DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

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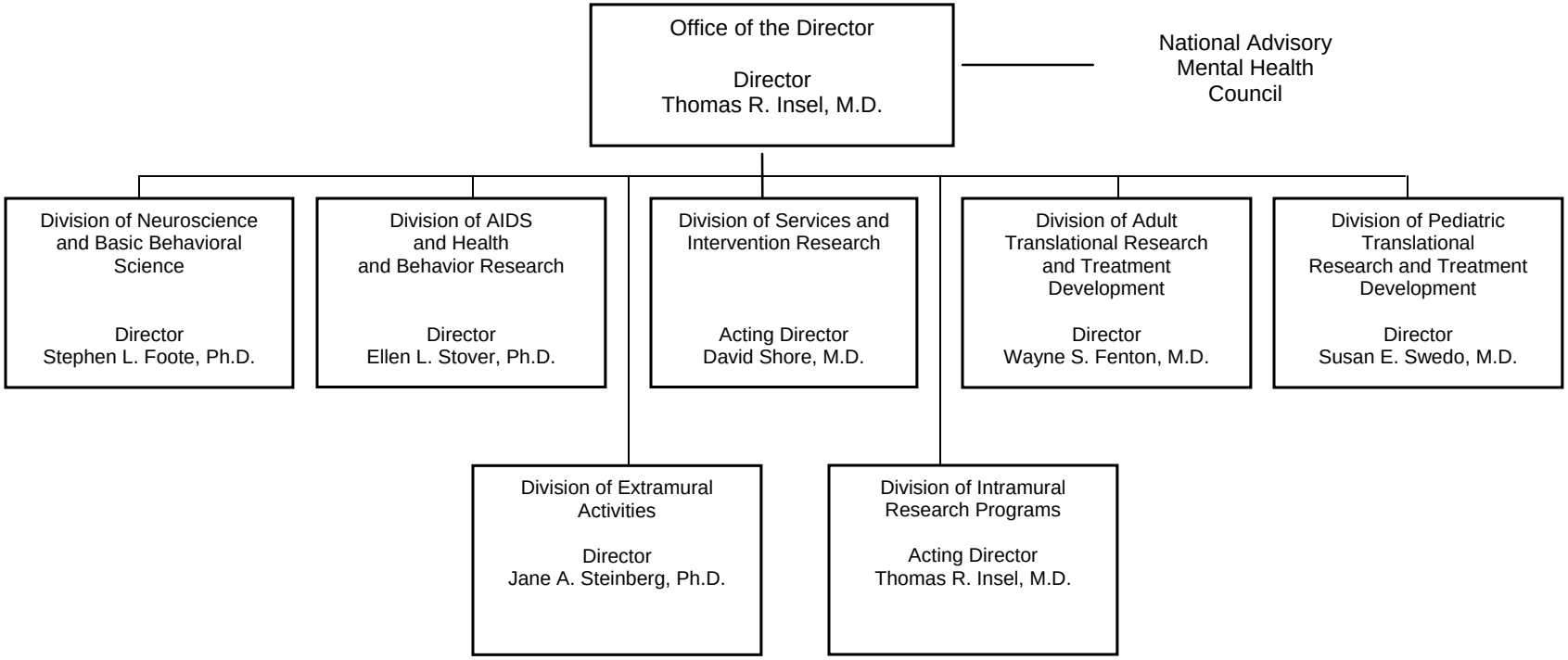

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

For carrying out section 301 and title IV of the Public Health Service Act with respect to mental health [$1,417,692,000], *$1,394,806,000*.

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

National Institutes of Health
National Institute of Mental Health

Amounts Available for Obligation 1/

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	$1,423,609,000	$1,417,692,000	$1,394,806,000
Enacted Rescissions	(11,676,000)	(14,177,000)	0
Subtotal, Adjusted Appropriation	1,411,933,000	1,403,515,000	1,394,806,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(8,926,000)	(12,542,000)	0
Comparative transfer from OD for NIH Roadmap	8,926,000	12,542,000	0
Subtotal, adjusted budget authority	1,411,933,000	1,403,515,000	1,394,806,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,411,933,000	1,403,515,000	1,394,806,000
Unobligated balance lapsing	0	0	0
Total obligations	1,411,933,000	1,403,515,000	1,394,806,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2005 - $4,760,000; FY 2006 - $5,000,000; FY 2007 - $5,070,000
Excludes $279,650 in FY 2006 and $280,000 in FY 2007 for royalties.

Justification

National Institute of Mental Health

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

Budget Authority:

FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
662	$1,411,933,000	698	$1,403,515,000	702	$1,394,806,000	4	($8,709,000)

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

INTRODUCTION

The mission of the National Institute of Mental Health (NIMH) is to reduce the public health burden of mental and behavioral disorders through research on mind, brain, and behavior. Mental disorders are common, chronic, and disabling. They cause more disability than any other class of medical illness in American adults.[1]

NIMH funded the National Comorbidity Survey Replication (NCS-R), a landmark study released in May 2005 documenting the prevalence and severity of specific mental disorders.[2] The study showed that half of all lifetime cases of mental illness begin by age 14, making these the chronic

[1] Murray CJ, Lopez AD (Eds), The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge, MA: Harvard University Press; 1996.

[2] Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):629-40.

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):617-27.

Wang PS, Berglund P, Olfson M, Pincus HA, Wells KB, Kessler RC. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):603-13.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005 Jun;62(6):593-602.

diseases of the young. The NCS-R also illustrates the severity of the mental health problem in the United States. About 6% of the US population is afflicted with a *severely disabling* mental disorder in a given year. In addition, despite effective treatments, there are long delays—sometimes decades—between first onset of symptoms and when people seek and receive treatment.

Unfortunately, this is not the only study indicating that severe mental illness can be a lifelong and prevalent problem. Another NIMH-funded study this year showed that a large percentage of Cambodian-born adults who fled the brutal Khmer Rouge regime remain severely disabled from this trauma after more than two decades of living in California.[3] Almost two-thirds of the 500 study participants (62%) suffer from post-traumatic stress disorder (PTSD) and 51% suffer from depression. About 42% of respondents reported both illnesses. The rates of disorder were higher among people who were older, poor, unemployed, retired or disabled, and who spoke English poorly. Efforts to reduce the burden of mental illness in the U.S. must address an increasingly diverse population.

Even those who do get treatment cannot be assured of a straightforward road to health. Evidence from other NIMH studies suggest that many people suffering from severe mental illness have had traumatic or harmful experiences while being treated in various psychiatric settings[4] and have been victimized while living in community settings[5].

The good news is that there now are some extraordinary new tools and technologies with which to address these urgent public health challenges. Multiple approaches to identifying abnormal functional activity in the brain are emerging. New discoveries in neuroimaging and genomics are revealing that mental disorders are brain disorders. This is a critical step in the creation of more effective strategies to diagnose, manage, treat, and even prevent these debilitating disorders. In the following pages are some examples of research that illustrate great progress across levels of analysis—from neurons to neighborhoods. Our major challenge is in integrating and translating basic and technological advances across these levels of analysis into practical strategies that can help all communities, including children, the socioeconomically disadvantaged, and those with various other barriers to mental health care.

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[3] Marshall GN, Schell TL, Elliott MN, Berthold SM, Chun CA. Mental health of Cambodian refugees 2 decades after resettlement in the United States. JAMA. 2005 Aug 3;294(5):571-9.

[4] Frueh BC, Knapp RG, Cusack KJ, Grubaugh AL, Sauvageot JA, Cousins VC, Yim E, Robins CS, Monnier J, Hiers TJ. Special Section on Seclusion and Restraint: Patients' Reports of Traumatic or Harmful Experiences Within the Psychiatric Setting. Psychiatr Serv 56: 1123-1133, 2005

Robins CS, Sauvageot JA, Cusack KJ, Suffoletta-Maierle S, Frueh BC. Special Section on Seclusion and Restraint: Consumers' Perceptions of Negative Experiences and "Sanctuary Harm" in Psychiatric Settings. Psychiatr Serv 56:1134-1138, 2005

[5] Teplin LA, McClelland GM, Abram KM, Weiner DA. Crime victimization in adults with severe mental illness: comparison with the National Crime Victimization Survey. Arch Gen Psychiatry 62(8): 911-21, 2005.

SCIENCE ADVANCES AND STORY OF DISCOVERY

I. Unlocking the Biological Basis of Mental Disorders

3-D Protein Structure May Aid Drug Development

Communication between neurons in the brain relies on the transmission of electrical signals. To transmit a signal, a neuron releases neurotransmitters—chemical messengers that bind to receptors on the surface of a neighboring neuron. This binding action initiates a cascade of changes in the neuron, causing it to fire and broadcast the electrical signal to other neurons. To prevent neurons from firing non-stop, neurotransmitters are taken back into the cell by proteins called transporters. A large family of transporters (sodium symporters) recycles many important neurotransmitters in the brain, such as dopamine and serotonin. The malfunctioning of these transporters contributes to serious brain disorders such as depression, Parkinson's disease, and epilepsy. In a major advance, NIMH-supported researchers used a technique called X-ray diffraction to characterize the structure of a critical piece of the transporter—the pocket to which the neurotransmitter binds—which is vital information to understand how these proteins recognize and move their neurotransmitters. Based on this detailed 3-D information, the researchers hypothesize that the pocket acts as a hinge that opens a gate and allows the neurotransmitter to move into the cell. Currently, several therapeutic agents, such as selective serotonin reuptake inhibitors (SSRIs) and anticonvulsants, target these transporters. The present findings will provide blueprints for designing more specific medications to treat mental disorders that involve transporter dysfunction.

Novel Pathway Discovered for the Behavioral Actions of Dopamine in Brain

Dopamine is an important neurotransmitter that regulates many physiological functions such as movement, mood, and motivation. Deficits in dopamine systems contribute to several brain disorders including Parkinson's, Huntington's, schizophrenia, major depression, and attention deficit hyperactivity disorder. Researchers have thought that most of the behaviors controlled by dopamine are mediated by one signaling pathway in the cell that relies on a molecule called cyclic AMP. When dopamine binds to certain receptors on the surface of a neuron, cyclic AMP is produced inside of the neuron. Cyclic AMP then modifies the structure and function of enzymes in the neuron, causing these enzymes to modify neuron activity, and subsequently, behavior. NIMH-supported researchers have discovered that some of the behavioral effects of dopamine are regulated by a new signaling pathway that requires a protein called beta-arrestin. Drugs that raise dopamine levels in the brain cause mice to move about their cages more. The researchers demonstrated that disrupting beta-arrestin signaling reduced this dopamine-induced movement. Using biochemical techniques, the scientists determined that when dopamine binds to one of its receptors, beta-arrestin activates a group of enzymes in the cell different from those activated by cyclic AMP. Further study of this novel pathway may elucidate the pathology of dopamine-associated brain disorders and may be a target for developing new medications.

Neonatal Infection May Increase Vulnerability to Adult Memory Impairment

Studies suggest that immune system activation around the time of birth may contribute to the development of neurological disorders such as schizophrenia, autism, and cerebral palsy. Recently, researchers have started to examine how different components of the immune system could influence brain development and susceptibility to mental disorders. In a new study, NIMH-funded scientists demonstrated mechanisms through which neonatal infection may impact memory formation later in life. The researchers infected four-day-old rat pups with bacteria,

which resulted in increased levels of immune molecules in the pups' brains for up to 72 hours post infection. As adults, the neonatally-infected rats were indistinguishable from non-infected rats in general health and in a test of learning and memory. The researchers then challenged the adult animals' immune systems for a second time. The neonatally-infected rats, but not the normal rats, responded with enhanced expression of interleukin 1 beta (IL1b), an immune molecule that promotes inflammation. The increased levels of IL1b were found in brain areas implicated in learning and memory. Furthermore, the neonatally-infected rats had profound memory deficits that could be reversed by inhibiting the synthesis of IL1b. The researchers hypothesize that IL1b may disrupt memory formation by interfering with communication between neurons. This study suggests that neonatal infection may "prime" the immune system in the brain for an exaggerated response later in life, possibly increasing vulnerability to mental and neurological disorders.

Harnessing the Power of Light to Activate and Image Neurons in the Living Brain
In the brain, neurons are wired into diverse, overlapping networks that regulate complex processes such as emotion, learning, and memory. A fundamental goal of neuroscience research is to understand how an individual neuron contributes to the functioning of the network as a whole. Currently, the only way to measure the activity of a single cell is to place electrodes directly in the brain. However, a rapidly advancing technique called optical imaging has the potential to be a non-invasive method to study individual neurons and large networks in the living brain. In contrast to other neuroimaging methods that rely on magnetic fields or radioactive tracers, optical imaging detects physiological changes by measuring how light is reflected by tissue. Surprisingly, one particular wavelength of light, near-infrared light, can penetrate several centimeters through tissue—even through the scalp and skull. NIMH-funded researchers have made an important step toward improving optical imaging techniques for detecting activity in the brain. The researchers shined near-infrared light through the surface of a rat brain and simultaneously twitched one of the rat's whiskers. Using a special video camera that they developed, the scientists captured high resolution images of neuronal activity scattering the light in response to this sensory input. In another study, investigators used light in a different way—to activate neurons. The researchers genetically modified cultured neurons to express Channelrhodopsin-2, a light-activated protein that is found in green algae. When the researchers illuminated neurons that expressed Channelrhodopsin-2, the resulting activation of this protein caused the neuron to fire. By pulsing the light, the scientists were able to cause fast neuronal firing that resembled activation in a living system. These methods to visualize and even control neuronal activity will be critical to understanding how neuronal circuits function in the healthy brain and in those with mental disorders.

II. Building Translational Science: Examples of Basic Science and Treatment Advances for Selected Mental Disorders

A. Mood Disorders

Abnormal Molecular Signals Detected in Major Depression

A fundamental goal in psychiatric research is to identify the differences in the brains of individuals with mental illnesses in order to understand the causes of illness and better target diagnostics and treatments. This goal has been unattainable for the most part, but investigators firmly believe that new molecular techniques will ultimately reveal the basic biology of disorders like depression. Human brain imaging studies have shown that patterns of brain activity in depressed patients occur in selective pathways, or circuits. Investigators reasoned that unusual circuit activation must have a molecular basis and adopted a new approach of measuring individual genes and their products in postmortem human brains. They found that several classes of genes are expressed differently in psychiatric cases. In major depression, genes associated with the brain circuits previously shown to have atypical activation, shared a common biological function. Specifically, these genes all belong to an important gene family (fibroblast growth factor—FGF) involved in cell signaling. The abnormal FGF gene expression seen in depressed subjects was also independent of drug treatment, suggesting a fundamental role in the disease process. The identification of FGF proteins and their receptor families and their association with depression make them key targets in medication development and for new studies to reveal the molecular mechanisms of depression.

Brain's Executive Hub Quells Alarm Center if Stressed

Lack of control over stressful life experiences has been implicated in mood and anxiety disorders, and current treatments are thought to work, in part, by helping patients gain control. Recent research has focused on the role of the medial prefrontal cortex (mPFC), a seat of higher order functions such as problem-solving and learning from experience. By examining rats with their mPFCs chemically inactivated, the researchers observed the same brainstem activation and eventually, the same behaviors characteristic of depression (failure to learn to escape) and anxiety (exaggerated fear conditioning) when the animals were exposed to an external stressor. These responses were similar to rats exposed to an uncontrollable stressor. The researchers also found that when it deems a stressor controllable, the mPFC quells an alarm center deep in the brainstem, preventing the adverse behavioral and physiological effects of uncontrollable stress. This study provides insight into the role of the mPFC in mediating the stress response and suggests that mood and anxiety disorders may be associated with the ability to identify controllable stressors and inhibit the fear response.

