DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

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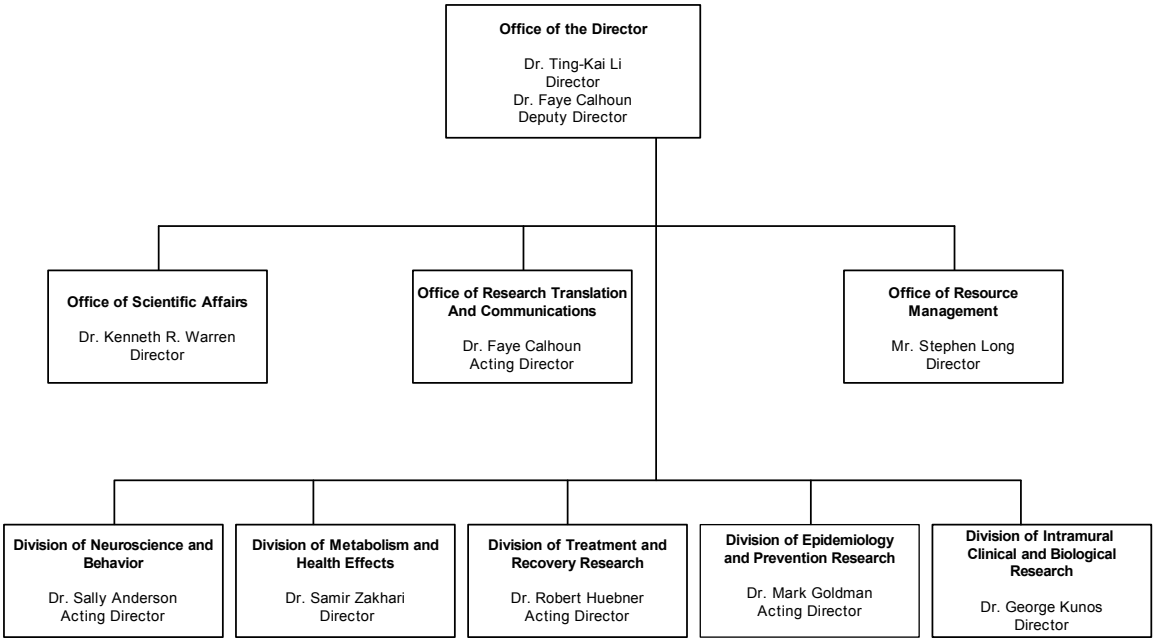

NATIONAL INSTITUTES OF HEALTH

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, [$431,471,000] *$441,911,000.*

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated Appropriations Act for Fiscal Year 2004]

National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism

Amounts Available for Obligation 1/

Source of Funding	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Appropriation	$418,773,000	$431,471,000	$441,911,000
Enacted Rescissions	(2,722,000)	(2,802,000)	---
Subtotal, Adjusted Appropriation	416,051,000	428,669,000	441,911,000
Comparative transfer from: Fogarty International Center for International Services Branch	16,000	0	0
Comparative transfer to NIBIB for Radiology Program	(28,000)	(28,000)	(0)
Comparative transfer to Buildings and Facilities	(132,000)	(216,000)	(0)
Comparative transfer to Office of the Director for program changes	(407,000)	(0)	(0)
Subtotal, adjusted budget authority	415,500,000	428,425,000	441,911,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	415,500,000	428,425,000	441,911,000
Unobligated balance lapsing	(91,000)	---	---
Total obligations	415,409,000	428,425,000	441,911,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2003 - $3,886,000; FY 2004 - $3,886,000; FY 2005 - $3,886,000
Excludes $5,203 in FY 2003 and $2,272 in FY 2004 for royalties.

Justification

National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
263	$415,500,000	244	$428,425,000	246	$441,911,000	2	$13,486,000

This document provides justification for the Fiscal Year 2005 research activities of the National Institute on Alcohol Abuse and Alcoholism, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2005 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

New findings dramatically underscore the importance of reducing underage drinking. We now know that most cases of alcohol dependence begin before age 25. After that age, new cases drop off precipitously. The message: youth is a critical window of opportunity for preventing alcoholism. Previous studies have suggested that this is so, but the new findings, which are now corroborated by independent sources, tell us that it is so.

Figure 1 provides striking evidence. This graph shows that people around the age of 18 have the highest percentage of new cases of alcohol dependence. New cases drop off markedly with each subsequent age group, a trend that stabilizes among age groups 25 and older.

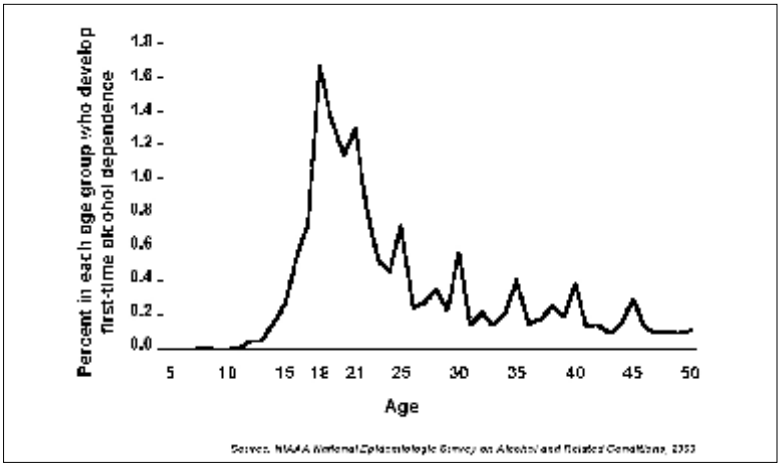

Figure 1. First-time Alcohol Dependence, by Age

Unpublished data by another group of investigators corroborate these findings. Figure 1 shows new cases of alcoholism for each age group, independent of other age groups. The unpublished data show that the cumulative incidence (that is, the number of new cases of alcohol dependence in each age group, incrementally added together) in a high-risk population begins to plateau at about age 25. New cases still occur in age groups older than 25, but at much lower rates.

More unpublished data, from the same researchers, show that children with two alcoholic parents become alcohol dependent in increasing numbers at incrementally lower age of first drink. They reach a 60 percent alcohol-dependence rate at age 25, after which new cases level off. Children with one alcoholic parent have a 40 percent rate, again leveling off at age 25. Children with no alcoholic parents have a lower rate, but still follow the pattern of a dramatic drop in new cases after about age 25.

Ongoing research may reveal a cause-and-effect relationship between early alcohol use and subsequent alcoholism, or it may reveal that common biological and environmental factors drive the risk for both measures of outcome, as well as certain other addictive and psychological disorders. In either case, these new data are a powerful indicator of the need for more effective preventive interventions for youth.

Magnitude of Underage Drinking

Given the implications of the new findings, the fact that alcohol use is so widespread among children and adolescents is troubling. For example:

- 47 percent of 8th graders, 67 percent of 10th graders, and 78 percent of 12th graders have used alcohol.

- 11 percent of 6th graders have reported binge drinking (5 or more drinks per occasion for males; 4 for females) in the past 2 weeks.

- 21 percent of 8th graders report having been drunk at least once.

- 30 percent of high-school seniors have reported binge drink at least once a month.

- 44 percent of college students have reported binge drinking in the past 2 weeks; 23 percent have reported that they binge drink frequently.

Stopping the Problem Before it Starts

At a recent Senate hearing on underage drinking, investigators noted that alcohol is the primary substance of abuse among American children (Sept. 30, 2003; Subcommittee on Substance Abuse, of the Senate Committee on Health, Education, Labor, & Pensions). Rural children are one subpopulation at particularly high risk. A major survey shows that rural children lead those in other geographical areas in a number of drinking patterns. Among rural children who reported drinking within the past year, almost twice as many used alcohol as used illegal drugs.

In this budget justification, we announce a major new initiative aimed at identifying risk factors common to rural children and children in small, urban areas (another high-risk group) and at developing and testing community-based, longitudinal prevention and intervention programs. Because adolescent brains have unique neurobiological factors that affect how this age group responds to alcohol, we will include neurobiological studies in the new initiative.

In addition to ongoing research, we also are continuing our outreach programs for youth. The *Leadership to Keep Children Alcohol-Free* has recruited 33 Governors' spouses to spearhead a national prevention campaign. The *Task Force on College Drinking* has brought together university presidents and researchers, and is making headway in efforts to reduce the seemingly intractable problem of drinking by college students.

The Consequences of Not Taking Action

Preventing alcohol-use disorders and their medical consequences, such as liver disease and cancer, is preferable to treating them. The 2002 report of the World Health Organization (WHO) reveals that, in developed nations, alcohol ranks #3 as a preventable risk factor for premature death. Figure 2 shows that alcohol is exceeded only by tobacco and hypertension, and is a greater risk factor than are cholesterol, obesity, low fruit and vegetable intake, lack of exercise, illicit drugs, and unsafe sex.

