0	13	13
Office of Scientific Affairs	25	10	10
Office of Research Translation and Communications	15	14	14
Office of Resource Management	33	32	32
Division of Epidemiology and Prevention Research	17	12	12
Division of Metabolism and Health Effects	12	10	10
Division of Neuroscience and Behavior	12	10	10
Division of Treatment and Recovery Research	10	10	10
Division of Intramural Clinical and Biological Research	119	111	111
Total	252	233	233
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2002	11.6
2003	11.6
2004	11.7
2005	12.1
2006	12.1

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	3	3	3
Total - ES Salary	$432,600	$437,000	$441,000
GM/GS-15	22	21	21
GM/GS-14	43	42	42
GM/GS-13	40	39	39
GS-12	22	21	21
GS-11	15	15	15
GS-10	1	1	1
GS-9	10	10	10
GS-8	7	7	7
GS-7	9	9	9
GS-6	3	3	3
GS-5	0	0	0
GS-4	2	2	2
GS-3	0	0	0
GS-2	0	0	0
GS-1	0	0	0
Subtotal	174	170	170
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	1	1	1
Senior Grade	5	5	5
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	6	6	6
Ungraded	62	62	62
Total permanent positions	182	177	177
Total positions, end of year	245	241	241
Total full-time equivalent (FTE) employment,end of year	252	233	233
Average ES salary	$144,200	$146,000	$147,000
Average GM/GS grade	12.1	12.1	12.1
Average GM/GS salary	$80,528	$82,139	$83,781