Early Life Experience Shapes Brain Development

Mental illnesses appear to result from an unfortunate match between genetic vulnerability and environmental experiences. Recently, the field of epigenetics has begun to define how the environment interacts with genetics by changing gene function (how a gene is expressed) without changing gene sequence. Through epigenetic studies, scientists are unraveling the mystery of how early life experiences influence gene expression in the developing brain, which in turn, affect how individuals respond to the environment. Previously, NIMH-supported researchers demonstrated that the early life experiences of a rat pup may alter the way certain genes are expressed in the brain and thereby modify the pup's physiological response to stress as

an adult. This variation in gene expression in turn affects the complex, underlying neural circuitry. Building on this premise, NIMH-funded researchers traced neural circuit development in the brains of rat pups and identified related anatomical changes. Pups repeatedly handled and separated from their mother had less-developed neural circuits (fewer cells) in specific regions of the brain that respond to stress and control emotional behavior, compared to pups left with their mother all the time. These findings are significant because they provide evidence of the genetic influences and early life experiences which shape subsequent adult behavior.

Families at High and Low Risk for Depression: A Three-Generation Startle Study
It has been well-established that when parents have a history of depression, children are at increased risk for affective disorders such as depression and anxiety. A recent three-generation family study of major depressive disorder (MDD) reported elevated rates of anxiety among children and adolescents whose parents or grandparents had MDD, suggesting that anxiety may be a vulnerability factor for the later development of depression. In this follow-up report to the same three-generation family study, a marker for anxiety (heightened startle response in threatening contexts) was examined as a potential vulnerability factor for depression among children and grandchildren of adults with MDD. The startle reflex, measured by intensity of the eye blink to a startling noise, was assessed in the adult children and grandchildren of elders who had a history of MDD. Startle response was elevated during a threat condition among adult children of parents with MDD compared to those without a parental history. Startle response also was elevated among female grandchildren of elders with MDD; however, there was no effect found among male grandchildren. Findings were not affected by lifetime history of psychopathology or use of medication among children and grandchildren. These results suggest that the startle response may differentiate those at high and low risk for depression, particularly for females. Together with other studies of startle, these findings suggest that heightened startle not only may be a vulnerability marker for anxiety, but that MDD, anxiety, and depression may also share common underlying biological mechanisms of risk.

Surgical Therapy Reverses Symptoms of Treatment-Resistant Depression
Major depression is one of the most common psychiatric disorders and, according to the *Global Burden of Disease*,[1] is the leading cause of disability. While many cases can be effectively treated with medication or psychotherapy, up to 20% of patients have no response to conventional treatments. To address the needs of this severely disabled population, researchers studied the effects of deep brain stimulation, a surgical therapy that has shown marked clinical benefits in patients with Parkinson's disease. In six individuals with treatment-resistant depression, the researchers specifically targeted the subgenual cingulate region, a brain area that in previous studies has consistently shown involvement in acute sadness and response to antidepressant treatments (medications, electroconvulsive therapy, etc.). Through chronic stimulation of this region, four of the six participants achieved significant and sustained remission of depressive symptoms. Further research is needed to confirm the results of this small study, but the authors suggest that deep brain stimulation may be an effective and novel intervention for severely disabled patients suffering from treatment-resistant depression.

New Psychosocial Therapy is Effective in Preventing Bipolar Episode Reoccurrence
Bipolar disorder, also called manic-depressive illness, causes dramatic mood swings—from overly "high" and/or irritable to sad and hopeless, and then back again, often with periods of

normal mood in between. Conventional treatment with lithium and other mood stabilizers works well in the short-term, but has limited long-term effectiveness and is sometimes insufficient to prevent recurring episodes. In an effort to develop complementary psychotherapies for conventional treatments, researchers evaluated 175 people with bipolar disorder in a randomized controlled trial of the short- and long-term effectiveness of a new psychosocial therapy called interpersonal and social rhythm therapy (IPSRT), designed to help prevent disruptions in daily routines and in personal relationships. IPSRT was compared against an intensive clinical management (ICM) approach that combined disease education with medical and behavioral interventions. Study participants received continuing treatment with either IPSRT or ICM, or they received one type of treatment following an episode and were switched to the other type during the remission maintenance phase. In addition, all study participants received the standard medication therapy for bipolar disorder throughout the trial. The study showed that patients in good physical health who received IPSRT soon after experiencing an episode were more likely to remain episode-free in the two years following the initial episode, compared to those who received other treatment combinations. However, patients with co-occurring medical problems or anxiety disorder responded better to ICM following an episode, perhaps due to the increased attention in this approach to their additional medical burden. In addition, IPSRT given during an acute phase may help protect against recurring manic episodes during the maintenance phase, regardless of the type of maintenance treatment used. The researchers suggested that modifications to this treatment model may improve long-term symptom management in bipolar disorder.

Treating Depression in the Workplace is Cost-Effective

In any given one-year period, 6.6% of the U.S. population, or about 14.2 million adults ages 18 and older, suffer from major depressive disorder.[6] Depressive illnesses often interfere with normal functioning, and can negatively impact productivity and performance in the workplace. Two studies by NIMH grantees focused on characteristics and consequences of depression in the workplace. The first study compared employees with depression to both healthy employees and those with rheumatoid arthritis—a chronic illness that can impair job performance. The researchers found that depressed employees were four to five times more likely to become unemployed or to change jobs, to have diminished productivity and job performance, and to miss work due to their illness. However, appropriate treatment for depression resulted in positive changes in all three areas. The second study provides evidence that offering appropriate, evidence-based depression treatment for employees is a cost-effective strategy for American businesses. Over the two-year study period, consistently employed people with depression who received treatment showed greater productivity and fewer days absent than those who did not receive treatment. The estimated annual value of treating a depressed employee was $1,982 in productivity and $619 in reduced absenteeism per person.

[6] Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS, National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289: 3095-105, 2003.

B. Anxiety Disorders and Grief

Translational Approaches to Understanding Fear and Anxiety

Three recent NIMH-funded studies on fear and anxiety demonstrate that 21st century translational science is successfully bridging the gap between molecular biology and human behavior. In response to the environment, the brain adapts the behavior of an organism by strengthening the connections (synapses) between neurons—the molecular foundation of learning and memory. Two groups of NIMH supported investigators have elucidated the molecular basis of learned fear. The researchers trained rats to associate a tone with an electric shock. Subsequently, the rats "froze" when presented with the tone alone, indicating memory of the fearful association. In the rats that learned to fear this tone, neurotransmitter receptors, called AMPA receptors, moved into the synapses of neurons in the lateral amygdala, a brain area that processes emotions including fear. Blocking AMPA receptor movement in as few as 20% of neurons in the lateral amygdala dramatically impaired learning, indicating that AMPA receptor movement mediates memory formation in this brain region. In a complementary study, scientists examined memory formation in the thalamus, the brain's principal sensory "relay station" that receives information about the environment and sends the information to different areas of the brain. In the case of learning to fear a sound (as the rats feared the tone), the thalamus sends information to the lateral amygdala. The researchers determined that memory formation was impaired by disrupting either a cell signaling pathway or gene expression in the thalamus, but disrupting protein synthesis had no effect on memory. These results suggest that the thalamus does not store long-term memories (a process that requires new protein), but that signaling in the thalamus influences memory formation in the lateral amygdala. A third study examined the biological basis of fear and anxiety in humans. The scientists used neuroimaging to observe brain activity as subjects experienced anxiety in anticipation of uncomfortable (but not painful) shocks to the wrist. Compared to men, women demonstrated increased activity in the subgenual anterior cingulate cortex—a brain region known to be critical for emotional control. This study points to a specific brain region that may underlie women's greater susceptibility to anxiety and affective disorders. Taken together, these three studies demonstrate the value of utilizing both animal and human studies to elucidate the biological basis of mental disorders.

Brain Region Size is Correlated with the Ability to Conquer Fear

Post-traumatic stress disorder (PTSD) is an anxiety disorder that can develop following a life-threatening event. A hallmark of PTSD is the inability to control fear, even when the threat is no longer present. Understanding the brain systems that control fear is critical to developing effective treatments for PTSD and other anxiety disorders. A psychological process that is central to overcoming a learned fear is called "extinction" or the reduction of fear following repeated exposure to a fearful event without unpleasant consequences (e.g. learning to enjoy bike-riding even though you had a bad fall as a child). Extinction is a process of learning new associations rather than erasing the original fear. Previous studies in animals and humans have demonstrated that increased activity in a brain region called the ventromedial prefrontal cortex (vmPFC) promotes the long-term extinction of fearful memories. In a recent advance, researchers used brain imaging techniques to investigate the relationship between the thickness of the vmPFC in healthy individuals and their ability to extinguish fearful memories. The subjects underwent a conditioning procedure during which they learned that a colored cue would be followed by a mild shock to the finger. Next, the subjects participated in extinction training; the colored cue was presented in the absence of the shock, and the subjects learned to no longer fear the cue. The investigators determined that the individuals who retained the extinction memory over time,

experiencing less fear upon re-exposure, had a thicker vmPFC compared to individuals whose fear persisted. These findings suggest that size differences in the vmPFC may explain why some individuals are better able to control fear responses than others. Measurements of the vmPFC, combined with behavioral tests for extinction ability, may predict vulnerability to PTSD and anxiety disorders and could aid in the choice of therapy for PTSD patients.

New Targeted Therapy Helps Overcome Disabling Grief

Recent research has identified the public health significance of a previously overlooked syndrome in adults who have lost a loved one. Complicated grief, a seriously debilitating condition with symptoms similar to both depression and post-traumatic stress disorder (PTSD), affects about 10% to 20%[7,8] of people suffering the loss of a loved one, or about one million people a year. While grief and depression are generally normal and adaptive responses to loss, in complicated grief the feelings of loss and disbelief do not go away after several months and become disabling, often for years. A targeted treatment developed specifically for complicated grief showed a better response in bereaved individuals when compared with interpersonal psychotherapy (IPT), a proven treatment for grief-related depression. The targeted grief treatment employs techniques used to treat depression but which are modified to include PTSD therapies that address issues of trauma and loss-specific distress. In a randomized controlled trial of 95 individuals with complicated grief, 51% of those treated with the targeted therapy showed improved scores on various measures of depression, compared with only 28% showing improvement from IPT. Thus, by using a targeted treatment specific to the features of complicated grief, many with this debilitating condition can once again become productive and lead pleasurable lives.

C. Schizophrenia and Psychosis

Teens with Deletion Syndrome Confirm Gene's Role in Psychosis

While the cause of schizophrenia is still unknown, it is widely agreed that a combination of genetic and environmental factors is likely involved. Recently, a number of studies have focused on the catechol-O-methyltransferase (COMT) gene, which codes for an enzyme that breaks down dopamine—a neurotransmitter that has been implicated in schizophrenia. In particular, two common versions of COMT, *val* and *met*, have been linked to increased risk for schizophrenia. Young people who are missing part of a chromosome carry only one copy of the COMT gene instead of the two copies that most people inherit; these youths already have a nearly 30-fold higher-than-normal risk of schizophrenia, but those who also had the *met* version of COMT developed worse symptoms. They were more prone to cognitive decline, psychosis and frontal lobe tissue loss by late adolescence, when schizophrenia symptoms begin to emerge. The *met* version appeared to worsen symptoms of the chromosomal deletion syndrome by chronically boosting dopamine to excessive levels in the brain's executive hub, the prefrontal cortex, during development. This study is the first to show the long-term effects of the dopamine-regulating gene, COMT, in a disorder related to schizophrenia, say the researchers.

[7] Middleton W, Burnett P, Raphael B, Martinek N, The bereavement response: a cluster analysis. Br J Psychiatry 169: 167-171, 1996.

[8] Jacobs SC, Pathologic Grief: Maladaptation to Loss. Washington DC: American Psychiatric Press; 1993.

Increased Expression of the CAPON Gene Found in Schizophrenia
Schizophrenia affects approximately 1% of the population worldwide,[9] and although the exact cause remains unknown, people who inherit certain variations in genes appear to be at higher risk. Studies of the inheritance of schizophrenia have revealed that it is a complex disease in which vulnerability is produced by non-genetic factors as well as multiple genes, each of which contributes a modest increase in risk. This study examines variations in the CAPON gene, only recently proposed as a candidate gene for schizophrenia, and the activity or expression levels of the gene. By comparing postmortem brain tissues of patients with schizophrenia or bipolar disorder against healthy controls, the researchers found that the CAPON gene is a template for two different proteins, a short form and a long form. Brain samples from patients with schizophrenia or bipolar disorder had higher levels of the short form than samples from patients without psychiatric illness. Moreover, higher levels of the short form were predominantly seen in people with a version of the CAPON gene that had been previously linked to schizophrenia. These findings suggest a need to learn more about the short version of CAPON and the CAPON gene's function in the brain.

Brain Scans Reveal Links between Genes, Brain Pathways, and Mental Disorders
Over the past decade a body of research has reported that variations in the sequence of certain genes increase the risk for developing schizophrenia or depression, two common and disabling brain disorders. How do these genetic variations act in the brain to increase vulnerability? To shed light on this mystery, NIMH scientists have used brain imaging techniques to visualize how variation in specific genes influences brain structure and function, resulting in changes that may contribute to mental disorders. By studying healthy individuals who are carriers for certain susceptibility genes, researchers are able to see if the brains of healthy individuals resemble the brains of those suffering from a mental disorder, thereby pointing to neural markers of vulnerability. In one study, researchers focused on a gene variant, called 5HTTLPR, which is associated with risk for depression. This gene codes for a serotonin "transporter," a protein that recycles the chemical messenger serotonin. Using neuroimaging, the researchers discovered that healthy individuals carrying a short version of the 5HTTLPR gene had less volume in brain regions that regulate emotion and had deficits in the circuit for processing negative emotion. These results suggest that the gene variant affects brain development, which alters the circuitry for emotional processing—changes that may increase vulnerability to depression. In another study, researchers at NIMH and the National Human Genome Research Institute demonstrated how variation in the COMT gene, which codes for an enzyme that breaks down dopamine, may slightly increase risk for schizophrenia. The scientists used different imaging methods to visualize overall brain activity and dopamine synthesis as participants engaged in memory tasks. In individuals with a common variation of the COMT gene, dopamine synthesis was reduced in the middle of the brain (midbrain), which impaired the cross-talk between the midbrain and the front of the brain (prefrontal cortex). These findings suggest that interactions between these brain regions can be "tuned" through the dopamine system, and tuning problems may occur in mental disorders such as schizophrenia. Collectively, these imaging studies are beginning to answer long-standing questions about the relationship between genes and how the brain works, while providing valuable markers that signal vulnerability to mental disorders.

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[9] Xu B, Wratten N, Charych EI, Buyske S, Firestein BL, Brzustowicz LM. Increased expression in dorsolateral prefrontal cortex of CAPON in schizophrenia and bipolar disorder. PLoS Med. 2005 Oct;2(10):e263.