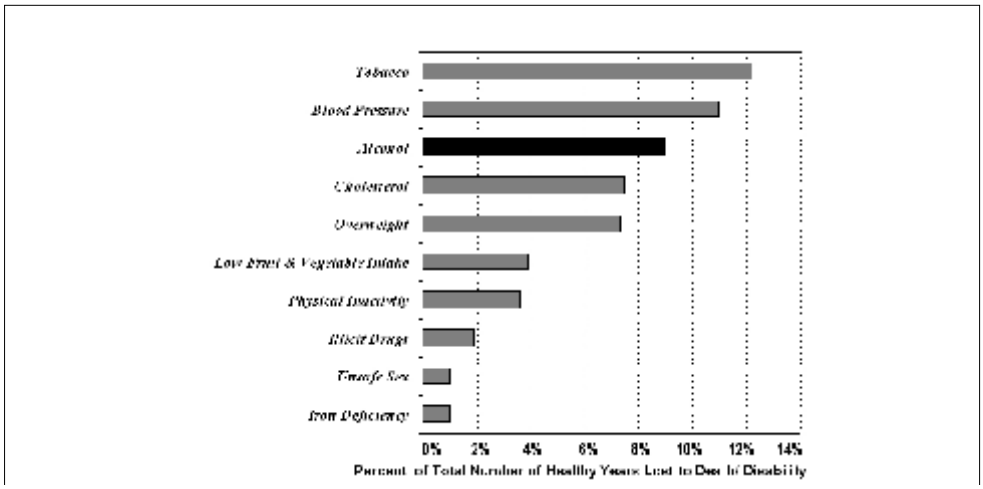

Figure 2. Burden of Disease Attributable to 10 Selected Leading Risk Factors in Developed Countries.

- 2002 report of the World Health Organization

Part of alcohol's power as a risk factor is that it not only leads to addiction and behavioral consequences that result in morbidity and mortality, as do some illicit drugs, but also may act as a toxic agent in almost any organ. A portion of alcohol's disability and death rate thus is attributable to physical illness, sometimes protracted and irreversible, that results from alcohol's actions on tissues and organs, at the cellular level. For example, alcohol damages the liver and alters functions of the immune and endocrine systems, and disrupts fetal development, with far-reaching effects.

Vulnerability

While early initiation of drinking is a powerful predictor of subsequent alcohol dependence, not everyone who uses alcohol at a young age later succumbs. Even among children with the biggest risk factors for alcoholism, such as having two alcoholic parents, only about one-half become alcoholic. The outcome is determined largely by the interplay of environmental and genetic/biological factors.

Environmental factors have the biggest influence on whether a child takes his or her first drink. However, genetic factors have a major influence on whether a child continues to drink. A major goal of our research is to understand how these factors result in initiation and continuation of drinking. Another of the new initiatives described in this document focuses on a critical genetic/biological aspect of drinking: the metabolism of alcohol. Variations in our genes result in variations in how our bodies absorb, distribute, and eliminate alcohol, and these variations influence how we respond to it – for example, why some people can tolerate large amounts, favoring drinking, or why alcohol makes others feel sick, making them want to avoid it.

Lying between these gene variants and the behavioral outcomes in which they result are enzymes and associated cellular systems that are potential biomarkers of risk of alcohol dependence, or protection from it, and molecular targets for intervention. Our new initiative on alcohol metabolism and behavioral outcomes is actually an expansion of a very active program of ongoing research in this area, in which recently developed animal models are providing unprecedented opportunities.

Binge Drinking

The new finding that alcoholism is most likely to develop by about age 25 should not be misinterpreted to mean that it's safe for people older than that to engage in risky drinking behaviors. Although new cases of alcohol dependence drop off dramatically after that age, some still do occur.

Binge drinking – episodes of heavy drinking – is a problem for people in any age group, whether or not the drinker is addicted to alcohol. Drinking too much, too fast in this manner carries risks. They include car crashes, injury, death, property damage, encounters with the justice system, and family, school, and workplace problems, to name only some.

We know that an alarming number of children and adolescents binge drink, but we also know that it is a major problem among U.S. adults and that it is increasing. American adults engaged in 1.5 billion binge-drinking episodes between 1993 and 2001, an increase of 17 percent. About half of these adults were otherwise moderate drinkers.

How their bodies and behaviors respond to binge drinking – whether they have high tolerance to alcohol, raising the risk of continued binges and risk of injury, disrupted lives, and organ damage – depends partly, again, on genetic variations that affect their ability to absorb, distribute, and eliminate alcohol. Our expanded initiative on alcohol metabolism will yield data relevant not only to alcohol dependence, but also to binge drinking and other patterns of drinking.

Understanding the genetic variants that cause differences in people's alcohol-metabolizing enzymes, for example, is the key to understanding how their bodies handle alcohol and how this response translates into behaviors.

Within the pathways of biological events that influence our response to alcohol are points of opportunity; for example, we could pharmacologically alter the activities of enzymes and related structures, thus blocking alcohol-induced behaviors or tissue damage. Environmental factors that contribute to development of alcohol-use disorders also provide points of opportunity. Part of our research also focuses on preventive interventions, at the individual, family, community, college, and policy levels.

Advances

Reflecting alcohol's complexity, both biochemically and socially, this budget justification includes the many topics that come under the realm of alcohol research.

For example, in the Science Advances section, we describe two new findings that involve genes. Epidemiology studies have shown beyond doubt that genes play a role in risk of alcoholism. Now we are directing our research toward discovering which genes are involved, what biochemical pathways they influence in brain cells, and how these pathways translate into specific behaviors. These kinds of findings provide us with clues about genetic/molecular events in the brain that influence drinking, and provide potential targets for pharmacological intervention.

New findings about a naturally occurring marijuana-like substance in the brain also provide potential new molecular targets for pharmacological intervention. The history of how these NIAAA-funded findings are adding to multidisciplinary discoveries involving this substance is described in a Story of Discovery. Again, the new findings provide molecular targets for medication development.

Alcohol is the leading preventable cause of mental retardation, manifesting as fetal alcohol syndrome. Another finding described in the Science Advances section provides strong evidence that a specific cellular mechanism is a necessary ingredient for alcohol-induced damage to the fetus, again providing potential molecular targets for intervention.

Binge drinking and heavy, chronic drinking are two patterns of alcohol use that lead to major problems, not the least of which is organ damage. Another pattern, moderate drinking, paradoxically appears to have protective effects against certain chronic diseases, for some people. (These apparent protective effects reach their maximum at about 1½ drinks a day, for overall mortality; beyond that amount, they begin to decline. At about four drinks a day, the risk of cardiovascular disease and alcohol dependence increases.) A new finding now suggests that moderate drinking has a protective effect against type 2 diabetes in younger women.

On the toxicity side, we have identified an important mechanism by which alcohol potentiates liver damage far beyond what normally would be expected from the combination of alcohol and hepatitis C. A Story of Discovery explains how decades of findings that cut across research

fields, including new technologies, enabled us to arrive at important new findings on alcoholic liver disease, which, along with hepatitis C, is one of the two major causes of cirrhosis.

Emphasis on Youth

Research on the many factors that comprise alcohol misuse and its medical consequences will continue to advance at NIAAA. However, the new findings revealing that a very substantial portion of alcohol dependence occurs among people who are younger than 25 calls for a major effort to prevent drinking by children and adolescents. It is our intent to increase the emphasis of this Institute's research on this age group over the coming years, to gain a clearer understanding of the environmental and biological factors that lead children to drink and to continue to drink, and to develop preventive interventions that will become effective tools for families, schools, and communities.

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Story of Discovery: Research Reveals the Power of an Enzyme

Alcohol can damage the liver, and often does. Most cases of cirrhosis – the eighth leading cause of death by disease in the U.S. – stem from alcohol abuse. How does alcohol damage the liver? How does it change the way liver cells work, resulting in damage to the entire organ? As scientists find answers to these questions, they improve their potential for developing medications for alcoholic liver disease.

An important clue emerged in 1966: rat-liver cells exposed to alcohol developed more protein-synthesizing "equipment." This equipment, endoplasmic reticulum (ER), is a tiny structure in liver cells (and other cells) and is part of their protein-producing process. Cells are like factories, and the proteins they make are crucial regulators of biochemical activities throughout the body.

Discovery of ER's proliferation in response to alcohol, in liver cells, led to more questions. Did the excess ER that alcohol induced in liver cells synthesize more protein? If so, which protein? What were the consequences? Finding answers was important. Most enzymes, the ubiquitous regulators of cell function, are proteins. Changes in their amount or composition, or in those of other proteins, can have dramatic effects. Scientists took a major step toward answering these questions in the late 1960s, when they found a family of enzymes – a protein – called CYP-450 in the endoplasmic reticulum of rat-liver cells. CYP-450 proliferated in rats given alcohol.

Here the story took an interesting turn. Alcohol is metabolized almost entirely by the liver, primarily by another enzyme (alcohol dehydrogenase). Scientists now found that when alcohol reached high blood levels, CYP-450 also began to metabolize it. It might seem that this additional metabolism of alcohol would help to clear it from the body, possibly reducing the risk of organ damage. But at the same time that metabolism sustains us, it can also hurt us by generating free radicals – molecules that can cause damage by disrupting the structure of other molecules, including those of liver cells. The result can be changes in cell function. Now scientists had new questions: Does CYP-450 metabolism of alcohol generate free radicals in liver cells? Do these radicals injure the cells?

At this juncture, several technological advances occurred in science, generally, spanning the 1970s through the 1990s. They would enable researchers to make leaps in their understanding of alcohol-induced liver injury and other diseases. The advances originated mainly in the fields of inflammation, pharmaceutical and chemical toxicity, and aging, which, though seemingly diverse, have common interests.