NIMH Study to Guide Treatment Choices for Schizophrenia

Currently, the treatment of choice for many people with schizophrenia is an "atypical" antipsychotic, such as risperidone or olanzapine. Though generally considered safer than older, "conventional" antipsychotics, many atypicals also cause some side effects that can affect a person's ability or willingness to take medication regularly, which is necessary for successful management of schizophrenia symptoms. Thus the importance of choosing the right medication for an individual, in the face of little information comparing medications, often puts patients and health care practitioners at a loss for finding the right treatment for individual cases. The large-scale Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study provides, for the first time, detailed information comparing the effectiveness and side effects of five antipsychotic medications—both new medications and an older one—that are currently used to treat people with schizophrenia. Overall, the medications were comparably effective but were associated with high rates of discontinuation due to intolerable side effects or failure to adequately control symptoms. One new medication, olanzapine, was slightly better than the other drugs but also was associated with significant weight-gain and metabolic changes that increase the risk for diseases such as diabetes. Surprisingly, the older, less expensive medication, perphenazine, used in the study generally performed as well as the newer medications. The information from this study will inform new approaches for improving outcomes in schizophrenia. Later phases of CATIE will address topics such as cost-effectiveness of the medications, quality of life, predictors of response, and will provide a more detailed picture of the interaction between patient characteristics, medication, and outcomes.

D. Autism

Scientists Close In On Genetic Links for Autism

While it is clear that autism is heritable, its genetic complexity makes it difficult for scientists to pinpoint predisposing genes. Although previous studies have suggested that multiple genes may be involved, without further replication studies confirming these linkages, research in this area has remained inconclusive. In an attempt to identify and confirm autism linkage, a group of NIMH-funded researchers scanned the genomes of two samples of autism-affected sibling pairs in search of regions that might harbor susceptibility genes. This research team became the first group to locate a genetic risk factor for autism and replicate their findings in an independent sample, thus adding more scientific validity to their linkage claim. The study confirmed a linkage (in families with affected males only) to a region on chromosome 17, specifically region 17q11-21, in both samples, making this the first such replication in autism. Using fine mapping techniques, they were able to get a closer look at this chromosomal region and found evidence for a linkage at a specific location, 17p21. As researchers gain a better understanding of the genes responsible for autism, they may be able to better distinguish between different variants of the disorder and to develop better targeted therapies and interventions to treat them.

Social Behavior Possibly Encoded in "Junk" DNA

Previous studies involving a species of rodent have linked specific bits of DNA to social behavior traits, such as monogamy. These repeating sequences of DNA, which were once dismissed as junk, are called microsatellites. Each species has its own signature microsatellites, which determine when and where a gene turns on. In voles, the length of microsatellites in the gene that codes for vasopressin, a key hormone receptor in the brain, was found to influence mating and parenting behaviors. Monogamous voles (prairie voles) tended to have much longer

vasopressin receptor microsatellites than polygamous voles (meadow voles). Other studies link alterations in the length of this microsatellite to autism, a disease of profound social deficit. Building on this line of evidence, researchers showed that differences in vasopressin receptor microsatellite length within a species could explain individual differences in social behavior. Using cell cultures, they demonstrated that the vole vasopressin receptor microsatellites could modify gene expression. By breeding prairie voles with longer vasopressin receptor microsatellite regions with those with that had shorter ones, they discovered that adult male offspring with longer microsatellites had more vasopressin receptors in brain areas involved in social behavior and parenting compared to offspring with shorter microsatellites. Offspring with longer microsatellites investigated female odors, greeted strangers more readily, and were more apt to form pairs and nurture their young. Since they had more receptors in neural circuits involving social recognition, release of vasopressin during social encounters facilitated social behavior. This study suggests that variability in vasopressin receptor microsatellite length might account for differences in normal human personality traits, such as shyness, and for social disorders like autism and social anxiety disorders. As scientists pinpoint how vasopressin receptor microsatellites function, the ways in which they interact with other genes to exert their influence on social behaviors may become clearer.

Scientists Uncover New Clues about Brain Function in Human Behavior

Scientists have discovered a genetically controlled brain mechanism responsible for social behavior in humans. The study compared the brains of healthy people to those with a genetic abnormality, Williams Syndrome, a rare disorder that causes unique changes in social behavior. People with Williams Syndrome eagerly and impulsively engage in social interactions; however, they experience nonsocial anxiety and worry constantly. Scientists have long suspected that the amygdala**,** the part of the brain that regulates emotional responses to daily life situations, may be involved in this striking pattern of behavior. Using brain imaging techniques, they investigated the response of the amygdala to social stimuli in people with Williams Syndrome and in healthy controls. The amygdala functioned abnormally in those with Williams Syndrome, with reduced response to highly socially relevant danger signals compared with controls; this is consistent with the lack of fear of social situations displayed by people with Williams Syndrome. Whole brain scans revealed that the orbitofrontal cortex, the brain region that modulates the amygdala by assigning emotional values to a situation, was not activated in subjects with Williams Syndrome, in contrast to healthy subjects. This is perhaps the first study to identify functional disturbances in a brain pathway associated with abnormal social behavior caused by a genetic disorder. It enabled researchers to both define a brain circuit for social function in the healthy human brain and to identify the specific way in which it was affected by genetic changes in Williams Syndrome.

Social Stimuli Produce Heightened Emotional Response in Autistic Individuals

Studies suggest that abnormal perception of faces and their social/communicative signals may contribute to the social impairment that is a core feature of autism. Related studies on brain function have also shown that the fusiform gyrus, which is strongly activated in typically developing individuals during face processing, is less activated during the same tasks in individuals with autism. In a recent study, NIMH-funded scientists used magnetic resonance imaging (MRI) to scan the brains of individuals with autism as they viewed pictures of human faces. The researchers demonstrated that in addition to under-activation of the fusiform gyrus,

individuals with autism showed over-activation in the amygdala, a brain structure involved in emotional response and regulation, compared with normal subjects. Amygdala activation was not specific to the emotional content of faces, but was a response to faces in general. Activation in the fusiform gyrus and the amygdala were both strongly associated with the time the individual spent studying the eye region of the stimulus face. These results indicate that the under-activation of the fusiform gyrus in individuals with autism during face processing tasks might be due to insufficient time spent studying the stimulus face. Over-activation in the amygdala suggests heightened emotional arousal in response to face processing, with greater time studying eyes associated with greater arousal. This is the first published study to provide a mechanism for how face processing deficits arise in individuals with autism: hyper-activation in the central circuitry of emotion produces a heightened response to social stimuli, which in turn leads to diminished eye gazing and atypical activation in the fusiform gyrus. These findings increase the understanding of how the brain functions in an individual with autism, which may one day lead to new treatment approaches.

Social Symptoms May Be Earliest Indicator of Autism

Studies suggest that there are different patterns of early development in autism. Children may experience a gradual course of onset during the first two years of life, developing typically in the beginning and then starting to lose skills; or they may lose skills initially and then develop atypically during the first two years. To describe the variation in the early course of development and examine the relationship between these variations and behavioral outcome at 3-4 years of age, researchers used a specially designed parental survey to assess the history of skills loss and the age of onset of symptoms in three different groups: children with autism, those with developmental delay, and typically developing children. Parents of children with autism reported more social and regulatory symptoms, such as poor eye contact and problems eating and sleeping, than parents of typical children by 3-6 months of age. These symptoms were about the same for children with developmental delay and those with autism until 13-15 months of age, after which more social symptoms became apparent in children with autism. By 3-4 years of age, children with autism with different courses of development and different histories of skill loss were indistinguishable on developmental outcome measures of IQ and autism symptom severity. This study will be useful in designing methods for early detection and treatment of autism. While symptoms associated with autism can develop very early, at least by 3-6 months, differentiating autism from developmental delay in children might be challenging before the first year. In this case, social symptoms, such as poor eye contact and lack of smiling, may be the best diagnostic indicators.

Long-Term Use of Risperidone Helps Control Behavior in Children with Autism

Children with autism sometimes display severe behavioral disturbances, such as aggression, self-injury, and prolonged tantrums, which can cause major functional impairment and distress. A previous NIMH-funded clinical trial indicated that 0.5-3.5 mg of risperidone a day was highly effective in improving behavior in the short term (eight weeks). Two reports by the NIMH-funded Research Units on Pediatric Psychopharmacology Autism Network expand on that finding by showing that therapeutic effects of risperidone persist in the long-term, but, upon drug discontinuation, behavioral problems recur in about two-thirds of the children. Side effects, especially drowsiness, increased appetite and weight gain, were common but seldom caused drug discontinuation. Over the six-month treatment period, average weight gain was about 11 pounds.

In addition to controlling behavioral disturbances, risperidone led to significant improvement in the restricted, repetitive, and stereotyped behavior patterns that are typical in autism, but did not change the deficits in social interaction and communication. Novel approaches are needed to develop interventions that can improve the core deficits of autism.

E. HIV/AIDS

Genetic Trait Linked to AIDS Resistance

With most diseases, genetics are believed to play a contributing role in causing disease as well as in disease progression. In the case of HIV, duplications of some gene sequences may produce a protective effect in some individuals. A team of investigators in the US, Great Britain, and Argentina showed that the likelihood of acquiring HIV and, once infected, of progressing to full-blown AIDS, is much greater in people who have a below-average number of copies of the gene that encodes for an immune system signaling chemical (chemokine) called CCL3L1. Researchers selected CCL3L1 for study because it interacts with a receptor (CCR5) that is the main entry point of HIV into cells. CCL3L1 is also the most potent agonist for CCR5, giving it strong anti-HIV properties. Individuals who possess both low numbers of the CCL3L1 gene and disease-accelerating CCR5 variants demonstrated a more than threefold greater risk of rapid progression to HIV-associated dementia and opportunistic infections, such as cytomegalovirus (CMV), which are associated with mental health disorders. These studies highlight a possible means to stratify, based on genetics, the susceptibility of individuals for disorders such as HIV-associated dementia.

Blood-Brain Barrier Integrity Plays Key Role in Regulating HIV Entry

An important area of AIDS research relates to understanding the mechanisms regulating viral entry into the nervous system. A key pathway for HIV-1 entry into the brain is through migration of infected monocytes (a type of precursor immune system cell) through the blood-brain barrier. Two papers published by NIMH grantees examine the complex interactions between viral proteins and the blood-brain barrier and the resultant changes in integrity of the barrier. Specifically, the authors studied the impact of the HIV protein Tat on the expression of certain blood-brain barrier proteins (ZO-1 and claudin-5), which help create a tight seal between cells and prevent the movement of dissolved substances from passing through cell membranes. HIV-1 Tat reduces the expression of these “tight junction” proteins, which could result in decreased blood-brain barrier integrity and increased migration of HIV-1 infected cells into the central nervous system. In studying the series of reactions involved in changing the expression and functioning of ZO-1 and claudin-5, the researchers found that multiple signaling pathways were involved. These findings add critical knowledge not only to understanding the pathways of HIV entry into the brain but also the regulatory mechanisms that are pivotal to the maintenance of blood-brain barrier integrity. Such knowledge could inform studies in other diseases relevant to mental health such as Alzheimer’s disease, where the blood-brain barrier plays a key role in pathophysiology.

Antibiotic May Be Effective in Treating HIV-Related CNS Disease

Despite the availability of antiretroviral therapy, few interventions are available to treat HIV central nervous system disease, a frequent cause of serious illness and death in HIV-positive individuals. To help fill this gap, researchers examined the ability of minocycline, an antibiotic

with strong anti-inflammatory and neuroprotective properties, to protect against simian immunodeficiency virus (SIV)-associated encephalitis (brain inflammation) and neurodegeneration in a pigtailed macaque model of HIV infection. Twelve macaques were infected with SIV and then treated with minocycline 21 days post-infection. Minocycline significantly decreased moderate and severe encephalitis in SIV treated animals and protected against axonal degeneration. Furthermore, minocyline suppressed HIV and SIV replication *in vitro*. These findings suggest the minocycline may be a readily available, cost efficient therapeutic agent to add to the anti-HIV armamentarium.

Online Training Provides Support for International HIV Intervention Efforts

Despite the need to transfer science advances to AIDS service providers globally, most providers have little access to scientific developments relevant to their programs. However, the internet provides an important new avenue for technology transfer. An international intervention study was conducted on nongovernmental HIV prevention organizations in 78 countries, which were randomized to be either a control site or an experimental technology transfer site. All organizations were given basic technology and training, while the experimental sites also received an interactive distance learning computer training curriculum and individualized distance consultation. Of the 42 organizations in the experimental group, 29 adopted the intervention in their communities or trained other agencies to also use it. The researchers concluded that advanced communication technologies can create a cost-effective infrastructure to disseminate new intervention models to service providers worldwide.

Cost-Effectiveness Study Supports Expanded US HIV Screening

Although US guidelines recommend routine HIV counseling, testing, and referral (HIVCTR) in clinical settings with one percent or more HIV prevalence, roughly 280,000 Americans remain unaware that they are infected.[10] The implication is that current guidelines, originally created by the Center for Disease Control and Prevention (CDC) for high-risk populations (pregnant women, STD clinic workers and clients), may not be rigorous enough to provide the most cost-effective screening. Investigators developed a computer simulation to compare routine, voluntary HIVCTR to current practice (background testing and detection upon presenting with an opportunistic infection). They evaluated these practices in three populations of varying risk. In the "high-risk" population, adding one-time screening to current practice was associated with earlier diagnosis of HIV and increased average survival time among HIV-infected patients. In all study populations, testing every three to five years increased the cost-effectiveness per quality-adjusted life year (QALY). The investigators concluded that in all but the lowest-risk populations, routine, voluntary HIV screening once every three to five years is justified on both clinical and cost-effectiveness grounds.

[10] Paltiel AD, Weinstein MC, Kimmel AD, Seage GR 3rd, Losina E, Zhang H, Freedberg KA, Walensky RP. Expanded screening for HIV in the United States--an analysis of cost-effectiveness. N Engl J Med. 2005 Feb 10;352(6):586-95.

Story of Discovery: Mental Health Practical Clinical Trials

To meet the Food and Drug Administration's (FDA) minimum standards for approval of a drug, clinical trials must show that the new medical treatment can be safely administered and that it produces an effect on symptoms (efficacy). Thus, to meet these minimum standards, traditional clinical trials are usually short (looking at effects over 6-12 weeks), limited in scope (selecting only participants with very specific diagnoses and health histories), take place in controlled environments (requiring participants to visit academic health centers), and compare the treatment against a placebo (an inactive treatment, such as a sugar pill) as opposed to comparing against another drug.

While a necessary step, these traditional efficacy trials answer different questions than practical clinical trials. Traditional efficacy trials demonstrate whether a new treatment is better than placebo, but not whether a new treatment is better or worse than an existing treatment. These traditional efficacy trials provide results with a very specific selection of patients, while practical clinical trials test effects of a medication in commonplace situations, where a patient may have multiple physical and/or mental illnesses, limited access to regular medical care, or other obstacles to treatment. In addition, efficacy studies typically focus on how well the medication reduced symptoms, not how the treatment affects everyday functions, like the ability to go to work or to take care of family responsibilities. In short, traditional clinical efficacy trials prove mainly that a particular treatment may be better at reducing symptoms than no treatment at all, but they do not answer numerous practical questions asked by clinicians, patients and families.

In an effort to advance the state of the science for those with mental disorders such as depression, schizophrenia, and bipolar disorder, for the last five years the National Institute of Mental Health (NIMH) has focused on developing large practical clinical trials. Practical clinical trials, or "effectiveness studies," are designed to examine changes in symptoms and functioning, changes which are vital to determining whether a treatment improves quality of life, caregiving burden, or health service use. The designs of these trials also increase relevancy to real-world clinical practice to help decision-makers faced with choices about patient care—both at the doctor-patient level and the policy level. A trial conducted in a typical community practice situation also greatly enhances the ability to bridge from science to service by showing how the treatment can be implemented in actual service settings. These trials are intended to provide unbiased, reliable answers to questions a community clinician might ask, such as:

- For this specific patient, what is the best of the available treatments?
- If the first treatment does not work, what is the next best option?
- How much of a response can my patient realistically expect, and in what time frame?
- What should I do if my patient is not sufficiently better in this period: continue or switch treatments?

In support of the NIMH's public health mission and with the benefit of the increase in NIMH's appropriation from 1998-2003, the Institute launched a series of practical clinical trials. Each of these trials should prove a landmark in the field as they provide results from the largest and longest studies designed to answer urgent questions about the treatment of depression, bipolar disorder, and schizophrenia. In addition, these trials advance the NIMH goal of designing individualized treatments for patients with mental illness.

<u>Examples of NIMH Practical Trials</u>

In the **Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study**, 1,432 patients from 56 sites including a variety of health care settings such as private practices, community health care centers, and state facilities were randomly assigned to treatment with one of five medications for 18 months. In the first phase of analysis of the results, the main measure of how well a medication worked in the CATIE study was how long a patient stayed on the medication, which is critical to both managing schizophrenia symptoms and preventing a relapse. Results from the first phase suggest that newer, "atypical" antipsychotics are not much more effective than older, conventional antipsychotics, though all the medications studied have unique side effect profiles. The older medication, perphenazine, was as well tolerated as the newer compounds and as effective as three of the four newer drugs. The fourth compound, olanzapine, was slightly better than all the others in terms of discontinuation and hospitalization rates but was also associated with higher rates of weight gain and metabolic side effects, increasing risk for diseases such as diabetes. Later phases of this study will examine issues such as switching from one treatment to another, use of health services, and cost-effectiveness.

Another published example of a practical clinical trial is the **Treatment for Adolescents with Depression Study**

(TADS), which compared short- and longer-term effectiveness of medication and psychotherapy for depression in 439 adolescents. TADS was designed to test best-practice care for depression and was carried out by 13 academic and community clinics across the country. Participants were treated with fluoxetine alone (an SSRI and the only FDA-approved depression medication for adolescents and children), cognitive-behavioral therapy (CBT) alone, fluoxetine combined with CBT, or placebo. At the end of the study, researchers found that fluoxetine in combination with CBT was more effective against adolescent depression than either one alone. In addition, clinically significant suicidal thinking improved significantly in all four treatment groups, with those receiving medication combined with cognitive therapy showing the greatest reduction.

Two large-scale practical clinical trials that are expected to publish results in early 2006 are the **Sequenced Treatment Alternatives to Relieve Depression Trial (STAR*D)** and the **Systematic Treatment Enhancement Program for Bipolar Disorder Trial (STEP-BD)**. STAR*D examined 4,041 adults with major depression, particularly those who previously showed poor outcomes to treatment. At 41 sites coordinated by 14 regional centers, participants whose symptoms remained after 8-12 weeks of treatment with an SSRI were offered up to four other levels of treatment, including other medications and cognitive therapy, or a combination of treatments. In contrast to efficacy trials that look for statistically significant changes in a rating scale, the main outcome measure for STAR*D was the extent to which participants experienced remission of symptoms or recovery. Preliminary evaluations of the first 1,500 STAR*D outpatients found that 53% had significant concurrent physical illness, a relatively common but often overlooked phenomenon. Those who were older, had lower income, had lower education levels, and did not report a family history of depression were more likely to have a significant concurrent physical illness. Another preliminary assessment of this STAR*D cohort found that major depressive disorder that begins before age 18 is a particularly severe and chronic condition with a distinct set of demographic and clinical traits, such as being female, having more episodes, having more suicidal thoughts or suicidal behaviors, and showing atypical symptoms (such as oversensitivity to rejection, overeating, oversleeping, etc). Moreover, in this sample, early-onset major depression was associated with significant psychosocial consequences, specifically lower educational attainment and marriage rates. The first set of results from STAR*D are expected in 2006.

STEP-BD set out to find the most effective long-term and acute treatments for people with bipolar disorder and ways to prevent relapse. The trial assessed 4,328 participants from 20 private, state and community practice sites. In evaluating the medications and psychosocial interventions that are considered among the best choices of treatment for bipolar disorder in everyday clinical practice, study participants have the opportunity to explore individualized care. Among the first 500 bipolar patients enrolled in STEP-BD, investigators have identified a 20% incidence of rapid cycling–defined as four or more mood episodes within one year. Participants with rapid cycling reported a younger age of onset of bipolar disorder than non-rapid cycling patients, and were more severely ill on a number of clinical measures at the outset of their trial participation. A separate assessment of the first 1,000 STEP-BD participants confirmed informal reports from the health care community that comorbid (concurrent) conditions, which are known to worsen the course of bipolar disorder, are common but under-treated. Nearly three-quarters of survey participants had a lifetime diagnosis of at least one comorbid mental disorder, most often a substance-use disorder (48%), and treatment with medications alone was inadequate.

These and other practical clinical trials seek to place current knowledge of mental health treatments into a real-world context and answer real-world questions from clinicians. These trials are complicated to design and difficult to conduct, often placing them outside the scope of privately funded efforts. However, the exceptional need for this research places the responsibility on NIMH and other Federal agencies to invest the time and resources required to bring such findings to light.

III. Treatment

Cognitive Behavioral Therapy Effective Treatment for Various Mental Illnesses

Mental illnesses involve a variety of symptoms that frequently call for a combination of treatments, including medications and some form of psychotherapy. Cognitive behavioral therapy (CBT) is a type of “talk” therapy that combines aspects of cognitive therapy, which helps people reshape thought patterns that may contribute to disease symptoms; and behavioral therapy, which teaches people to recognize and adjust their reactions to troubling situations.

Recent studies using CBT for treatment have highlighted its wide-ranging potential as a complementary therapy to medication.

In one study, researchers developed a manualized group intervention that combined CBT with social skills training (SST), another therapy-based treatment. To evaluate this treatment, they conducted a randomized clinical trial of 76 middle-aged and older people with schizophrenia (ages 42-74) in which every participant received "treatment as usual" (TAU), defined as continuation of whatever care the person had been receiving prior to joining the study, and some were selected to receive the CBT/SST therapy in addition. After six months of treatment, people in the TAU plus CBT/SST group engaged in social functioning activities more frequently and were more objective and self-reliant in assessing psychotic experiences (they looked for evidence to support their beliefs and showed less overconfidence in their own conclusions about unusual experiences), leading to greater reductions in those symptoms. These improvements in social functioning and cognitive insight are the first published clinical trial evidence that older psychotic patients can significantly benefit from a psychosocial or rehabilitative intervention. The study also suggests that this form of psychotherapy may help address the negative and cognitive symptoms that medications generally do not.

Investigators with the Pediatric OCD (obsessive compulsive disorder) Treatment Study (POTS) have also evaluated CBT in treating children and adolescents, another population for whom there is little information about differences in disease presentation and progression or treatment outcomes. Ninety-seven 7-17 year-olds with OCD completed 12 weeks of treatment with CBT, the SSRI sertraline, combination treatment, or a placebo. Combining sertraline and CBT was more effective than treatment with just one or the other. CBT alone proved superior to sertraline, which, in turn, was better than a placebo. This research spotlights the need for improved access to CBT, which was a significantly more effective treatment than the drug intervention, since most young people with OCD currently receive only antidepressant medication, often combined with an antipsychotic medication.

In another clinical trial using CBT, 120 adults who had recently attempted suicide were randomly assigned either to receive CBT or not, though all participants were encouraged to receive usual care from clinicians in the community. Over the 18-month follow-up period, only 24% of those in the CBT group made repeat suicide attempts, compared to 42% of the usual care group. Although the groups did not differ significantly in suicidal thoughts, those who received cognitive therapy scored better on measures of depression severity and hopelessness, which the researchers suggest "may be more highly associated with a reduced risk of repeat suicide attempts." Studies such as these indicate the broad applicability of CBT to many different types of mental illness, in some cases as a stand-alone therapy and in others as a complementary therapy.

NIH ROADMAP INITIATIVE

NIMH plays a lead role along with NHGRI in the NIH Roadmap Molecular Libraries Initiatives. The goal of these initiatives is to provide the research community with small organic chemical compounds that can be used as tools or molecular probes for understanding cellular events involved in health and disease; these ultimately could help identify possible new targets for

diagnosis, treatment and prevention. The extensive progress on these initiatives is summarized as follows:

Molecular Libraries Screening Centers Network (MLSCN): In June 2005, nine extramural screening centers were awarded a total of $88.9 million over three years and along with the intramural screening center, formed the MLSCN. This collaborative network will use high-throughput screening methods to compare assays provided by the research community with a large library of small molecules maintained in a central Small Molecule Repository. All results from the MLSCN's activities will be placed into a public database called PubChem, and information about probe compounds will be made available to researchers in both public and private sectors for their use in studying biology and disease. The MLSCN, is funded by all of the NIH Institutes, and co-administered by NIMH and NHGRI. Descriptions of the ten network screening centers are available at http://nihroadmap.nih.gov/molecularlibraries/fundedresearch.asp. Identifying biologically active small molecules can potentially affect all areas of biomedical research. In mental health research, small molecules relevant to the brain can be used to probe brain function and to investigate novel therapeutic targets for mental disorders.

Another Roadmap initiative, The NIH Director's Pioneer Award (NDPA) Program, is designed to support individual scientists of exceptional creativity who propose pioneering approaches to major contemporary challenges in biomedical research. The second competition was opened in March 2005; the 13 awardees, selected out of an original pool of about 840 applicants from all areas of biomedical research, included three NIMH grantees.

Finally, NIMH is involved in Interdisciplinary Research Centers Roadmap initiatives. An announcement was issued April, 2005 for one-year administrative supplements aimed at stimulating interdisciplinary research in humans that integrates the behavioral or social sciences with the biological sciences. The funds provided are intended to support partnerships between behavioral or social scientists and biological scientists to foster the melding of these disciplines' typically disparate perspectives, approaches, and methodologies into interdisciplinary research efforts that will improve our ability to prevent, detect, diagnose and treat disease and disability and to improve symptom management and health. Fourteen supplements were funded, four of which were to NIMH grantees.

The second phase of the Interdisciplinary Research Centers program was launched with a notice released in February 2005. This program began with a Request for Applications (RFA) using the P20 mechanism and soliciting planning center grants to develop new interdisciplinary approaches to solving significant and complex biomedical research problems. Twenty-one of these planning centers have been funded, and information about each center can be found at http://www.ncrr.nih.gov/ncrrprog/roadmap/ecirdirectory.asp. Each planning center was funded for three years, and the awards for these centers will expire in July 2007. In the second phase, all of the Institutes and Centers at NIH plan to participate in a follow-up program to support Interdisciplinary Research Centers starting in fiscal year 2007. We anticipate that we will fund 8-10 centers with direct costs of approximately $3 million each year. It is expected that these centers will be funded for five years.

NIH Neuroscience Blueprint

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

The first Blueprint initiatives, released in FY 2005, include a comprehensive inventory and analysis 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 programs in genome analysis and in neuroimaging. Blueprint initiatives for FY 2006 develop training programs, genetic mouse models, neuroimaging tools, core research facilities, and tools to enhance the value of clinical research conducted by each Blueprint institute for the missions of all.

The Blueprint was inspired by recognition that unifying themes in neuroscience research are fundamental to understanding the normal and disordered nervous system and to developing better prevention and treatment strategies. Three themes bear on the missions of all Blueprint institutes and centers: (1) neurodegeneration from disease and aging, which will be the focus of the Blueprint in 2007; (2) development of the nervous system throughout the lifespan; and (3) plasticity, the capacity of the nervous system to change in response to the environment, experience, injury, and disease. Neuroscience research provides an understanding of the fundamental mechanisms of brain function in health and disease that can then be translated to advances in the diagnosis, prevention and treatment of mental disorders. The Neuroscience Blueprint is a cost effective way to pool resources from multiple Institutes, providing neuroscientists with tools and infrastructure that can expedite discovery and thereby advancing the NIMH mission.

Initiatives

Improved Understanding of the Causes of Autism: The Autism Phenome Project
Autism is a developmental brain disorder with a wide range of symptoms that vary in degree of severity. Core deficits include difficulty in communicating, expressing emotion, and relating to others socially. It is one of a broader continuum of five disorders commonly known as autism spectrum disorders (ASD). At the request of the House and Senate conferees considering the FY 2003 appropriations for DHHS, the Interagency Autism Coordinating Committee (IACC), for which NIMH is the lead Institute, convened a panel of outstanding scientists to assess the field of autism research, and identify roadblocks that may be hindering progress in understanding its causes and best treatment options. In collaboration with this panel of experts, the IACC developed a matrix (http://www.nimh.nih.gov/autismiacc/congapprcommrep.pdf) of short and long term goals toward finding the causes and effective treatments for autism. One goal of the matrix is to

develop and launch an autism phenome project. Just as the Human Genome Project identified the sequence and organization of human DNA, the phenome project seeks to identify the various clinical characteristics (phenotype) and subtypes of autism. Identifying specific phenotypic subtypes for autism and autism spectrum disorders will facilitate research on genetic and other potential causes and suggest more specific approaches to treatment. Such efforts help advance the NIMH mission of reducing the burden of mental illness and behavioral disorders through research. Representatives of the NIH Autism Coordinating Committee, the Centers for Disease Control and Prevention, and the Department of Energy met on November, 2005 to develop plans for organizing and launching the project, scheduled to begin in FY 2007.