For one thing, scientists developed better methods of detecting free radicals. These elusive molecules can't be measured directly. Old methods of detecting them weren't as sensitive as scientists needed them to be and could be used only *in vitro* (test tubes). New methods were more sensitive, reduced background "noise," and could be used in animals, a much more revealing model.

Genetics technology blossomed. New methods enabled scientists to manipulate specific genes (in animal models), to see how disabling or enabling them affected various diseases or disease-promoting behaviors. Other methods enabled scientists to scan thousands of genes at once, and to understand how multiple genes interact with each other and with cells to regulate biological functions.

During these decades, alcohol researchers developed animal models of alcoholic liver disease essential to progress. They also created a line of *in vitro* liver cells that were immortal, enabling researchers to observe long-term effects of alcohol-induced free radicals and free-radical blockers. Alcohol researchers also made major contributions to other fields during this period. For example, the alcohol field led the way in developing antibodies that could detect metabolic products of free radicals.

In the 1980s, studies strengthened the evidence for CYP-450 being somehow involved in alcoholic liver disease. Using different animal models and techniques, scientists kept coming to the same conclusion: There did appear to be a link. They also narrowed the field down to a specific member of the CYP-450 enzyme family. By 1993, the enzyme had a name: CYP-2E1. Meanwhile, studies were suggesting that *free radicals* generated by CYP-2E1 were, indeed, linked to liver injury in animal models of alcoholic liver disease. Blocking CYP-2E1 with chemicals reduced liver damage by about half.

One problem researchers were having, however, was that liver cells are short-lived in laboratory dishes, making it hard to determine long-term effects of CYP-2E1. Since cancer cells are immortal, they're a better vehicle for observing long-term outcomes. In 1996, investigators took hepatocytes, the main functional cells of the liver, that were cancerous and genetically engineered them to contain human CYP-2E1. In tests of these long-lived cells, too, the link between CYP-2E1, free radicals, and liver injury persisted.

A discovery in 1998 raised the implications of the research to a new level. Studies thus far had been done in animals and test tubes. Now, liver biopsies showed that CYP-2E1 plays a role in development of alcoholic liver disease in humans.

Again, researchers turned to their model of long-lived, cancerous hepatocytes that contained human CYP-2E1. In 2002, they mixed them with other specialized liver cells, stellate cells, whose function is to produce the protein collagen. In normal amounts, collagen gives the liver structure. In excess, though, collagen eventually can turn into scars that render liver tissue almost nonfunctional, as happens in the late stages of cirrhosis. In this experiment, free radicals derived from CYP-2E1 in hepatocytes activated the stellate cells, which proliferated and produced more collagen than usual.

This raises a new question: If we block this CYP-2E1-induced excess of collagen, will we see a reduction in liver injury? If so, will we see a complete reduction, or a partial reduction – a much more likely scenario suggesting that other mechanisms of excess collagen formation also contribute to liver disease?

Researchers further implicated CYP-2E1 in 2002. They asked what would happen if they genetically engineered mice to produce more CYP-2E1 than normal. They were on the right track: the mice sustained more liver injury from alcohol than did mice with normal CYP-2E1 levels. No matter the approach researchers have taken, their results have revealed a pattern: alcohol, CYP-2E1, free radicals, and liver damage are linked. (The only exception is a 1999 study of mice, in which CYP-2E1 didn't appear to be linked to the early stages of the disease.)

We now know that alcohol-induced CYP-2E1 plays a major role in toxicity of other compounds; for example, common environmental compounds, the anesthetic halothane, and some pharmaceuticals (such as acetaminophen) increase in toxicity when alcohol induces CYP-2E1 in the liver. CYP-2E1 also appears to activate some precursors of cancer-producing compounds, resulting in tumors. It plays a role in insulin resistance (the inability of cells to use sugar for fuel), which is associated with non-alcoholic fatty liver injury and obesity – both, like alcoholic liver disease and cancer, major public-health issues.

CYP-2E1 is just one of the mechanisms that underlie alcohol-induced liver damage. We already know of other enzymes that generate free radicals that probably are involved. The next step for the alcohol field is to discover whether other members of the CYP-450 family of enzymes, besides CYP-2E1, are involved in liver damage, and their molecular pathways of injury – potential points for pharmaceutical intervention, as is CYP-2E1 itself.

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Story of Discovery: The Bliss Connection

Your brain makes its own bliss – literally. In recent years, researchers have found a key biochemical ingredient: a naturally occurring molecule they named anandamide, from the Sanskrit word for bliss.

But it turns out that anandamide does more than cause euphoria. It's part of a biochemical system that contributes to many health-related states, the brain being just one site of action. Researchers are finding that anandamide and its "docking sites" on brain cells play a role in propensity to drink alcohol, making them potential targets of medications for alcoholism. Alcohol researchers are about to start clinical trials on one such medication (Rimonabant).

Research advanced to this point the same way most scientific progress is achieved: by building on previous findings, over decades. As with most scientific breakthroughs, discovery of anandamide has opened up possibilities for a variety of health-related conditions, including alcoholism.

Early Building Blocks

The story of anandamide began with studies of marijuana's effects. In 1964, Israeli researchers isolated the chemical in marijuana, THC, that makes people high. They suspected that for THC to exert its effects, it had to bind to a receptor – a docking site made of a protein molecule – on brain cells. By the late 1980s, scientists had identified that receptor and named it "CB1." When THC molecules bind to the CB1 receptor, the cascade of biochemical events it initiates in cells results in effects on the brain.

While the discovery of the CB1 receptor was a major advance, scientists suspected that it didn't exist only to act as a THC receptor. THC molecules just happen to come into contact with the receptor when people smoke marijuana. The molecules just happen to fit into the shape of the receptor.

Why, then, is the CB1 receptor there? In 1992, researchers studying cannabinoids (substances like THC) discovered that anandamide is at least one of the reasons. Anandamide is a naturally occurring molecule, produced by the brain, that binds to the CB1 receptor and activates it. Its psychotropic effects are similar to those that result when THC activates the receptor, but much more temperate.

Alcohol Enters the Picture

Alcohol has ubiquitous actions in the body. While any other substance of abuse is fairly narrow in the neurotransmitter system it targets, alcohol instead acts on a multitude of neurotransmitter systems. Studies began to suggest that the system on which THC acts is one of them.

Meanwhile, scientists studying alcohol's effects on lipid metabolism in brain tissue saw something puzzling. Alcohol was causing nerve-cell membranes to release some of their fatty acids -- but once released, these fatty acids weren't showing up in any of the biological products they would then normally go on to form. Scientists found that the fatty acids were instead becoming ingredients for compounds such as anandamide. When researchers subjected nerve cells to chronic alcohol exposure in 1999, the cells produced more anandamide than usual.

At about the same time, scientists discovered that chronically exposing cells to alcohol also resulted in reduced numbers of CB1 receptors. Taken together, these data suggested that alcohol stimulates production of anandamide and similar molecules.

In 1997, a study had shown that rats given a drug that blocks the CB1 receptor drank less alcohol, implicating the CB1/anandamide system in propensity for drinking. As they continued their search, scientists were finding that alcohol exerts its effects through a multiplicity of actions. Generation of anandamide and activation of the CB1 receptor appear to be just two of them. Alcohol acts on most of the major neurotransmitter systems studied to date.

Where We Are Now

Two groups of researchers recently began to explain the link between alcohol and the CB1 receptor system. Alcohol causes some nerve cells to release dopamine, a neurotransmitter, in a part of the brain associated with the desire to drink. In these studies, mice genetically altered to lack CB1 receptors drank less alcohol and had none of the alcohol-induced release of dopamine that usually occurs in this "reward area" of the brain, when they did drink.

The researchers then used a second approach, using a different set of mice that were genetically intact and did have CB1 receptors. They blocked the CB1 receptors with a drug, and, again, the reward area of the brain lacked the release of dopamine that alcohol usually would have induced.

A separate study was based on observations that appetite for both alcohol and food diminishes with age. Investigators found that the same phenomenon occurs in normal mice. But when scientists knocked out the gene that produces the CB1 receptor, even young mice had diminished appetites. The investigators discovered that as normal mice grow old, CB1 and anandamide levels stay normal, but CB1 *activity* (signals the receptor sends to initiate cellular responses) diminishes in the reward area of the brain. The tendency to become alcoholic decreases with age in humans, and this newly observed reduction of CB1 signaling in the brain's reward area appears to be a factor.

The story of anandamide and the CB1 receptor doesn't end with alcohol. Scientists now know that the receptor (or its cousin, CB2) appear throughout the body, and that other naturally occurring cannabinoids bind to them. Studies are showing that these receptors and innate cannabinoids also have physiological effects on the immune, cardiovascular, and gastrointestinal systems.

Some of these effects appear to be beneficial; some, like the potential link between the CB1/anandamide system and alcoholism, don't. Our upcoming clinical trials of the CB1 blocker Rimonabant, for treatment of alcoholism, are a step toward understanding how we can alter these kinds of natural receptor/cannabinoid systems to improve health.

Science Advances

Scientists Find Points in a Human Gene and Related Pathways that Indirectly Influence Alcohol-Drinking Behaviors

Background: Because proteins are highly biologically interactive, variations in their amounts can have significant consequences for cell function and, ultimately, behavior and health. Some

variations alter cell function in ways that promote alcohol dependence and alcohol-related tissue damage.