Re-Adjustment After Military Deployment: Prevent Chronic Illness and Early Death
American soldiers in Iraq and Afghanistan face unprecedented challenges, not only in theatre but also when returning from deployment. While we have learned much about the risks of post-traumatic stress disorder (PTSD) and other mental disorders from earlier wars, the current engagement involves more women, more National Guard members, more Reservists, and more double deployment than in previous wars. NIMH will be collaborating with the Department of Defense (DoD) and the Department of Veterans Affairs (VA) to study the mental health needs of active duty, National Guard, and Reserve personnel including their transition to VA health services. The goal is to establish representative groups of men and women on active duty or in the National Guard and Reserves who can be studied longitudinally to:

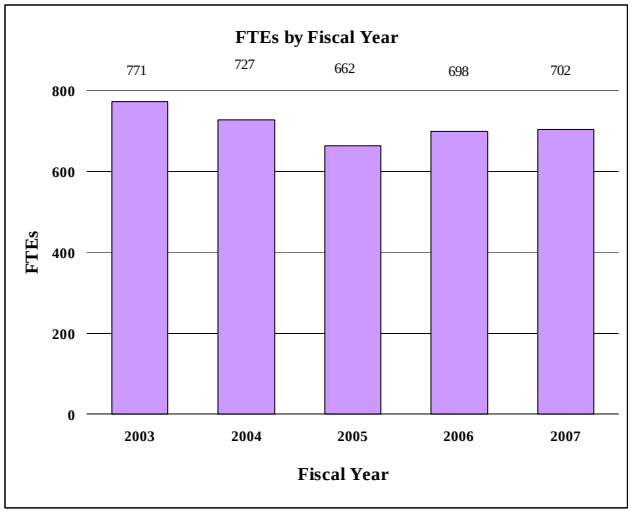
- assess post-deployment adjustment difficulties, including post-traumatic mood and anxiety disorders, substance use and abuse disorders, impairment in occupational, family, and social functioning, and regulation of behavior, including violent behavior towards others and self;
- study the pathophysiology of PTSD and identify the biological markers that increase risk for developing chronic, disabling PTSD;
- determine whether early detection and intervention with post-deployment adjustment difficulties leads to decreases in the occurrence of long-term illness;
- determine what health and economic benefits may result from early intervention in troops manifesting early symptoms;
- decrease the risk of developing chronic conditions, including PTSD and depression, as well as disability and death in those with adjustment difficulties; and
- establish a model inter-departmental continuum of care that links administrative and health data for screening, assessment, and referral services.

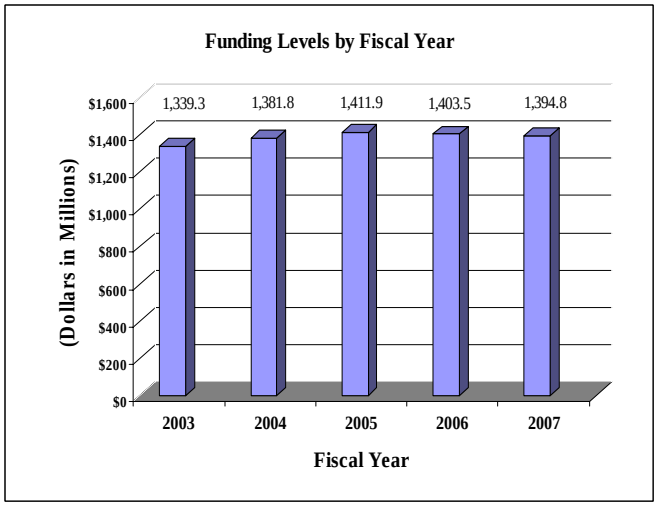
The controlled environments provided by the armed forces and VA systems of care create a rich and unique opportunity to optimize prospective tests of early detection and intervention, including longitudinal follow-up through the VA system. This initiative is planned for FY 2007.

NIMH BUDGET POLICY

The Fiscal Year 2007 budget request for the NIMH is $1,394,806,000, a decrease of $8,709,000 and 0.6 percent below the FY 2006 Appropriation. Included in the FY 2007 request is NIMH's support for the trans-NIH Roadmap initiatives, estimated at 1.2 percent of the FY 2007 budget request. A full description of this trans-NIH program may be found in the NIH Overview.

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





NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. We estimate that the average cost of competing RPGs will be $313,000 in FY 2007. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NIMH has committed to a programmatic increase for an award, such increases will be provided.

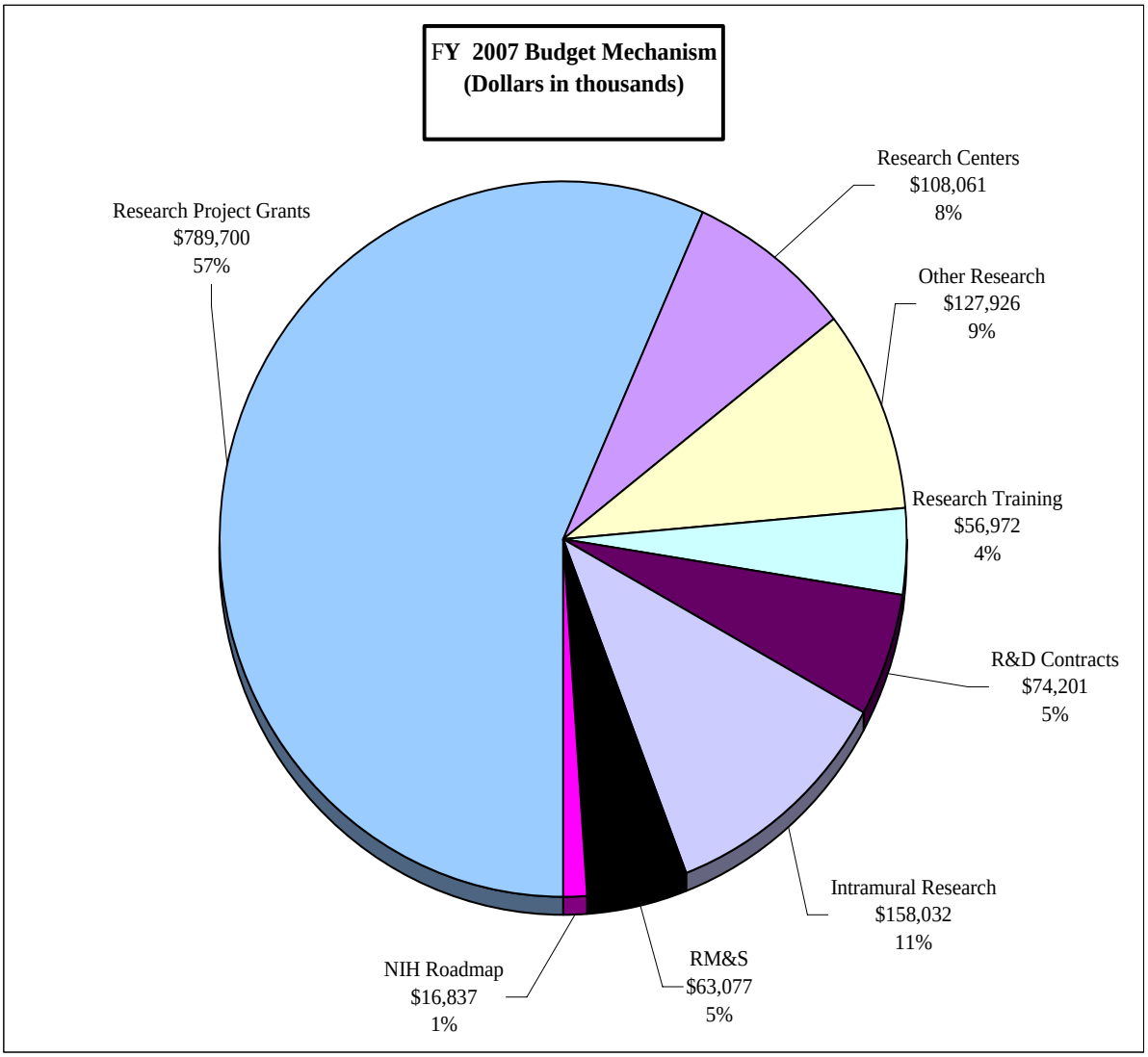
NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NIMH, $900,000 will be used to support 10 awards for the new K/R "Pathway to Independence" program.

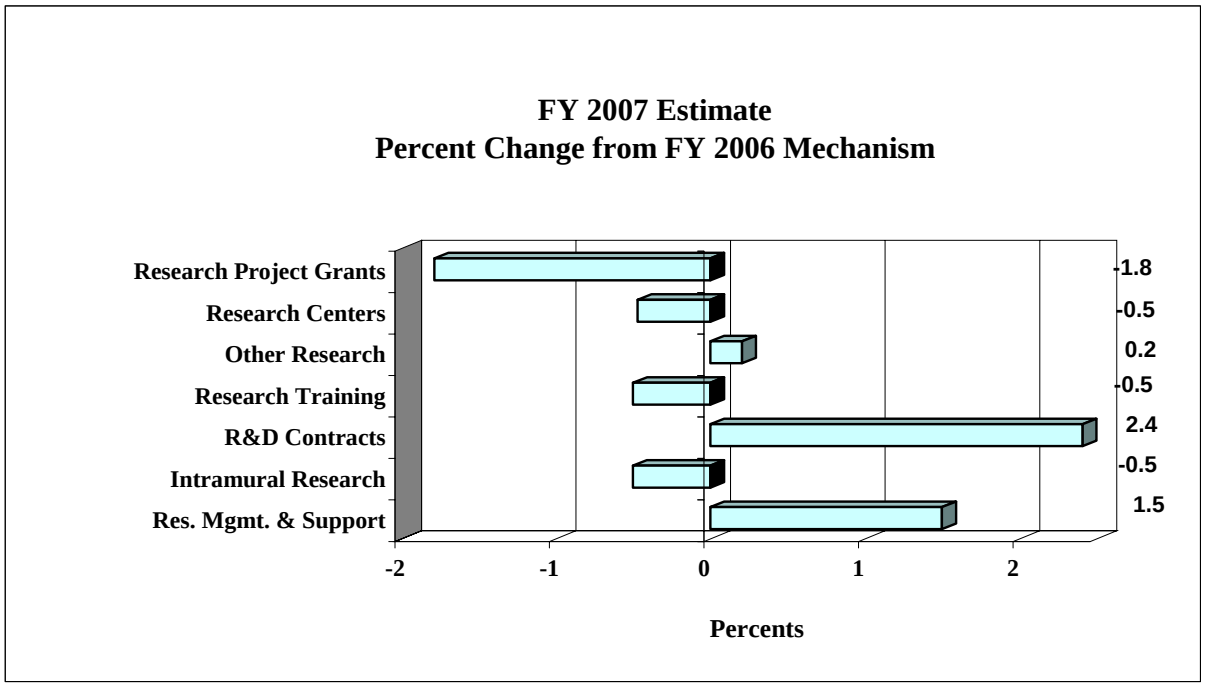
NIMH will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes $2,109,000 to support this project.

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

The FY 2007 request includes funding for 70 research centers, 672 other research grants, including 506 career awards, and 181 R&D contracts. Intramural Research decreases by 0.5 percent. Research Management and Support increases by 1.5 percent.

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


FY 2007 Budget Mechanism
(Dollars in thousands)
Research Centers
$108,061
8%
Other Research
$127,926
9%
Research Training
$56,972
4%
R&D Contracts
$74,201
5%
Intramural Research
$158,032
11%
RM&S
$63,077
5%
NIH Roadmap
$16,837
1%
Research Project Grants
$789,700
57%


FY 2007 Estimate
Percent Change from FY 2006 Mechanism
Research Project Grants
Research Centers
Other Research
Research Training
R&D Contracts
Intramural Research
Res. Mgmt. & Support
-1.8
-0.5
0.2
-0.5
2.4
-0.5
1.5
-2
-1
0
1
2
Percents

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Budget Mechanism - Total

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	1,651	$600,218,000	1,625	$598,139,000	1,571	$564,379,000
Administrative supplements	(45)	8,785,000	(45)	8,688,000	(44)	8,644,000
Competing:						
Renewal	138	54,250,000	133	52,278,000	148	58,147,000
New	428	123,506,000	414	119,455,000	462	133,241,000
Supplements	3	380,000	3	380,000	4	507,000
Subtotal, competing	569	178,136,000	550	172,113,000	614	191,895,000
Subtotal, RPGs	2,220	787,139,000	2,175	778,940,000	2,185	764,918,000
SBIR/STTR	83	25,976,000	80	25,112,000	79	24,782,000
Subtotal, RPGs	2,303	813,115,000	2,255	804,052,000	2,264	789,700,000
Research Centers:						
Specialized/comprehensive	70	109,581,000	70	108,373,000	70	107,861,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	200,000	0	200,000	0	200,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	70	109,781,000	70	108,573,000	70	108,061,000
Other Research:						
Research careers	503	74,188,000	498	73,372,000	506	73,905,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	18	18,588,000	18	18,384,000	18	18,292,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	0	0	0	0	0
Other	149	36,308,000	148	35,908,000	148	35,729,000
Subtotal, Other Research	670	129,084,000	664	127,664,000	672	127,926,000
Total Research Grants	3,043	1,051,980,000	2,989	1,040,289,000	3,006	1,025,687,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	308	11,004,000	300	10,883,000	299	10,829,000
Institutional awards	1,116	46,890,000	1,093	46,375,000	1,088	46,143,000
Total, Training	1,424	57,894,000	1,393	57,258,000	1,387	56,972,000
Research & development contracts	180	73,261,000	180	72,455,000	181	74,201,000
(SBIR/STTR)	(21)	(6,112,000)	(21)	(6,045,000)	(21)	(6,015,000)
	FTEs		FTEs		FTEs	
Intramural research	425	158,036,000	460	158,826,000	460	158,032,000
Research management and support	235	61,836,000	235	62,145,000	239	63,077,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
NIH Roadmap for Medical Research	2	8,926,000	3	12,542,000	3	16,837,000
Total, NIMH	662	1,411,933,000	698	1,403,515,000	702	1,394,806,000
(Clinical Trials)		(124,522,000)		(123,454,000)		(122,300,000)

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

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2005 Actual FTEs	FY 2005 Actual Amount	FY 2006 Appropriation FTEs	FY 2006 Appropriation Amount	FY 2007 Estimate FTEs	FY 2007 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Extramural research		$1,183,135		$1,170,002		$1,156,860		($13,142)
Subtotal, Extramural research		1,183,135		1,170,002		1,156,860		(13,142)
Intramural research	425	158,036	460	158,826	460	158,032	0	(794)
Res. management & support	235	61,836	235	62,145	239	63,077	4	932
NIH Roadmap for Medical Research	2	8,926	3	12,542	3	16,837	0	4,295
Total	662	1,411,933	698	1,403,515	702	1,394,806	4	(8,709)

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

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Summary of Changes

FY 2006 Estimate				$1,403,515,000
FY 2007 Estimated Budget Authority				1,394,806,000
Net change				(8,709,000)
	FY 2006 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$64,013,000		$884,000
b. Annualization of January 2006 pay increase		64,013,000		496,000
c. January 2007 pay increase		64,013,000		1,056,000
d. Payment for centrally furnished services		28,664,000		430,000
e. Increased cost of laboratory supplies, materials, and other expenses		66,149,000		1,201,000
Subtotal				4,067,000
2. Research Management and Support:				
a. Within grade increase		29,001,000		493,000
b. Annualization of January 2006 pay increase		29,001,000		225,000
c. January 2007 pay increase		29,001,000		478,000
d. Payment for centrally furnished services		8,886,000		134,000
e. Increased cost of laboratory supplies, materials, and other expenses		24,258,000		440,000
Subtotal				1,770,000
Subtotal, Built-in				5,837,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Summary of Changes--continued

CHANGES	FY 2006 Appropriation		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	1,625	$606,827,000	(54)	($33,804,000)
b. Competing	550	172,113,000	64	19,782,000
c. SBIR/STTR	80	25,112,000	(1)	(330,000)
Total	2,255	804,052,000	9	(14,352,000)
2. Research centers	70	108,573,000	0	(512,000)
3. Other research	664	127,664,000	8	262,000
4. Research training	1,393	57,258,000	(6)	(286,000)
5. Research and development contracts	180	72,455,000	1	1,746,000
Subtotal, extramural				(13,142,000)
	FTEs		FTEs	
6. Intramural research	460	158,826,000	0	(4,861,000)
7. Research management and support	235	62,145,000	4	(838,000)
8. NIH Roadmap for Medical Research	3	12,542,000	0	4,295,000
Subtotal, program		1,403,515,000		(14,546,000)
Total changes	698		4	(8,709,000)

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Budget Authority by Object

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	698	702	4
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$155,078	$160,196	$5,118
Average GM/GS grade	11.7	11.7	0.0
Average GM/GS salary	$81,170	$83,849	$2,679
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$95,771	$98,931	$3,160
Average salary of ungraded positions	116,649	120,498	3,849

OBJECT CLASSES		FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$38,585,000	$40,091,000	$1,506,000
11.3	Other than Full-Time Permanent	23,882,000	24,815,000	933,000
11.5	Other Personnel Compensation	1,375,000	1,429,000	54,000
11.7	Military Personnel	1,390,000	1,444,000	54,000
11.8	Special Personnel Services Payments	10,318,000	10,721,000	403,000
	Total, Personnel Compensation	75,550,000	78,500,000	2,950,000
12.0	Personnel Benefits	16,490,000	17,134,000	644,000
12.2	Military Personnel Benefits	974,000	1,012,000	38,000
13.0	Benefits for Former Personnel	0	0	0
	Subtotal, Pay Costs	**93,014,000**	**96,646,000**	**3,632,000**
21.0	Travel & Transportation of Persons	3,009,000	2,951,000	(58,000)
22.0	Transportation of Things	258,000	253,000	(5,000)
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	2,000	2,000	0
23.3	Communications, Utilities & Miscellaneous Charges	1,944,000	1,907,000	(37,000)
24.0	Printing & Reproduction	999,000	980,000	(19,000)
25.1	Consulting Services	2,168,000	2,126,000	(42,000)
25.2	Other Services	5,861,000	5,748,000	(113,000)
25.3	Purchase of Goods & Services from Government Accounts	129,913,000	127,413,000	(2,500,000)
25.4	Operation & Maintenance of Facilities	633,000	621,000	(12,000)
25.5	Research & Development Contracts	37,974,000	39,352,000	1,378,000
25.6	Medical Care	1,136,000	1,114,000	(22,000)
25.7	Operation & Maintenance of Equipment	1,404,000	1,377,000	(27,000)
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**179,089,000**	**177,751,000**	**(1,338,000)**
26.0	Supplies & Materials	7,935,000	7,782,000	(153,000)
31.0	Equipment	7,165,000	7,027,000	(138,000)
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,097,547,000	1,082,659,000	(14,888,000)
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	11,000	11,000	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**1,297,959,000**	**1,281,323,000**	**(16,636,000)**
	NIH Roadmap for Medical Research	**12,542,000**	**16,837,000**	**4,295,000**
	Total Budget Authority by Object	**1,403,515,000**	**1,394,806,000**	**(8,709,000)**

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

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Salaries and Expenses

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$38,585,000	$40,091,000	$1,506,000
Other Than Full-Time Permanent (11.3)	23,882,000	24,815,000	933,000
Other Personnel Compensation (11.5)	1,375,000	1,429,000	54,000
Military Personnel (11.7)	1,390,000	1,444,000	54,000
Special Personnel Services Payments (11.8)	10,318,000	10,721,000	403,000
Total Personnel Compensation (11.9)	**75,550,000**	**78,500,000**	**2,950,000**
Civilian Personnel Benefits (12.1)	16,490,000	17,134,000	644,000
Military Personnel Benefits (12.2)	974,000	1,012,000	38,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**93,014,000**	**96,646,000**	**3,632,000**
Travel (21.0)	3,009,000	2,951,000	(58,000)
Transportation of Things (22.0)	258,000	253,000	(5,000)
Rental Payments to Others (23.2)	2,000	2,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	1,944,000	1,907,000	(37,000)
Printing and Reproduction (24.0)	999,000	980,000	(19,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	2,090,000	2,049,000	(41,000)
Other Services (25.2)	5,861,000	5,748,000	(113,000)
Purchases from Govt. Accounts (25.3)	79,364,016	76,463,036	(2,900,980)
Operation & Maintenance of Facilities (25.4)	633,000	621,000	(12,000)
Operation & Maintenance of Equipment (25.7)	1,404,000	1,377,000	(27,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**89,352,016**	**86,258,036**	**(3,093,980)**
Supplies and Materials (26.0)	7,921,000	7,768,000	(153,000)
Subtotal, Non-Pay Costs	103,485,016	100,119,036	(3,365,980)
Total, Administrative Costs	**196,499,016**	**196,765,036**	**266,020**

National Institutes of Health

National Institute of Mental Health

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

Item

Down syndrome — The Committee encourages NIMH to develop new strategies for cataloging, understanding, diagnosing and treating behavioral disorders that are common in people with Down syndrome. They include autism, pervasive developmental disorder, obsessive compulsive disorder, depression and psychosis. The Committee urges NIMH to coordinate its research on Down syndrome with NICHD, NINDS, NIA and other institutes. (p. 92)

Action taken or to be taken

Although NIMH does not have projects specifically focused on Down syndrome, it supports many studies that are relevant to understanding and treating psychiatric disorders in cognitively impaired people. To further research on psychopathology in the context of intellectual disabilities, including Down syndrome, NIMH has issued a program announcement (PA) entitled "Research on Psychopathology in Intellectual Disabilities (Mental Retardation)." This PA is a clear signal to the field that NIMH is very interested in receiving applications of support in this area.

Item

Alzheimer's disease — Combining imaging with genetics, a team of NIMH-funded scientists recently identified a possible genetic marker for Alzheimer's disease, a variant of the gene that codes for APOE, a protein involved in metabolizing cholesterol. PET scans of normal individuals in their fifties and sixties who carry this variant showed decreased activity in regions of the brain known to be affected by Alzheimer's. PET scans of younger individuals who carry this variant found lowered metabolism in the same brain areas, suggesting that the process at work in Alzheimer's starts decades before memory deficits become apparent. The Committee strongly encourages NIMH to continue to advance understanding of Alzheimer's disease. (p. 93)

Action taken or to be taken

NIMH continues to support an active research portfolio on Alzheimer's disease. This work includes all phases of research, from basic neuroscience studies to treatment and services research. The Institute supports research examining various aspects of the pathophysiology and genetics of Alzheimer's disease; studies examining behavioral, emotional and psychiatric symptoms associated with the disorder and their treatment; as well as other issues of clinical relevance, such as decision making capacity as it relates to the participation of cognitively impaired persons in research. Last year, NIMH spent 4 percent of its annual budget on studies of Alzheimer's disease.

As a component of its large study entitled "Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE)," the Institute has supported the examination of antipsychotic medications for the treatment of agitation and other behavioral disturbance in Alzheimer's disease. This 35-site study compared the effectiveness of several atypical antipsychotic medications for persons with Alzheimer's disease to determine the best medication regimen. The first published report from this trial should be available later this year.

In addition, NIMH participates in an Inter-Institute Work Group on Alzheimer's Disease, and it will continue to collaborate with other NIH institutes in Alzheimer's related research initiatives.

Item

Fragile X — Fragile X is the most common single-gene neuropsychiatric disease known. It causes cognitive impairment, mental disorders such as obsessive-compulsive disorder, and extreme anxiety. The Committee commends NIMH for spearheading three focused research meetings in the past four years devoted to identifying critical research needs. The Committee encourages NIMH to pursue the highest priority needs identified by the meeting panels. These include controlled studies of existing and new pharmacological treatments for Fragile X and identification of the key molecular targets which are likely candidates for designing drug treatments for Fragile X and related disorders such as autism. The Committee also recommends that NIMH include Fragile X in its studies of related neuropsychiatric disorders and to work with other Institutes such as NICHD and NINDS to develop cooperative research support mechanisms in this area. In addition, the Committee suggests that NIMH work with industry and academia to test available medications and bring new treatments to market. (p. 93)

Action taken or to be taken

NIMH has already begun to implement this strategy. In May 2005, the Institute issued a Program Announcement (PA) entitled "Shared Neurobiology of Fragile X Syndrome (FXS) and Autism." This activity represents a public-private partnership among NIMH, two other NIH institutes (NINDS and NICHD), the Canadian Institutes of Health Research, the Health Research Board, Ireland, Cure Autism Now, the National Alliance for Autism Research, Autism Speaks and the FRAXA Research Foundation. The goal of the PA is to promote research that has as its aims the characterization, understanding and treatment of mechanisms common to both FXS and autism. Applications submitted in response to this PA are expected to focus on a topic related to understanding neural pathways, circuits, systems and molecules that play a role in the etiology or pathophysiology of FXS and may be implicated in autism (including other autism spectrum disorders such as Rett syndrome). There is particular interest in studies emphasizing the identification of drug targets for new medications to treat FXS and autism. In addition, NIMH is actively exploring the inclusion of Fragile X in molecular genetic and other studies being planned within the Autism STAART (Studies to Advance Autism Research and Treatment) centers funded by several NIH institutes (NIMH, NICHD, NINDS, NIDCD, NIEHS). Children with autism identified by these centers will provide a natural population in which to identify youth diagnosed with Fragile X and to be included in research including clinical trials.

The NIMH grant portfolio on Fragile X includes preclinical studies of cognitive processes disrupted in Fragile X and possible biological mechanisms by which they occur. NIMH supports a multi-site MRI study that examines the relationships between the Fragile X mental retardation

1 gene (FMR1), brain abnormalities, and behavior by following a cohort of toddlers for two years in order to examine the developmental trajectory of these relationships. Another longitudinal study is examining 120 school-age children with Fragile X and their families to assess the biological and environmental factors contributing to clinical outcomes. NIMH continues to support an active training program at the University of Colorado School of Medicine, which has for the past 22 years been a source of postdoctoral training for clinician researchers with an interest in developmental disabilities including Fragile X. Additionally, NIMH supports two postdoctoral fellowships at Brown University that focus on understanding the regulation and activation of the FMR1 gene. Through the program announcement "Research on Psychopathology in Intellectual Disabilities," NIMH solicits research designed to elucidate the epidemiology, etiology, treatment, and prevention of mental disorders in persons of any age with intellectual disabilities, including Fragile X.

Item

Adolescent depression and suicide — Major depressive disorder in adolescence, one of the major risk factors for suicide, has become increasingly common. Suicide now accounts for 13 percent of all adolescent deaths and ranks third as a cause of death among teenagers. The Committee encourages NIMH to strengthen its investment in understanding the clinical epidemiology of suicidal behavior and thinking in children and adolescents; improving the criteria for identifying those at risk; and examining the outcomes of actions taken to assist those found to be at risk. (p. 93)

Action taken or to be taken

NIMH supports a number of research initiatives aimed at understanding suicidal behavior in adolescence and identifying risk factors that can be reduced through preventive interventions. Much of this research support is focused on clinic-based studies that examine the rates, clinical course and service use patterns of adolescents who are depressed and suicidal, as well as studies to identify risk factors and improve preventive interventions. For example, NIMH supports a pilot study on the effects of pharmacological, psychotherapeutic and combined interventions for high-risk depressed adolescents who have recently attempted suicide. In partnership with NIDA, NIAAA and the American Foundation for Suicide Prevention, the Institute funds three research centers that are entirely devoted to suicide prevention efforts. The focus of these centers is on the development of new trials to reduce adolescent suicidality, particularly among youth with substance use and mood disorders. In conjunction with several other NIH funded centers (including a VA-funded site), the centers are working together to coordinate activities to improve research methodology in the study of suicidality, including standardizing measurement of suicide risk and side effects and exploring the role of impulsivity.

In addition to these centers, NIMH participates in several other collaborative efforts. In collaboration with SAMHSA, NIMH will provide technical assistance to an upcoming meeting with Garrett Lee Smith Memorial Act grantees to better integrate state-of-the-science youth suicide prevention with best practices being tested across the nation. With IHS, SAMHSA, NIDA, NIAAA, Health Canada and the Canadian Institutes of Health Research, NIMH is also supporting an international conference on indigenous suicide prevention, with a major focus on increasing research on suicide among American Indian and Alaska Native youth. NIMH and

AHRQ have recently collaborated on a systematic analysis of large patient databases to identify associations between use of antidepressant medications and suicidal behavior in adolescents.

Item

Mental health for older Americans — The Committee is aware that demographics will demand an increased focus on mental disorders in older persons. The Committee encourages NIMH to strengthen research in this area through all available mechanisms to advance the geriatric mental health research agenda. (p. 93)

Action taken or to be taken

In FY 2004, NIMH established an integrated extramural program of aging-related studies in a Geriatrics Research Branch to promote and coordinate efforts in this research area. The Institute's commitment to this domain is evidenced by its significant investment in research support and participation in trans-NIH activities related to aging. NIMH funds numerous projects in this area, including studies on understanding relevant brain mechanisms for late-life mental disorders; developing new animal models and diagnostic tools; and, improving diagnosis and treatment of late-life mental disorders. It has an extensive research portfolio examining depression, anxiety disorders and psychosis among older adults across diverse settings and delivery systems. For example, the Geriatrics Research Branch supports several clinical research centers devoted to studies of geriatric mood and anxiety disorders and one directed toward research on psychotic disorders in old age. In FY 2004, the branch initiated a 6-site clinical trial of treatment for late-life bipolar disorder.

In addition, NIMH recently held a workshop entitled "Translational Research in Late-Life Mood Disorders: Implications for Future Intervention and Prevention Research." Workshop participants outlined research directions to expand geriatric mental health studies, including increased use of the neuroscientific tools of genetics and structural and functional brain imaging to advance work in this area.

FY2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

Adolescent depression and suicide — Major depressive disorder in adolescence--one of the major risk factors for suicide--has become increasingly common. Suicide now accounts for 13 percent of all adolescent deaths and ranks third as a cause of death among teenagers. The Committee notes that NIMH has conducted a major trial on adolescent depression which has yielded valuable knowledge about effective treatments for depression. The Committee strongly encourages NIMH to strengthen its investment in understanding the clinical epidemiology of suicidal behavior and thinking in children and adolescents; improving the criteria for identifying those at risk; and examining the outcomes of actions taken to assist those found to be at risk. (pp. 143-144)

Action taken or to be taken

Please refer to Page 37of this document for NIMH 's response to this significant item regarding NIMH's commitment to research on adolescent depression and suicide.

Item

Alzheimer's disease — Combining imaging with genetics, a team of NIMH-funded scientists recently identified a possible genetic marker for Alzheimer's disease, a variant of the gene that codes for APOE, a protein involved in metabolizing cholesterol. PET scans of normal individuals in their fifties and sixties who carry this variant showed decreased activity in regions of the brain known to be affected by Alzheimer's. PET scans of younger individuals who carry this variant found lowered metabolism in the same brain areas, suggesting that the process at work in Alzheimer's starts decades before memory deficits become apparent. The Committee strongly encourages NIMH to continue to advance understanding of Alzheimer's disease. (p.144)

Action taken or to be taken

Please refer to Page 35 of this document for NIMH's response to this significant item regarding NIMH's commitment to Alzheimer's disease.