The genes that carry the blueprints for such proteins are of intense interest to alcohol researchers. So is the expression of these genes; that is, the regulatory process that turns them on and off and determines how much or how little of a given protein a cell produces. In this study, scientists examined the role of the gene for the protein dopamine beta-hydroxylase (DBH). This enzyme catalyzes synthesis of norepinephrine, a chemical messenger in the nervous system. Several studies suggest that norepinephrine plays a role in alcohol-related behaviors.

Investigators first used bioinformatics tools to analyze patterns in large numbers of genes. In further studies of the DBH gene, they identified a specific segment of the regulatory region – the part that turns the gene on and off – that responds to alcohol.

Advance: Scientists found that alcohol causes an increase in expression of the DBH gene and that the gene's regulatory region is implicated. Using recently developed genetics technologies (pharmacogenomics) in human nerve-cell cultures, they also identified a number of cellular pathways involved in alcohol's enhancing effect on DBH production. Notable among them were components of a cellular chemical-messenger system (cyclic adenosine monophosphate or cAMP, for short) known to be involved in propensity for alcohol. Now it appears that these cAMP components play a major role in alcohol's enhancing effect on the DBH gene's "on-off switch."

The scientists blocked other important components of cellular pathways (protein kinase A, casein kinase II, and MAPK), which also reduced alcohol-induced response of the same regulatory region of the DBH gene.

Implications: This research increases our understanding of how alcohol affects the DBH gene and the cellular pathways that interact with it. It paves the way for work that can tell us how these biological factors – potential points for intervention – contribute to alcohol's effects on behavior and organs.

Gene Variation Appears to Influence Preference for Alcohol

Background: A gene that carries the blueprint for the protein alpha-synuclein has been implicated in neurodegenerative diseases and in the plasticity that enables the nervous system to develop normally. Alpha-synuclein is thought to regulate synthesis of dopamine, a chemical-messenger system present in many biochemical pathways that influence brain-cell function. Dopamine is essential for normal function of the nervous system, but it has also been implicated in several neuropsychiatric disorders and in alcohol and drug dependence. In the findings described below, scientists studied the alpha-synuclein gene in rats that had been bred with either an alcohol-preferring or nonpreferring trait.

Advance: Scientists reported in the *Proceedings of the National Academy of Sciences* that rats bred to prefer alcohol have variations in the alpha-synuclein gene, compared to rats bred without

the alcohol-preferring trait. They also pinpointed the alpha-synuclein gene's location in rats; it appears on chromosome 4, in an area previously identified as being likely to carry genes whose variants promote development of alcoholism, or protection from it, in humans.

The researchers found that expression of the gene (the process that turns it on and off and determines how much of the alpha-synuclein protein cells produce) resulted in production of twice as much of the protein in alcohol-preferring rats, compared with nonpreferring rats. These high levels appeared in areas of the brain previously implicated in alcohol's actions – the hippocampus and caudate putamen.

Scientists identified two genetic variations between the alcohol-preferring and non-preferring rats, in a specific region of the gene. Additional studies by the same researchers demonstrated that one of the two genetic variations may be responsible for the difference in production of alpha-synuclein. Combined with the findings above, these results suggest that differences in alpha-synuclein gene expression may contribute to alcohol preference, in rats.

Implications: An intricate combination of inter-related neurobiological factors is involved in alcohol preference. These findings suggest that variations in the alpha-synuclein gene is among them. Ultimately, the pathways of cellular activities related to this and other factors may become targets for intervention.

Moderate Alcohol Use Decreases Diabetes Risk in Women; Heavy Use Raises Risk

Background: Adult-onset diabetes is an enormous public health issue, and its already high rate of occurrence is rising to unprecedented levels in the United States. A study recently published in the *Archives of Internal Medicine* examined association between risk of diabetes and alcohol use in about 110,000 women 25 to 42 years old. In conducting their research, the investigators excluded women who had pre-existing health conditions that might have contributed to development of diabetes. Most of the women were premenopausal.

Advance: Scientists found that women in this age group who drink low to moderate amounts of alcohol have a lower risk of developing diabetes, compared to those who abstain from drinking. Women who drink more than a moderate amount have a higher risk of developing the disease.

Implications: Alcohol acts on the body through a multiplicity of mechanisms, and its actions are widespread. In its ubiquitous reach, alcohol can have toxic effects that damage virtually any organ in the body. Brain and liver damage are the most widely publicized examples. Heavy drinking, in particular, is a well-established risk factor for alcohol-induced damage. On the other hand, moderate drinking appears to have a protective effect against some chronic diseases, including coronary artery disease.

Some people are genetically or environmentally vulnerable to alcoholism or alcohol-induced organ damage, and drinking in even low or moderate amounts is risky for them. Until we have reliable tests to determine who is at high genetic and environmental risk and which

subpopulations are likely to benefit (or not) from moderate drinking, a blanket recommendation to drink for health could pose a serious risk for many people.

Research in this area is ongoing. Among our goals is to identify gene-environment interactions that predict benefit or risk from moderate drinking in specific subpopulations, and to identify biological mechanisms that underlie beneficial aspects. Information gained from this kind of research raises the possibility of designing pharmaceuticals that induce these beneficial mechanisms without incurring alcohol's toxic effects.

Why the Combination of Hepatitis C and Alcohol Delivers More than a Double Punch

Background: Scientists have known for some time that alcohol use worsens liver damage in people with the hepatitis C virus (HCV). At first, this might seem like an obvious conclusion, since both hepatitis C and alcohol can cause liver damage. But concurrent HCV infection and alcohol use hasten liver damage beyond what would be expected from the combination of the two; for example, HCV patients who drink alcohol are more likely to develop cirrhosis or liver cancer. Furthermore, people who use alcohol respond poorly to interferon alpha, the main therapy for HCV.

Alcohol increases the number of viral particles in patients with HCV, which raises questions. Does alcohol somehow promote the virus's ability to replicate itself, resulting in a larger amount of the virus in patients' bodies? In this study of cultured human cells, researchers found evidence to suggest that this is at least one of the ways that alcohol potentiates HCV liver damage. But how? To search for answers, investigators used HCV replicons – artificial, incomplete viral packets that mimic the replication process.

Advance: Scientists found that alcohol enhances the replication process of the HCV replicon and thus, presumably, the replication process of the complete viral particle.

Going a step further, the researchers found a potential explanation for this increase in HCV replicons. Alcohol activates a cellular factor (NF-κB) needed for production of immune substances (cytokines) that promote inflammation. When researchers chemically blocked this alcohol-induced activation of NF-κB, the process that produces HCV replicons also was blocked.

In addition, the investigators discovered that naltrexone, a medication used for treatment of alcoholism, abolishes alcohol's interference with treatment for interferon therapy for HCV.

Implications: Alcohol appears to promote replication of the hepatitis C virus, suggesting that it results in a greater amount of the virus in the body. This finding has implications for health practitioners counseling patients about alcohol use, and eventually may be the source of potential targets for preventing or mitigating HCV/alcohol liver damage.

The medication naltrexone works on a chemical messenger system, the opioid system, known to mediate some of alcohol's effects. This preliminary finding now implicates the opioid system in

HCV replication – an area for researchers to examine as they look for ways of blocking the proliferation of the virus.

Protein Fragment Blocks a Mechanism of Alcohol Damage to Fetal Brain

Background: Fetal alcohol exposure is the leading cause of preventable mental retardation in the United States. Evidence suggests that alcohol exerts damage on the fetal brain, in part, by preventing cells from migrating and adhering to each other to form the specialized tissues of the nervous system. Specifically, alcohol disrupts a molecule, "L1," involved in this essential process of tissue formation.

In this study, investigators focused on NAP, a fragment of brain protein that protects nerve cells from a wide range of damage from different causes. Researchers asked whether NAP prevents alcohol's damage to fetal brain cells by (1) keeping alcohol from disrupting L-1 cell adhesion or (2) conferring a more general protection of the cells. Their findings were published in the *Proceedings of the National Academy of Sciences.*

Advance: NAP's ability to prevent alcohol from damaging fetal brain cells is due more to its protective effects against disruption of L-1 cell adhesion, specifically, than to its more general neuroprotective properties.

The investigators also pinpointed specific regions of the NAP molecule that must be present for NAP to protect nerve cells from alcohol-induced disruption of L-1 cell adhesion. They also found evidence suggesting that NAP interacts with at least two different molecular targets to exert its protective effects.

Turning from cultured nerve cells to cultures of whole-mouse embryos, the investigators found that NAP significantly prevented alcohol-induced growth retardation.

Implications: Particularly impressive is that NAP so consistently prevents alcohol-induced pathological changes in fetal brain cells, even though alcohol disrupts fetal development through a host of other biological mechanisms, as well.

This finding also adds to research on L-1 cell adhesion reported to the Appropriations Committee last year. We reported that octanol, a member of the alcohol family with a molecular structure different from that of ethanol (beverage alcohol), also inhibited L-1 cell adhesion and prevented alcohol-induced damage to fetal brain cells. Both octanol and NAP are useful probes that ultimately may help scientists identify molecular targets for compounds that can block alcohol's harmful actions in the fetus.

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NIH Roadmap Initiatives Accelerate Alcohol Research

NIH Roadmap Initiatives will provide NIAAA with valuable tools that will accelerate alcohol research. Two examples follow.

Metabolomics – Alcohol-related pathology includes (1) adaptations in the brain that lead to alcohol dependence and (2) toxicity to tissues and organs. A major goal in alcohol research is to identify and measure metabolic processes involved in both. Within these processes lie molecules involved in metabolism, as well as byproducts of metabolism, that can serve as biomarkers of risk of alcohol-related pathologies, as well as biomarkers of the various stages of the diseases themselves.

Virtually every field of health research has an interest in the metabolic processes that underlie disease. The cross-cutting resources that the NIH Metabolomics Roadmap Initiative can provide will enhance our ability to accomplish our goal, and will advance our understanding of how metabolic systems interact with each other in the development of alcohol-related pathology. Within these interactions lie points for intervention.

Proteomics – Nerve cells receive and send biochemical signals that initiate critical functions. Research has implicated several signaling pathways, including those regulated by the chemical messengers dopamine and serotonin, in behavioral aspects of alcohol abuse and dependence. Proteins are essential components of these signaling pathways; for example, receptors that act as docking sites for chemical messengers are proteins. In an effort to find more effective treatments, researchers have used compounds to inhibit these pathways; however, they've found that doing so has a very limited effect on alcohol abuse and alcoholism, suggesting that other molecules (notably proteins) and pathways also play a role in development of these conditions.

Tools being developed under the NIH Proteomics Roadmap Initiative will be invaluable in uncovering other pathways that may serve as targets for medications development for alcohol-use disorders. This initiative will enable scientists to determine, in real time, the amounts, locations, and interactions of large numbers of individual proteins within a single cell. Proteomics technologies also will be extremely useful in identifying medications to treat alcohol-related medical sequelae, such as liver disease, and for identifying biomarkers of disease progression.

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NIAAA New or Expanded Initiatives

Preventing Underage Drinking in Rural and Small Urban Areas – As a recent Congressional hearing on underage drinking attested, alcohol is the primary substance of abuse among the nation's children. Among children who use alcohol, one group is notable for its particularly high risk: rural youth. In a major survey*, rural children topped the geographical list of youth who reported drinking within the past year (and almost twice as many used alcohol as used illegal drugs). The percentage of 12- to 17-year-olds who reported binge drinking within the past

month was higher among rural children than among children in any other geographic region in the U.S. Research literature that could help us understand this problem and develop effective preventive interventions is unavailable.

We need to know why children in this high-risk population drink and how to prevent them from doing so and from harming themselves and others. An initiative in this area could identify risk factors common to youth in rural and small urban communities, another high-risk population, and would develop and implement community-based, longitudinal prevention and intervention programs. Academic health centers would be ideal candidates for this research, since they can add a medical component to the range of disciplines and services (for example, social work and those related to the justice system), usually involved in these kinds of studies.

Adolescents have in common unique neurobiological factors that affect risk and resiliency vis-a-vis alcohol use. Few studies have addressed neurobiological mechanisms and consequences of heavy drinking in this group. The utility of rural and urban cohorts could be maximized by including neurobiological studies, whose results would apply to adolescents in general.

The Substance Abuse and Mental Health Services Administration, the Department of Education, NIDA, and NCI will be invited to collaborate in this initiative.

* *Substance Abuse and Mental Health Services Administration, Office of Applied Studies, National Survey on Drug Use and Health, 2002.*

Alcohol Metabolism – Critical questions about alcohol metabolism remain to be answered. The overarching question is how 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 pathological responses to these compounds. This kind of information is necessary for identifying biomarkers of risk and disease, and can indicate potential points for intervention.

Alcohol consumption can result in generation of damaging molecules called free radicals. The highly reactive new compounds that result from free-radical activity – adducts – can bind to proteins, thereby altering cell function, damaging organs (including the brain), and altering behavior. For example, alcohol is one of the two main causes of upper gastrointestinal tract cancer in industrialized countries, and products of alcohol metabolism are thought to be responsible for this toxicity. Adducts also are formed by the alcohol metabolite acetaldehyde, a primary area of interest. Evidence suggests that another alcohol metabolite, acetate, also should be explored further.

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 modulated in some way to mitigate damage to proteins and cells?

Medication Development for Alcoholism: (1) Bypassing the IND Bottleneck and (2) Human Laboratory Studies and Early Phase II Clinical Trials – Developing more widely effective medications is one of the most pressing needs in alcohol research. NIAAA currently has at least nine compounds that merit preclinical testing. The infrastructure and resources required for Investigational New Drug approval continue to be a bottleneck for this Institute. We intend to make use of NIDA's medications-development infrastructure for preclinical studies, which largely bypasses roadblocks to progress. Through interagency agreements, NIAAA can avoid the duplication of effort (and expense) that would be involved in creating its own, similar infrastructure to test compounds that show promise as alcoholism treatments.

As a separate activity, NIAAA will develop its own contracts for Phase I human laboratory studies and early Phase II clinical trials of compounds with potential to treat alcoholism. The intent of this activity is to discover whether a compound is worth pursuing further before expending resources for Phase III trials. Candidate compounds currently are available.

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Other Areas of Interest

Influence of Gene/Environment Interactions on Drinking Behaviors – Alcohol-use disorders are the result of a complex combination of genetic and environmental interactions that influence how people respond to alcohol and their initial propensity for using alcohol. Longitudinal studies of these genetic and environmental factors are crucial for understanding (1) early initiation of drinking, (2) transition to harmful alcohol use, abuse, and dependence, and (3) remission and abatement of alcohol-related problems in untreated populations. This research has potential to identify mechanisms and markers of vulnerability and protection.

Influence of Gene/Environment Interactions on Health-Related Benefits and Consequences of Alcohol Use – People have a wide range of variability, across the lifespan, in their responses to alcohol, including variability in consequent health and social problems. Health consequences are not the only issue at hand; moderate alcohol use is associated with benefits to certain aspects of health. An important area of research is the interplay of biological factors and environmental factors that contribute to the consequences or benefits of alcohol use at various stages of life.

Prevention of Alcohol Abuse and Alcoholism – Preventive interventions for alcohol-use disorders and related problems can be improved through early detection and diagnosis, and through testing of new behavioral strategies at the individual, family, and community levels. Of particular interest are longitudinal data on children entering the age of risk, adolescents and young adults in high-risk environments (college and the military), and women of child-bearing age. Points for interventions to prevent early-onset drinking can be gleaned through studies that identify biomarkers, precursors, and factors that stimulate and support this behavior.

Translational Research – Integration of genetic, cellular, and animal-model research with patient-oriented and clinical research is essential to development of new, more

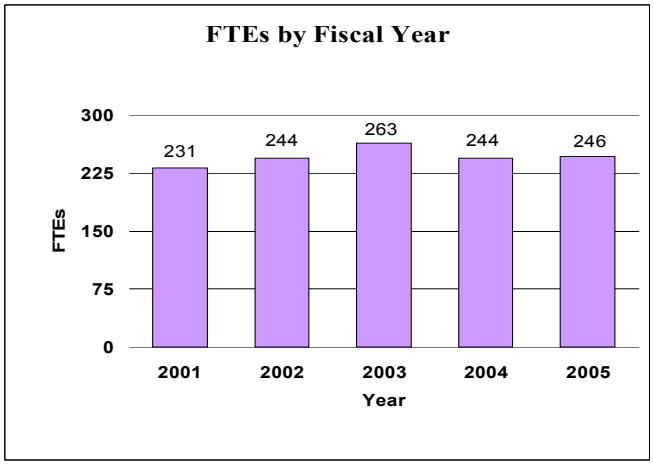
effective medications to reduce alcohol abuse and related organ damage. Ultimately, our goal is to accelerate the rate at which basic-science findings are incorporated in clinical practice.

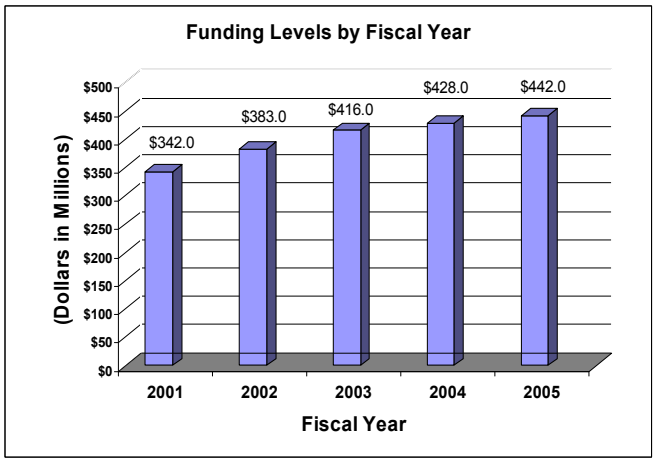
Improving Effectiveness of Treatment – Developing, evaluating, and improving efficacy and cost-effectiveness of treatments is a central goal in alcohol research. Objectives include: develop and test new behavioral therapies; conduct clinical trials in existing treatment settings, to reveal cost-effectiveness of behavioral and pharmaceutical therapies; clarify mechanisms of action that make effective medications and behavioral treatments successful; and conduct trials of dissemination strategies, to test how effective they are at introducing behavioral and pharmacological treatments into real-world clinical practice.

Budget Policy

The Fiscal Year 2005 budget request for the NIAAA is $441,911,000, an increase of $13,486,000 and 3.1 percent over the FY 2004 Final Conference Level. Also included in the FY 2005 request is NIAAA's support for the trans-NIH Roadmap initiatives, estimated at 0.63% of the FY 2005 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. Note that the Fiscal Year 2001 FTE figure is not comparable to figures in the succeeding years due to NIH's consolidation of its Human Resources function in FY 2003.