Item

Aging and mental health — The Committee commends the NIMH for recently recognizing the need to place a higher priority on the mental health needs of older persons through the 2004 recommendations promulgated by the NIMH Aging Research Workgroup and the restructuring of the Adult and Geriatric Treatment and Preventive Intervention Research Branch. However, the Committee believes it is critical that studies related to the elderly keep pace with the rapid growth of this cohort. The Committee encourages the NIMH to devote greater resources to research on adults over age 65 to reflect the growth in numbers of this population. Therefore, the Committee strongly encourages NIMH to significantly expand research in this area.

The Committee is pleased with NIMH's continued emphasis on research involving mental disorders in the elderly population, especially since the causes of depression in the elderly and the factors affecting its course are not well understood. The Committee urges NIMH to continue its level of support in this area. (p. 144)

Action taken or to be taken

Please refer to Page 38 of this document for NIMH's response to this significant item regarding NIMH's commitment to geriatric mental health.

Item

Basic behavioral science — The Committee encourages NIMH to continue its commitment to support basic behavioral research focused on fundamental psychological domains and factors that promote mental health or become disturbed in mental disorders. The Committee is concerned that the institute may be diminishing its support for some areas of relevant scientific inquiry and urges the institute to support a balanced program of grant funding and to maintain its support for research on the promotion of mental health and the study of psychological, social, and legal factors that influence behavior. (pp.144-145)

Action taken or to be taken

NIMH is committed to the principle that support of a strong basic science research program, including basic behavioral science, is critical in advancing its mission. At the same time, the Institute must ensure that its support of basic science is properly targeted in order to optimally

inform those research programs that more directly address critical clinical issues in research on mental disorders. At the suggestion of the National Advisory Mental Health Council, NIMH convened a workgroup in FY 2004 to examine our basic science research priorities in both the brain and behavioral sciences. After extensive deliberations, this group made a series of detailed recommendations for specific scientific areas in which NIMH should maintain, increase or decrease its research commitment. Further, the workgroup emphasized that: (1) it was important that NIMH-supported basic science research be undertaken in the service of the public health mission of the Institute; and (2) basic science research that translates across levels of analysis from genetic, to molecular, cellular, systems levels, all the way to complex, overt behaviors should be given high priority. Following the workgroup report, NIMH reorganized support of all its extramural research programs in the Fall of 2004, creating a structure to reflect these recommendations and encourage basic scientists to work on research issues that will eventually stimulate new advances in clinically relevant research. A new branch was created in the basic science division, the Behavioral Science and Integrative Neuroscience Research Branch. This branch supports work in a number of basic behavioral science areas, including cognitive science, as well as studies of aspects of affect, emotion, and social behavior. In addition, basic behavioral science research that seems ready for more immediate translation into clinically relevant findings is assigned to newly created translational research divisions where the focus is on taking basic science findings and turning these into results that directly address the mental health needs of all Americans. NIMH remains committed to supporting basic behavioral science research as an important component of its overall portfolio of basic science research. The Institute will continue to support basic behavioral science research that will meaningfully inform research with clinical implications for mental disorders as one component of a properly balanced research agenda.

Item

Combat veterans — The Committee is concerned about the mental health effects of military service in Iraq and Afghanistan, particularly since so many of the combatants are members of the National Guard or Reserves who will have to assimilate quickly back into civilian life after service. The Committee urges NIMH to work closely with the Veterans Administration and with the Department of Defense in efforts to best address this looming problem. (p.145)

Action taken or to be taken

NIMH is actively collaborating with the VA and DOD on a number of initiatives designed to address the mental health needs of combat veterans. In September 2005, NIMH, the VA and DOD jointly issued a request for applications entitled “Intervention and Practice Research for Combat Related Mental Disorders and Stress Reactions” designed to solicit research on the identification, prevention and treatment of combat related post-traumatic psychopathology and similar adjustment problems among active-duty or recently separated National Guard and Reserve troops. The goal of this initiative is to establish collaborations involving the VA, DOD, community clinicians and researchers that provide screening, assessment, and direct care to people who are at risk for or diagnosed with post-traumatic psychopathology. The objectives of this initiative include new research to build resilience against the development of mental illness, including such interventions as: pilot screening, referral and rapid treatment protocols to ensure access and continuity of care; new or modified group treatments and short-term treatments; novel pharmacological, psychosocial and combination treatments; application and testing of new

technologies (e.g., World Wide Web, DVD, Virtual Reality, Tele-health) for initiating and providing therapy; pilot projects to incorporate mental health screening, treatment, and triage in primary care settings; and models for sustaining improvement in symptoms and functioning after successful treatment and for disseminating evidence-based interventions.

Additionally, NIMH is collaborating with the VA and DOD in an ongoing research portfolio review to coordinate programs on post-traumatic stress disorder to ensure complimentary and adequate coverage of key public health and clinical research areas. Other recent collaborations include joint NIMH, VA, and DOD workshops on translating the scientific knowledge base into practice guidance and the science of early mental health intervention/prevention.

NIMH maintains an active program announcement entitled "Mental Health Consequences of Violence and Trauma" to enhance scientific understanding about the etiology of psychopathology related to violence and trauma, as well as studies to develop and test effective treatments, services, and prevention strategies in this area.

Item

Demographics — The Committee is aware that demographics will demand a greatly increased focus on mental disorders in older persons, and consequently the Committee continues to be concerned about funding for late-life mental health research at the National Institute of Mental Health [NIMH]. The Committee encourages NIMH to expand research in Adult and Geriatric Treatment and Preventive. (p. 145)

Action taken or to be taken

Please refer to Page 38 of this document for NIMH's response to this significant item regarding NIMH's commitment to demographics on late-life mental health.

Item

Disease prevalence — The Committee is aware that NIMH has supported a major study that will provide critical information concerning the prevalence of most mental disorders in this country, as well as about the availability of quality care. When the study is published, the Committee would like to have a briefing to summarize the results of that study for interested Members of Congress and staff. (p.145)

Action taken or to be taken

NIMH supports several major studies of the prevalence of mental disorders. Important findings emerged recently from a large multi-site collaborative study called the National Comorbidity Survey Replication, which is a household survey of the prevalence of mental disorders in 9,282 English-speaking respondents. Findings from this survey were recently published and are summarized in a press release issued by NIMH in June of 2005. The Institute would be pleased to undertake a briefing to share these results and their public health implications with the Committee and other interested Members.

The National Comorbidity Survey Replication is an expansion of the 1990 National Comorbidity Survey, which was the first study to estimate the prevalence of mental disorders using state-of-the-art research methods. The published results revealed that mental disorders are common in

the United States, with 26 percent of the general population reporting a diagnosable mental illness within the previous 12 months and about 6 percent of the population reporting a serious mental disorder that involves substantial impairment in activities. The mean impairment period for those with serious mental disorders was 88 days in the previous 12-month survey period. Unlike most disabling physical illnesses, half of all mental disorders begin by age 14; the risk of developing a mental disorder decreases substantially with age. Approximately 80 percent of those with a mental disorder eventually sought treatment, but about 60 percent of those with a mental disorder reported having received no treatment within the previous 12 months. The study documents a median delay of almost 10 years from the onset of mental illness and the first treatment. These findings demonstrate that mental disorders are chronic and frequently begin at an early age. It appears that the earlier in life a mental disorder begins, the longer it takes an individual to seek treatment, and the more persistent the disorder becomes.

The NIMH epidemiological research portfolio contains several projects that parallel the 2005 National Comorbidity Survey Replication. These projects examine mental disorders in focused populations, such as adolescents and minority groups. The respective projects are looking at the prevalence of mental disorders in 10,000 adolescents; 6,000 African-Americans; and 5,000 Latino- and Asian-Americans. It is expected that these studies will provide information on diagnosis, impairment, and service use in the designated populations.

Item

Down syndrome — The Committee encourages the NIMH to develop new strategies for cataloging, understanding, diagnosing and treating behavioral disorders that are common in people with Down syndrome. They include autism, pervasive developmental disorder, obsessive compulsive disorder, depression and psychosis. The Committee urges NIMH to coordinate its research on Down syndrome with NICHD, NINDS, NIA and other Institutes. The Committee encourages NIMH to continue their studies on imaging of the brains of persons with Down syndrome broadening their focus to include behavior and motor coordination. (p.145)

Action taken or to be taken

Please refer to Page 35 of this document for NIMH's response to this significant item regarding NIMH's commitment to research on Down syndrome.

Item

Epilepsy — Recent evidence of connections between depression and epilepsy point to relationships between the two disorders that suggest potential common pathogenic mechanisms. Research could help improve care for both groups of patients. The Committee strongly urges the Institute to make research in epilepsy a priority and to coordinate research efforts with NINDS. (p.146)

Action taken or to be taken

Although not the lead NIH institute studying this disorder, NIMH recognizes the likelihood that common pathogenic mechanisms may underlie epilepsy and depression. In response, the Institute supports a substantial basic and clinical research portfolio dedicated to understanding the pathophysiology of depression and its treatment, which includes studies of how seizure induction (i.e., electroconvulsive therapy) modifies depression and how anti-seizure medications

exert mood-stabilizing effects in patients with bipolar disorder. Further, NIMH is an active participant on the Interagency Epilepsy Coordinating Committee and has been involved in a number of epilepsy-related meetings and conferences. Most recently, NIMH and NINDS co-sponsored a meeting in May 2005 on the treatment of non-epileptic (psychogenic) seizures, for which a publication is in preparation. Finally, NIMH in collaboration with NINDS is soliciting research proposals on the neurobiological mechanisms of neurodegenerative diseases through a recently released request for applications (RFA) entitled "Collaborative Research on Mental and Neurological Disorders." This RFA specifically identifies epilepsy as a key area of interest.

Item

Fragile X — Fragile X is the most common single-gene neuropsychiatric disease known. It causes cognitive impairment, mental disorders such as obsessive-compulsive disorder, and extreme anxiety. The Committee commends NIMH for spearheading three focused research meetings devoted to identifying critical research needs, in November 2001, January 2003, and July 2004. The Committee urges NIMH to pursue the most critical needs identified by the meeting panels. These include controlled studies of existing and new pharmacological treatments for Fragile X and identification of the key molecular targets which are likely candidates for designing drug treatments for Fragile X and related disorders such as autism. The Committee also urges NIMH to include Fragile X in its studies of related neuropsychiatric disorders and to work with other Institutes such as NICHD and NINDS to develop cooperative research support mechanisms in this area. In addition, the Committee urges the NIMH to work with industry and academia to test available medications and bring new treatments to market. (p.146)

Action taken or to be taken

Please refer to Page 36 of this document for NIMH's response to this significant item regarding NIMH's commitment to research on Fragile X.

Item

Hepatitis — The Committee urges the National Institute of Mental Health [NIMH] to conduct and/or facilitate research to explore the etiology and effective therapeutic management of neuropsychiatric symptoms and disorders associated with chronic hepatitis C and interferon-based antiviral treatment. (p.147)

Action taken or to be taken

The NIMH Center for Mental Health Research on AIDS has recognized the importance of Hepatitis C infection and associated treatment in contributing to neuropsychiatric and neurologic complications, particularly in HIV infected individuals. In response to this emerging public health problem NIMH organized two companion workshops in October, 2003. The goal of the first workshop, entitled "HIV/Hepatitis C Co-Infection: Impact on Nervous System Disease Burden," was to define the burden of neurologic and neuropsychiatric disease in the setting of HIV/HCV co-infection and identify future research priorities in the areas of neuropathogenesis, as well as treatment. NIDA and NINDS also contributed to this workshop. The goal of the second companion workshop, entitled "HIV/Hepatitis C Co-Infection: Behavioral and Clinical Research in Mental Health and Drug Abuse," was to build on the most current information and

provide a clearer focus for mental health and drug abuse-related research on the behavioral and clinical aspects of HIV/HCV co-infection (i.e., risk and prevention, services, treatment).

These workshops should act as a stimulus for future research on vulnerable populations; neurocognitive, neuropsychologic, neurologic and neuropsychiatric complications resulting from HIV/HCV co-infection; virologic studies of HCV infection of the central nervous system; treatment and treatment services; and prevention. A supplement to the journal *AIDS* entitled "HIV/Hepatitis C Co-Infection: Basic Behavioral and Clinical Research in Mental Health and Drug Abuse" is based on the proceedings of both workshops and will be published in the Fall of 2005.

In FY 2005, NIMH supported research designed to determine further the underlying biological mechanisms and etiology of neurocognitive dysfunction encountered in HCV infection, particularly in HIV/HCV co-infection. An additional area of study focused on the impact of co-morbid medical and psychiatric conditions on adherence to medical treatment in HCV infected and HIV/HCV co-infected patients.

NIMH has provided continued support for the National Neuro-AIDS Tissue Consortium (NNTC). The consortium is a multi-site effort to collect blood, urine and cerebrospinal fluid, as well as tissues and organs, from well-characterized patients with advanced AIDS and HIV-negative volunteers, and distribute them to qualified investigators for research into the pathogenesis of Neuro-AIDS. In addition, the NNTC collects information that is essential to study the association between co-morbid medical conditions, such as HCV infection, and has stimulated the development of independently supported projects examining HCV and the nervous system. In FY 2005, NIMH also provided continued support of the "CNS HIV Anti-Retroviral Effects Therapy Research" (CHARTER) contract. This study was expanded to support testing of HCV seroprevalence and HCV viral load in AIDS patients on HAART therapy, with the intent to determine whether there is a correlation between HCV and the development of neurological complications as they arise in the enrolled patients.

Item

Learning Disabilities — The Committee commends NIMH for the work conducted to explore the neurological and behavioral aspects of learning disabilities. The Committee looks forward to learning the results of this work and encourages the Institute to continue to coordinate with other Institutes working on related activities. (p.147)

Action taken or to be taken

Although NICHD serves as the lead institute for research on learning disabilities, NIMH's portfolio does include projects relevant to learning disabilities. However, they are more heavily weighted toward basic neuroscience and behavioral research on various aspects of learning (e.g., memory, motor learning, conditioning), normal reading acquisition and processing, and relationships of learning disabilities to childhood mental disorders. For example, it is known that depression in children interferes with their abilities to concentrate and take in new information.

NIMH focuses on understanding brain mechanisms that support various forms of learning, particularly in relationship to anxiety, mood and other emotional conditions. In addition, NIMH

supports considerable research on attention deficit-hyperactivity disorder (ADHD), a behavioral disorder with significant comorbidity/overlap with learning disabilities.

NIMH participates in a number of trans-NIH pediatric neuroimaging initiatives focused on understanding normal pediatric brain development. These studies will form the basis for understanding deviations in brain development associated with disorders, including learning disabilities. One such project is a longitudinal multi-site study that uses magnetic resonance imaging (MRI) to map healthy brain development from age 7 days through young adulthood. This project, supported by NICHD, NIDA, NIMH and NINDS, will yield a database that can be utilized by researchers studying disorders, including learning disorders and ADHD.