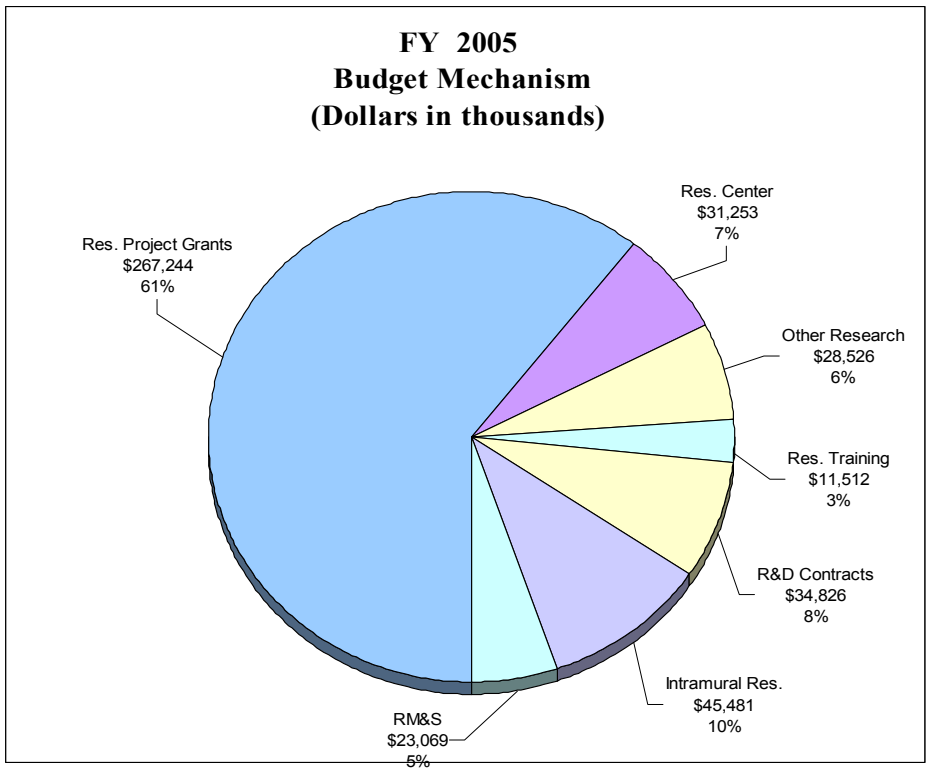
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2005 NIH request provides for an aggregate 1.3 percent increase in the average cost for Research Project Grants, consistent with the Gross Domestic Product Deflator. The NIAAA is providing an aggregate average cost increase of 1.9 percent for direct recurring costs in noncompeting continuation awards. Competing RPGs are based on an average cost increase of 1 percent.

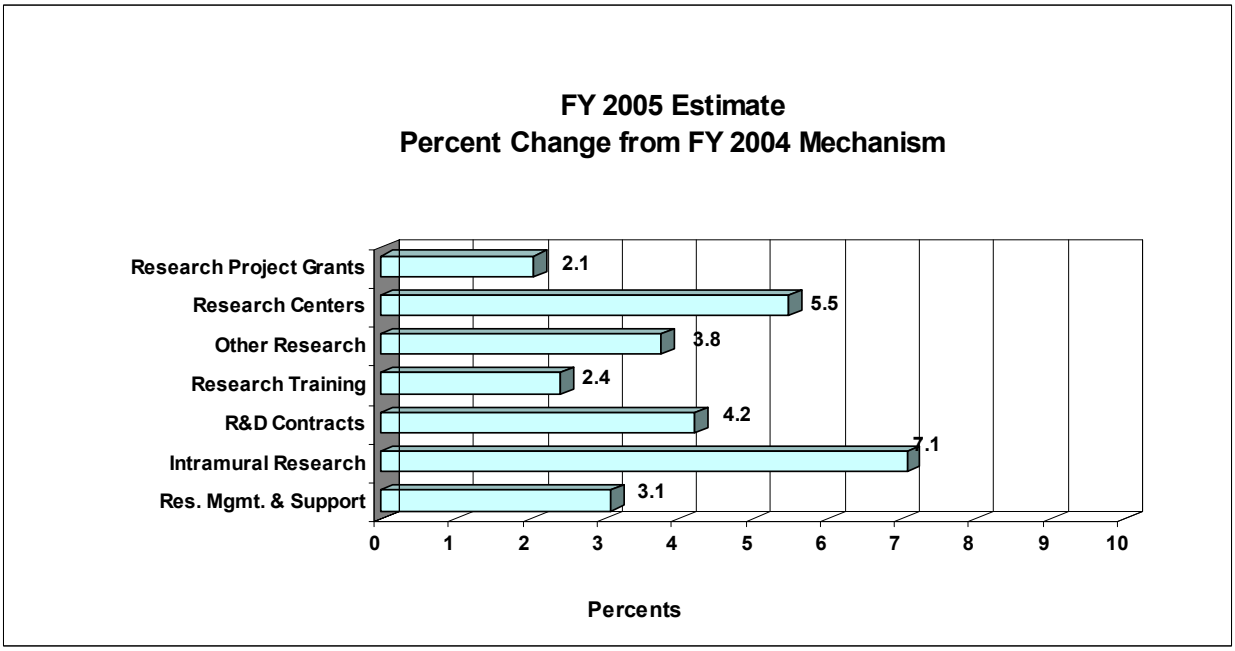
Advancement in medical research is dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2005 request, NIAAA will support 253 pre- and post-doctoral trainees in full-time training positions. Stipend levels for pre-doctoral and post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels.

The Fiscal Year 2005 request includes funding for 16 research centers, 112 other research grants, including 83 clinical career awards, and 30 R&D contracts. Intramural Research and Research Management and Support receive increases to support increased pay and estimated inflationary increases in FY 2005.

The Fiscal Year 2005 request for NIAAA includes $1,040,000 for obesity research. NIAAA will focus its efforts in obesity research in the area of neurobiology.

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 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	529	$182,097,000	529	$194,237,000	506	$190,123,000
Administrative supplements	(34)	1,963,000	(34)	1,953,000	(34)	2,062,000
Full funded	1	142,000	1	145,000	1	146,000
Single year	187	60,716,000	170	56,792,000	200	67,800,000
Renewal	37	15,444,000	33	14,449,000	39	17,116,000
New	150	45,272,000	137	42,343,000	161	50,684,000
Supplements	0	0	0	0	0	0
Subtotal, competing	188	60,858,000	171	56,937,000	201	67,946,000
Subtotal, RPGs	717	244,918,000	700	253,127,000	707	260,131,000
SBIR/STTR	32	7,593,000	36	8,692,000	29	7,113,000
Subtotal, RPGs	749	252,511,000	736	261,819,000	736	267,244,000
Research Centers:						
Specialized/comprehensive	16	26,126,000	16	29,441,000	16	30,973,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	184,000	0	280,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	45,000	0	0	0	0
Subtotal, Centers	16	26,171,000	16	29,625,000	16	31,253,000
Other Research:						
Research careers	80	9,688,000	81	10,110,000	83	10,554,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	13	11,326,000	13	10,108,000	13	10,411,000
Biomedical research support	0	0	0	8,000	0	10,000
Minority biomedical research support	0	0	0	0	0	0
Other	16	7,294,000	15	7,259,000	16	7,551,000
Subtotal, Other Research	109	28,308,000	109	27,485,000	112	28,526,000
Total Research Grants	874	306,990,000	861	318,929,000	864	327,023,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	58	1,916,000	53	1,974,000	53	1,994,000
Institutional awards	197	8,524,000	197	9,266,000	200	9,518,000
Total, Training	255	10,440,000	250	11,240,000	253	11,512,000
Research & development contracts	32	35,772,000	30	33,409,000	30	34,826,000
(SBIR/STTR)	(2)	(1,576,000)	(2)	(1,188,000)	(3)	(3,000,000)
	FTEs		FTEs		FTEs	
Intramural research	116	40,969,000	108	42,471,000	110	45,481,000
Research management and support	147	21,329,000	136	22,376,000	136	23,069,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Total, NIAAA	263	415,500,000	244	428,425,000	246	441,911,000
(RoadMap Support)		(0)		(1,472,000)		(2,783,000)
(Clinical Trials)		(41,841,000)		(43,142,000)		(44,433,000)

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

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

ACTIVITY	FY 2003 Actual FTEs	FY 2003 Actual Amount	FY 2004 Final Conference FTEs	FY 2004 Final Conference Amount	FY 2005 Estimate FTEs	FY 2005 Estimate Amount	Change FTEs	Change Amount
~~Extramural Research:~~								
Alcohol Biomedical and Behavioral Research		$353,202		$363,578		$373,361		$9,783
Subtotal, Extramural research		353,202		363,578		373,361		9,783
Intramural research	116	40,969	108	42,471	110	45,481	2	3,010
Res. management & support	147	21,329	136	22,376	136	23,069	0	693
Total	263	415,500	244	428,425	246	441,911	2	13,486

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Summary of Changes

FY 2004 Final Conference				$428,425,000
FY 2005 Estimated Budget Authority				441,911,000
Net change				13,486,000
	FY 2004 Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$13,232,000		$165,000
b. Annualization of January 2004 pay increase		13,232,000		136,000
c. January 2005 pay increase		13,232,000		149,000
d. One less day of pay		13,232,000		(51,000)
e. Payment for centrally furnished services		6,782,000		203,000
f. Increased cost of laboratory supplies, materials, and other expenses		22,457,000		2,208,000
Subtotal				2,810,000
2. Research Management and Support:				
a. Within grade increase		15,102,000		256,000
b. Annualization of January 2004 pay increase		15,102,000		155,000
c. January 2005 pay increase		15,102,000		170,000
d. One less day of pay		15,102,000		(59,000)
e. Payment for centrally furnished services		2,278,000		68,000
f. Increased cost of laboratory supplies, materials, and other expenses		4,996,000		103,000
Subtotal				693,000
Subtotal, Built-in				3,503,000

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Summary of Changes--continued

CHANGES	FY 2004 Budget Base No.	FY 2004 Budget Base Amount	Change from Base No.	Change from Base Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	529	$196,190,000	(23)	($4,005,000)
b. Competing	171	56,937,000	30	11,009,000
c. SBIR/STTR	36	8,692,000	(7)	(1,579,000)
Total	736	261,819,000	0	5,425,000
2. Research centers	16	29,625,000	0	1,628,000
3. Other research	109	27,485,000	3	1,041,000
4. Research training	250	11,240,000	3	272,000
5. Research and development contracts	30	33,409,000	0	1,417,000
Subtotal, extramural				9,783,000
	~~FTEs~~		~~FTEs~~	
6. Intramural research	108	42,471,000	2	200,000
7. Research management and support	136	22,376,000	0	0
Subtotal, program		428,425,000		9,983,000
Total changes	244		2	13,486,000

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Budget Authority by Object

	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease	Percent Change
Total compensable workyears:				
Full-time employment	244	246	2	0.8
Full-time equivalent of overtime & holiday hours	1	1	0	0.0
Average ES salary	$144,000	$145,000	$1,000	0.7
Average GM/GS grade	11.7	11.7	0.0	0.0
Average GM/GS salary	$75,815	$76,952	$1,137	1.5
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$68,437	$70,490	$2,053	3.0
Average salary of ungraded positions	96,442	97,889	1,447	1.5

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease	Percent Change
Personnel Compensation:				
11.1 Full-Time Permanent	$15,200,000	$15,839,000	$639,000	4.2
11.3 Other than Full-Time Permanent	4,314,000	4,537,000	223,000	5.2
11.5 Other Personnel Compensation	420,000	440,000	20,000	4.8
11.7 Military Personnel	526,000	552,000	26,000	4.9
11.8 Special Personnel Services Payments	2,547,000	2,691,000	144,000	5.7
Total, Personnel Compensation	23,007,000	24,059,000	1,052,000	4.6
12.1 Civilian Personnel Benefits	4,830,000	5,049,000	219,000	4.5
12.2 Military Personnel Benefits	497,000	524,000	27,000	5.4
13.0 Benefits for Former Personnel	0	0	0	0.0
Subtotal, Pay Costs	**28,334,000**	**29,632,000**	**1,298,000**	**4.6**
21.0 Travel & Transportation of Persons	599,000	626,000	27,000	4.5
22.0 Transportation of Things	146,000	152,000	6,000	4.1
23.1 Rental Payments to GSA	2,594,000	2,689,000	95,000	3.7
23.2 Rental Payments to Others	565,000	604,000	39,000	6.9
23.3 Communications, Utilities & Miscellaneous Charges	1,143,000	1,215,000	72,000	6.3
24.0 Printing & Reproduction	117,000	119,000	2,000	1.7
25.1 Consulting Services	656,000	674,000	18,000	2.7
25.2 Other Services	1,492,000	1,586,000	94,000	6.3
25.3 Purchase of Goods & Services from Government Accounts	32,361,000	33,998,000	1,637,000	5.1
25.4 Operation & Maintenance of Facilities	7,731,000	8,187,000	456,000	5.9
25.5 Research & Development Contracts	15,784,000	16,718,000	934,000	5.9
25.6 Medical Care	799,000	855,000	56,000	7.0
25.7 Operation & Maintenance of Equipment	417,000	443,000	26,000	6.2
25.8 Subsistence & Support of Persons	0	0	0	0.0
25.0 Subtotal, Other Contractual Services	**59,240,000**	**62,461,000**	**3,221,000**	**5.4**
26.0 Supplies & Materials	3,075,000	3,285,000	210,000	6.8
31.0 Equipment	2,443,000	2,593,000	150,000	6.1
32.0 Land and Structures	0	0	0	0.0
33.0 Investments & Loans	0	0	0	0.0
41.0 Grants, Subsidies & Contributions	330,169,000	338,535,000	8,366,000	2.5
42.0 Insurance Claims & Indemnities	0	0	0	0.0
43.0 Interest & Dividends	0	0	0	0.0
44.0 Refunds	0	0	0	0.0
Subtotal, Non-Pay Costs	**400,091,000**	**412,279,000**	**12,188,000**	**3.0**
Total Budget Authority by Object	**428,425,000**	**441,911,000**	**13,486,000**	**3.1**

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Salaries and Expenses

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease	Percent Change
Personnel Compensation:				
Full-Time Permanent (11.1)	$15,200,000	$15,839,000	$639,000	4.2
Other Than Full-Time Permanent (11.3)	4,314,000	4,537,000	223,000	5.2
Other Personnel Compensation (11.5)	420,000	440,000	20,000	4.8
Military Personnel (11.7)	526,000	552,000	26,000	4.9
Special Personnel Services Payments (11.8)	2,547,000	2,691,000	144,000	5.7
Total Personnel Compensation (11.9)	**23,007,000**	**24,059,000**	**1,052,000**	**4.6**
Civilian Personnel Benefits (12.1)	4,830,000	5,049,000	219,000	4.5
Military Personnel Benefits (12.2)	497,000	524,000	27,000	5.4
Benefits to Former Personnel (13.0)	0	0	0	0.0
Subtotal, Pay Costs	**28,334,000**	**29,632,000**	**1,298,000**	**4.6**
Travel (21.0)	599,000	626,000	27,000	4.5
Transportation of Things (22.0)	146,000	152,000	6,000	4.1
Rental Payments to Others (23.2)	565,000	604,000	39,000	6.9
Communications, Utilities and Miscellaneous Charges (23.3)	1,143,000	1,215,000	72,000	6.3
Printing and Reproduction (24.0)	117,000	119,000	2,000	1.7
Other Contractual Services:				
Advisory and Assistance Services (25.1)	533,000	549,000	16,000	3.0
Other Services (25.2)	1,492,000	1,586,000	94,000	6.3
Purchases from Govt. Accounts (25.3)	4,757,000	5,524,000	767,000	16.1
Operation & Maintenance of Facilities (25.4)	7,731,000	8,187,000	456,000	5.9
Operation & Maintenance of Equipment (25.7)	417,000	443,000	26,000	6.2
Subsistence & Support of Persons (25.8)	0	0	0	0.0
Subtotal Other Contractual Services	**14,930,000**	**16,289,000**	**1,359,000**	**9.1**
Supplies and Materials (26.0)	3,074,000	3,284,000	210,000	6.8
Subtotal, Non-Pay Costs	20,574,000	22,289,000	1,715,000	8.3
Total, Administrative Costs	**48,908,000**	**51,921,000**	**3,013,000**	**6.2**

NATIONAL INSTITUTES OF HEALTH

National Institute on Alcohol Abuse and Alcoholism

SIGNIFICANT ITEMS IN HOUSE AND SENATE
APPROPRIATIONS COMMITTEE REPORT

FY 2004 House Appropriations Committee Report Language (H.R. Report 108-193)

Item

Underage rural drinking– The Committee understands that alcohol is the number one drug of choice among children and adolescents in this country. There are relatively few studies about the extent of the problem in rural and small urban areas, and the Committee would like to see more research in this area. 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 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. These model programs should focus not only on reducing alcohol problems among people in this age group, but should also recognize other high-risk behaviors such as tobacco use, other illegal drug use, risky sexual behavior and psychological and parental risk factors for these problem behaviors. The Committee expects NIAAA to provide leadership by working collaboratively with the Substance Abuse and Mental Health Services Administration, the Department of Education, NIDA and NCI. The Committee encourages NIAAA to utilize the expertise of academic health centers in this effort. The Committee requests that NIAAA be prepared to report its progress in developing model prevention programs during the fiscal year 2005 appropriations hearings. (p. 83)

Action Taken or to Be Taken

Among children who use alcohol, one group is notable for its particularly high risk: rural youth. A 2002 survey conducted by Substance Abuse and Mental Health Services Administration (SAMHSA) found that rural children topped the geographical list of youth who reported drinking within the past year (and almost twice as many used alcohol as used illegal drugs). The percentage of 12- to 17-year-olds who reported binge drinking within the past month was higher among rural children than among children in any other geographic region in the U.S. Investigations into factors that contribute to onset of drinking among children in this high-risk group are urgent, as are studies of how to prevent drinking and its consequences. A previous study funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Project Northland, significantly prevented drinking among rural youth. We are now funding a major study that will test Project Northland's effectiveness in economically and ethnically diverse

urban neighborhoods. We also currently fund six longitudinal studies on the impact of gene/environment interactions, beginning in adolescence and throughout life. Such studies will likely have relevance to rural underage drinking. NIAAA also participates in the National Children's Study, led by the National Institute of Child Health and Human Development (NICHD), which follows children from before birth to age 21, to assess the impact of environmental influences on their health.