Item

Morbidity and mortality — The burden of mental disorders is staggering, in terms of both morbidity and mortality. Researchers supported by NIMH have found that half of all lifetime cases of mental illness begin by age 14, and that despite effective treatments, there are long delays between the appearance of the first symptoms of illness and provision of even adequate treatment. Unlike most other disabling medical diseases, mental illness begins very early in life. Mental disorders, then, can very aptly be called the chronic diseases of the young. Young people with mental disorders suffer disability when they are in the prime of life, when they would normally be most productive. The NIMH study also found that mental disorders really are quite common--26 percent of the general population reported that they had symptoms sufficient for diagnosing a mental disorder during the past 12 months. Although some of these cases are mild ones that will resolve without formal interventions, many more will not. The Committee urges NIMH to continue its current efforts to focus on research that promises to yield effective results that can be translated to the benefit of patients, with the goal of finding new ways to intervene early in the development of disease--or even prevent its occurrence, and, when prevention is not possible, to achieve rational treatments that are tailored to be most effective to the individual patient. (p.147)

Action taken or to be taken

It is the mission of NIMH to reduce the burden of mental illness and behavioral disorders through research on mind, brain, and behavior. NIMH recognizes the magnitude of the burden of serious mental illness and is committed to supporting research that can advance early diagnosis, prevention, and treatment of serious mental illness. By a better understanding of the pathophysiology of mental disorders, it should become possible to identify and prevent or treat mental illness in individuals through more personalized care. New technologies will lead to the identification of those prone towards specific illnesses and new and improved interventions could prevent the illness from ever manifesting itself. For those individuals suffering from serious mental illness, new technology will lead to better refined diagnostics, and ultimately to better treatments tailored to the individual in which the core pathology is addressed, and not just the symptoms of the disease. With greater knowledge of the pathophysiology of these disorders, and a further refinement of treatment and prevention strategies, a new era in mental health treatment will be possible in which individualized treatment will be based on a rational understanding of who is susceptible to what disorder and who will benefit from what treatment. Examples of this vision are already in place. For example, in order to enhance early diagnosis of the devastating disease of schizophrenia, the Institute currently supports a project on assessment

of prodromal schizophrenia, which is designed to develop and refine methods that can identify schizophrenia in its very early stages so that treatment can begin before the disorder becomes chronic and disabling. To enhance preventive efforts, the Institute supports a multitude of studies, such as one on the early assessment of young people to identify risk factors for anxiety and depression. Another study examines insomnia as a modifiable risk factor for major depressive disorder.

The Institute supports innumerable projects to develop new treatments for a multitude of disorders. For example, NIMH supports research on new treatment procedures for generalized anxiety disorder, depression with co-occuring panic disorder, obsessive-compulsive disorder, partner violence, pathological gambling, primary insomnia, social phobia, and treatment-refractory schizophrenia. As an example of early treatment, the Institute supports a project on the development of an early intervention for first episode schizophrenia that is to be given before the disorder becomes chronic. Through its commitment to projects such as these and the many others that make up the NIMH research portfolio, the Institute is assured of providing a knowledge base that will lead to improved diagnostic abilities, stronger prevention programs, and a host of new and improved treatment interventions that can make significant strides towards the reduction of the burden of mental illness.

Item

Parkinson's disease — The Committee encourages continued collaborations including additional intramural activities between NINDS, NIMH, and NIA to enhance understanding of neurodegenerative diseases, particularly Parkinson's. (p.147)

Action taken or to be taken

NIMH has long recognized the importance of co-occurring mental disorders with neurodegenerative diseases, particularly Parkinson's disease. The Institute's commitment to this area is evidenced by its significant investment in research support, participation in numerous trans-NIH activities, collaborations with advocacy groups, and information it provides to patients and their family members. NIMH funds numerous projects in this area, including studies on understanding relevant brain mechanisms; developing new animal models and diagnostic tools; and improving diagnosis and treatment of co-morbid mood disorders. In regard to trans-NIH activities, NIMH continues to actively participate in the Interagency Parkinson's Disease Coordinating Committee and to function as the co-leading institute with NINDS on the Parkinson's disease matrix activity, "Clinical Trials of Non-Motor Symptoms." In July 2005, NIMH held a workshop to discuss the neural basis of depression in Parkinson's disease. A larger, follow-up meeting to this highly productive workshop is being planned. NIMH is also working with NINDS to convene an expert panel to discuss treating psychosis in Parkinson's disease, and is co-sponsoring the first World Parkinson Congress to be held in February 2006 in Washington, D.C. The Institute in collaboration with NINDS is soliciting research proposals on the neurobiological mechanisms of neurodegenerative diseases through a recently released request for applications (RFA) entitled "Collaborative Research on Mental and Neurological Disorders." This RFA specifically identifies Parkinson's disease as a key area of interest. Finally, NIMH staff interact regularly with Parkinson's disease patient advocate groups to support and educate their members. For example, NIMH participates annually in the Parkinson's Action Network Research and Education Forum.

Item

Psoriasis — Psoriasis is associated with elevated rates of mental disability, depression and suicidal ideation. The Committee urges NIMH to conduct research into the mental health aspects of psoriasis, especially as it relates to quality of life and burden of the disease. Furthermore, a 2005 study of 44 autoimmune diseases found that only psoriasis, when present in women around the time of pregnancy, was significantly associated with autism, doubling the risk of autism spectrum disorder in their children. The Committee urges NIMH to support further study of the link between psoriasis and autism. (pp.147-148)

Action taken or to be taken

NIMH solicits applications on the mental health aspects of physical disorders through the program announcement (PA) "Research on Co-Morbid Mental and Other Physical Disorders."

With regard to a possible association between psoriasis and autism, NIMH supports an investigation into the association of pregnancy and birth complications with autism and other severe mental disorders. Using the medical birth register and psychiatric case register of Denmark for births from 1973-1993, investigators expect to identify over 1,000 cases of autism based on prevalence estimates in this population. Maternal health variables and other potential risk factors will be assessed. NIMH also funds a study of potential biological markers for autism, in which investigators will retrospectively analyze biological samples (maternal sera and neonatal blood samples) that were drawn as part of a state-mandated prenatal screening program in California. This study could provide evidence of associations between maternal health during pregnancy and autism.

In addition to these projects, NIMH continues to solicit research on the causes of autism through several mechanisms:

- NIMH led the development of the 2004 autism research "matrix" published in a major report to Congress that was produced by the Interagency Autism Coordinating Committee (IACC). The matrix calls for research that will identify environmental factors (which includes maternal health and other prenatal factors) contributing to autism. The matrix and report may be found at http://www.nimh.nih.gov/autismiacc/CongApprCommRep.pdf.
- NIMH in collaboration with NICHD, NINDS, NIDCD, and NIEHS will participate in implementation of the new Autism Centers of Excellence (ACE) Research Program. The ACE plans to issue a request for applications in early FY 2006. The ACE Centers will focus on the causes and best treatments of autism, as identified in the 2004 matrix.
- NIMH participates in a PA "Research on Autism and Autism Spectrum Disorders," which solicits research on the causes and treatments of autism.

Item

Psychological impacts of terrorism — The Committee supports NIMH research related to the psychological impact of both acute and chronic exposure to threats of violence, including terrorism and war, with particular emphasis on vulnerable populations, such as trauma survivors, children and older adults. The Committee encourages NIMH to expand its research portfolio to

include research related to factors that promote detection or prediction, prevention, and post-exposure recovery and resilience. (p.148)

Action taken or to be taken

NIMH has an active research program on the psychobiological impact of acute and chronic exposure to violence and threats of violence (e.g., war, terrorism, interpersonal violence, community violence, disasters, major accidents). The portfolio includes research initiated in response to fears of and actual terrorist attacks. For example, in the wake of the terror attacks of September 2001, NIMH supported studies on the nature and extent of mental health effects in the general population, as well as perceptions of exposure and compliance with public health and clinical interventions in the wake of anthrax episodes. Ongoing projects focus on understanding the origins of healthy and abnormal adjustment to stress, trauma and bereavement among children; the relationship between parental stress/fear and child mental health; novel interventions for first responders and survivors; and services research on the types of care that are available and accessed as well as barriers to care.

To enhance prediction, prevention, and recovery from the psychological effects of trauma, NIMH is supporting prospective longitudinal studies to improve pre-morbid identification of those most likely to suffer chronic psychological effects, including studies to understand the interaction of environmental events, individual/biological factors, and social factors. NIMH is also supporting cutting-edge early intervention/prevention trials of medications and psychosocial therapies to advance prevention and post-exposure recovery. Noteworthy among these studies is one that is screening thousands of trauma victims (terrorism, accidents, interpersonal violence) at the emergency room of an Israeli hospital and tracking the development of post-traumatic stress disorder (PTSD) and depression while studying the efficacy and effectiveness of early intervention.

To further enhance the NIMH portfolio on prediction, prevention, and post-exposure recovery and resilience, NIMH sponsors scientific workshops; coordinates within and across DHHS, DHS, DOJ, VA, DOD research agencies; and co-sponsors state-of-the-science meetings to summarize research advances and generate practice guidance.

In order to be responsive to scientific recommendations of the Institute of Medicine Report "Preparing for the Psychological Consequences of Terrorism – A Public Health Strategy" and the U.S. Department of Health and Human Services "Strategic Plan to Combat Bioterrorism and Other Public Health Emergencies," NIMH has consolidated its research efforts related to mass trauma and terrorism into one program. The objective of this interdisciplinary program is to coordinate research within and between agencies, improve epidemiology and surveillance, and improve understanding of and interventions for acute and chronic PTSD.

Item

Suicide — In addition to being disabling and chronic, mental disorders can be fatal. Depression is an important risk factor for suicide, the third leading cause of death among adolescents. The Committee notes that there are far more suicides each year in this country than there are homicides. The Committee supports NIMH efforts to enhance suicide awareness and prevention, and encourages the institute to continue its ongoing collaborative efforts with other institutes and

with SAMHSA to address this painful topic. (p. 148)

Action taken or to be taken

NIMH supports a number of research initiatives aimed at understanding suicidal behavior in all age groups and identifying risk factors that can be reduced through preventive interventions. These interventions need to be effective as well as safe. While it is an important public health fact that suicide risk is increased in the presence of depression, conveying such information in an effective and safe manner to various audiences (e.g., individuals at risk, family members, health care providers, teachers) requires systematic research. In a 2003 NIMH workshop focused on public messaging for suicide prevention, cosponsored by SAMHSA and CDC, significant concern was raised about "normalizing" suicide as an outcome of depression for various populations. Since that workshop the NIMH staff have supported several scientific panels on approaches to developing and testing safe suicide awareness and prevention efforts.

NIMH-supported research has shown that a depression intervention for older adults in primary care can reduce suicidality and possibly mortality. An intervention using cognitive therapy for suicidal individuals seeking care in emergency departments reduced re-attempt rates by half. Dissemination research to learn how to implement these effective interventions in other settings is in its early stages. Recently, NIMH provided support for experts to present on topics that included "lessons learned" on community messaging and adolescent help-seeking at a SAMHSA meeting of Garrett Lee Smith Memorial Act grantees. NIMH staff also collaborate with SAMHSA on anti-stigma campaigns for mental disorders and opportunities with the entertainment industry to acknowledge accurate media coverage of mental disorders. With IHS, SAMHSA, NIDA, NIAAA, Health Canada and the Canadian Institutes of Health Research, NIMH is also supporting an international conference on indigenous suicide prevention, with a major focus on asking American Indian and Alaska Native communities about their perceptions of suicide and its risk and protective factors.

NIMH has a significant investment in research aimed at understanding suicidal behavior in adolescence and identifying risk factors that can be reduced through preventive interventions. Much of this research support is focused on clinic-based studies that examine the rates, clinical course and service use patterns of adolescents who are depressed and suicidal, as well as studies to identify risk factors and improve preventive interventions. For example, NIMH supports a pilot study on the effects of pharmacological, psychotherapeutic and combined interventions for high-risk depressed adolescents who have recently attempted suicide. In partnership with the NIDA, NIAAA and the American Foundation for Suicide Prevention, the Institute funds three research centers that are entirely devoted to suicide prevention efforts. The focus of these centers is on the development of new trials to reduce adolescent suicidality, particularly among youth with substance use and mood disorders. In conjunction with several other NIH funded centers (including a VA-funded site), the centers are working together to coordinate activities to improve research methodology in the study of suicidality, including standardizing measurement of suicide risk and side effects and exploring the role of impulsivity.

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2006 Amount Authorized	FY 2006 Appropriation	2007 Amount Authorized	FY 2007 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,346,257,000	Indefinite	$1,337,834,000
National Institute of Mental Health	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	57,258,000		56,972,000
Total, Budget Authority				1,403,515,000		1,394,806,000

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

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1998	628,739,000 2/	744,235,000	759,956,000	750,241,000
1999	699,679,000 2/ 3/	815,707,000	861,208,000	861,208,000
Rescission				(570,000)
2000	758,892,000 2/	930,436,000	969,494,000	978,360,000
Rescission				(5,214,000)
2001	896,059,000 2/	1,114,638,000	1,117,928,000	1,107,028,000
Rescission				(492,000)
2002	1,238,305,000	1,228,780,000	1,279,383,000	1,248,626,000
Rescission				(533,000)
2003	1,359,008,000	1,359,008,000	1,350,788,000	1,349,788,000
Rescission				(8,774,000)
2004	1,382,114,000	1,382,114,000	1,391,114,000	1,390,714,000
Rescission				(8,940,000)
2005	1,420,609,000	1,420,609,000	1,436,800,000	1,423,609,000
Rescission				(11,676,000)
2006	1,417,692,000	1,417,692,000	1,460,393,000	1,417,692,000
Rescission				(14,177,000)
2007	1,394,806,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research
3/ Reflects a decrease of $2,111,000 for the budget amendment for Bioterrorism

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	89	89	90
Division of Neuroscience and Basic Behavioral Science	30	30	31
Division of AIDS and Health and Behavior Research	23	23	23
Division of Services and Intervention Research	27	28	28
Division of Adult Translational Research and Treatment Development	14	14	15
Division of Pediatric Translational Research and Treatment Development	11	11	12
Division of Extramural Activities	43	43	43
Division of Intramural Research Programs	425	460	460
Total	662	698	702
Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research			
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2003	11.2
2004	11.6
2005	11.7
2006	11.7
2007	11.7

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

Detail of Positions

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	5	5	5
Total - ES Salary	$758,699	$775,390	$800,978
GM/GS-15	50	51	51
GM/GS-14	77	80	82
GM/GS-13	78	84	85
GS-12	74	80	81
GS-11	69	76	76
GS-10	1	1	1
GS-9	56	58	58
GS-8	27	34	34
GS-7	21	24	24
GS-6	5	6	6
GS-5	2	2	2
GS-4	1	1	1
GS-3	0	0	0
GS-2	0	0	0
GS-1	0	0	0
Subtotal	461	497	501
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	9	9	9
Senior Grade	1	1	1
Full Grade	0	0	0
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	10	10	10
Ungraded	186	186	186
Total permanent positions	478	514	518
Total positions, end of year	662	698	702
Total full-time equivalent (FTE) employment,end of year	662	698	702
Average ES salary	$151,740	$155,078	$160,196
Average GM/GS grade	11.7	11.7	11.7
Average GM/GS salary	$79,423	$81,170	$83,849

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

NATIONAL INSTITUTES OF HEALTH
National Institute of Mental Health

New Positions Requested

	FY 2007		
	Grade	Number	Annual Salary
Health Science Administrator	GS-14	2	$111,666
Health Science Administrator	GS-13	1	93,063
Program Analyst	GS-12	1	77,122
Total Requested		4	