Most significantly, we have undertaken an initiative to identify risk factors common to youth in rural and small urban communities that would develop and implement community-based, longitudinal prevention and intervention programs. NIAAA undertakes this initiative in partnership with the Association of Academic Health Centers (AHC). Academic health centers will add a rigorous medical component to the social science- and education-related disciplines that will be essential elements of the rural underage drinking initiative. Other important allies with whom we ultimately will partner in this effort include SAMHSA, the Department of Education, the National Institute on Drug Abuse (NIDA), the National Cancer Institute (NCI), and NICHD. Working together, NIAAA and AHC leadership have identified academic health centers, throughout the United States, that have demonstrated skill in establishing community partnerships in rural and small urban settings, to improve health status and health care of residents. Leaders of these academic health centers will participate in an advisory planning meeting in early 2004. These experts will offer advice about science-based methods community partners can use to combat drinking by children and adolescents. Deliberations of the meeting will contribute to development of a Request for Applications NIAAA will announce in 2004.

Previous research has shown that, among adolescents, common unique neurobiological factors affect risk and resiliency vis-a-vis alcohol use. Few studies have addressed neurobiological mechanisms and consequences of heavy drinking in this group. The utility of rural and urban cohorts could be maximized by including neurobiological studies, whose results would apply to adolescents in general.

FY 2004 Senate Appropriations Committee Report Language (Senate Report 108-81)

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. 147)

Action Taken or to Be Taken

NIAAA, SAMHSA, and representatives of the State of Alaska met in late 2002, to discuss what kind of forum would be most helpful to alcohol- and drug-treatment providers and to the State. It has been decided that we will work through the newly-funded American Indian/Alaska Native Research Center to plan future activities. Discussion is ongoing.

Item

Alcoholic Liver Disease– Alcoholic liver disease remains a major cause of morbidity and mortality in the United States. The Committee notes that recent research suggests that free radicals are a principal vehicle through which alcohol damages the liver, and that antioxidants look increasingly promising as a potential treatment. The Committee encourages the Institute to expand its research on alcoholic liver disease, particularly regarding the interaction between hepatitis C and alcohol in liver disease. (p. 147)

Action Taken or to Be Taken

The NIAAA is participating with other NIH Institutes to develop an action plan for liver disease research. Like alcoholic liver disease (ALD), the harmful synergy resulting from hepatitis C infection and alcohol abuse is an ongoing research topic at NIAAA, and we have expanded in these areas.

The recently established Section on Liver Biology in NIAAA's Intramural Program is already yielding findings; for example, investigators have found that treating mice with interleukin-6 (a naturally occurring component of the immune system) protects them against liver disease and hepatitis. The investigators plan to identify genes whose activation by interleukin-6 results in anti-oxidant and anti-cell-death actions in liver disease. Data from these kinds of studies will provide potential targets for therapy. The Section on Liver Biology also is collaborating with researchers from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute (NHLBI) to study the synergistic effect of alcohol and viral hepatitis, and other liver toxins, on liver injury.

During the past year, NIAAA awarded four new grants on various aspects of immunology and liver function in ALD; was the primary funding agency for five new grants on hepatitis C and ALD; and collaborated with other Institutes in funding an additional 10 grants on related topics.

In addition, NIAAA cosponsored, with the Office of Dietary Supplements, a workshop on the role of fatty liver, dietary fatty acids, and obesity in progression of ALD. The proceedings and recommendations from the workshop will be disseminated via publication in a scientific journal. Other proceedings from a similarly cosponsored workshop on the role of iron in ALD, held in 2002, were disseminated through publication in an international journal in 2003.

Following an NIAAA-sponsored workshop on potential use of stem cells for treatment of alcohol-related conditions, we issued a Request for Applications to encourage research in this area. In 2003, we funded a grant investigating the molecular bases of cirrhosis in ALD.

NIAAA joined NIDDK, NCI, the National Institute of Allergy and Infectious Diseases, and NIDA in sponsoring a 2002 Request for Applications on hepatitis C. NIAAA has funded a grant aimed at determining how alcohol aggravates liver damage induced by the hepatitis C virus.

The NIAAA also sponsored a workshop on the direction that alcohol-specific research on hepatitis C should take to achieve advances in prevention and treatment. Recommendations from the workshop have been published in a journal with broad readership and are expected to engender new investigator-initiated grant applications in this important area.

Item

Health Disparities– Evidence suggests that alcohol affects genders and subpopulations differently, and that some groups suffer more adverse effects than others. The Committee encourages the Institute to work collaboratively with the NCMHD to study the role of gender, ethnicity, socioeconomic status, and other variables in determining the effects of alcohol use and abuse. (p. 148)

Action Taken or to Be Taken

In FY 2003, NIAAA and the National Center on Minorities and Health Disparities (NCMHD) cofunded nine projects, with two major goals in mind. One goal is to develop alcohol_research capacity at minority_serving institutions, through collaborations between students, faculty, and clinicians and established alcohol investigators.

We are also co_funding the career-development award of a Native Alaskan alcohol investigator. We are taking this approach because minority investigators and minority_serving institutions tend to have the cultural sensitivity and perspectives needed for alcohol research in the populations they serve. The grants we fund in this area are intended to develop sustained programs in alcohol research, increase the number of minority scientists who will successfully pursue biomedical and behavioral alcohol research careers, and emphasize research on alcohol problems in minority populations and communities. Collaborative projects involve American Indian, Native Hawaiian, Hispanic, and African_ American institutions and communities.

Another goal is to support studies on specific risk and protective factors for alcohol_related problems in minority and rural populations. Projects funded last year investigated risk factors for alcoholism among minority and rural populations, prevention and treatment of alcoholism in American Indian or Alaska Native communities, and the relationships among alcohol, violence, and health services in rural populations.

Item

Multidisciplinary Research on Fetal Alcohol Syndrome– The Committee recognizes that fetal alcohol syndrome is among the most common preventable cause of mental impairment. The Committee supports the Institute's efforts to understand the biological mechanisms through which alcohol causes damage to the developing fetus. The Committee continues to urge the

Institute to aggressively pursue research that will lead to effective strategies for the prevention and treatment of fetal alcohol syndrome. (p. 148)

Action Taken or to Be Taken

In 2003, we awarded 13 grants to conduct studies under a new initiative, called the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) that will greatly facilitate research on alcohol-induced fetal damage. The CIFASD is intended to speed translation of findings into clinical applications, and will accelerate our research by integrating resources and basic, behavioral, and clinical investigations, and by developing essential new resources. Investigators from outside the alcohol field also will be recruited, resulting in the application of new ideas and technology to fetal-alcohol studies. The CIFASD approach will foster rapid exchange of information that consortium members from various disciplines can integrate into their research.

Alcohol results in a spectrum of neurological, behavioral, and physical deficits, each of which correlates with the trimester of pregnancy in which the fetus was exposed. Defining when in gestation each of these deficits occurs and discovering the biological mechanisms that lead to it hinge on our ability to integrate information from various fields of study. Likewise, developing treatments for children and adults who sustained alcohol-induced damage while in the womb requires integration of multiple disciplines, from behavior to molecular biology.

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2004 Amount Authorized	2004 Final Conference	2005 Amount Authorized	2005 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$417,185,000	Indefinite	$430,399,000
Abuse and Alcoholism	Section 464H	42§285n	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	11,240,000	b/	11,512,000
Total, Budget Authority				428,425,000		441,911,000

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/
1996	$185,712,000 2/	$198,607,000	$183,733,000 2/	$198,607,000
Rescission				(195,000)
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			

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 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Office of the Director	9	8	8
Office of Scientific Affairs	28	27	27
Office of Research Translation and Communications	17	15	15
Office of Resource Management	31	33	33
Division of Epidemiology and Prevention Research	24	17	17
Division of Metabolism and Health Effects	14	13	13
Division of Neuroscience and Behavior	12	12	12
Division of Treatment and Recovery Research	12	11	11
Division of Intramural Clinical and Biological Research	116	108	110
Total	263	244	246
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2001	11.6
2002	11.6
2003	11.7
2004	11.7
2005	11.7

NATIONAL INSTITUTES OF HEALTH
National Institute on Alcohol Abuse and Alcoholism

Detail of Positions

GRADE	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
ES-6			
ES-5	1	1	1
ES-4			
ES-3	2	2	2
ES-2			
ES-1			
Subtotal	3	3	3
Total - ES Salary	$427,500	$432,000	$435,000
GM/GS-15	28	27	27
GM/GS-14	50	48	49
GM/GS-13	37	35	35
GS-12	26	25	25
GS-11	14	13	13
GS-10	2	2	2
GS-9	17	16	16
GS-8	8	8	8
GS-7	11	10	10
GS-6	5	5	5
GS-5	3	3	3
GS-4	7	6	6
GS-3	0	0	0
GS-2	0	0	0
GS-1	1	1	1
Subtotal	209	199	200
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	1	1	1
Senior Grade	6	6	6
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	7	7	7
Ungraded	51	51	51
Total permanent positions	208	200	201
Total positions, end of year	270	260	261
Total full-time equivalent (FTE) employment,end of year	263	244	246
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$142,500	$144,000	$145,000
Average GM/GS grade	11.7	11.7	11.7
Average GM/GS salary	$74,328	$75,815	$76,952