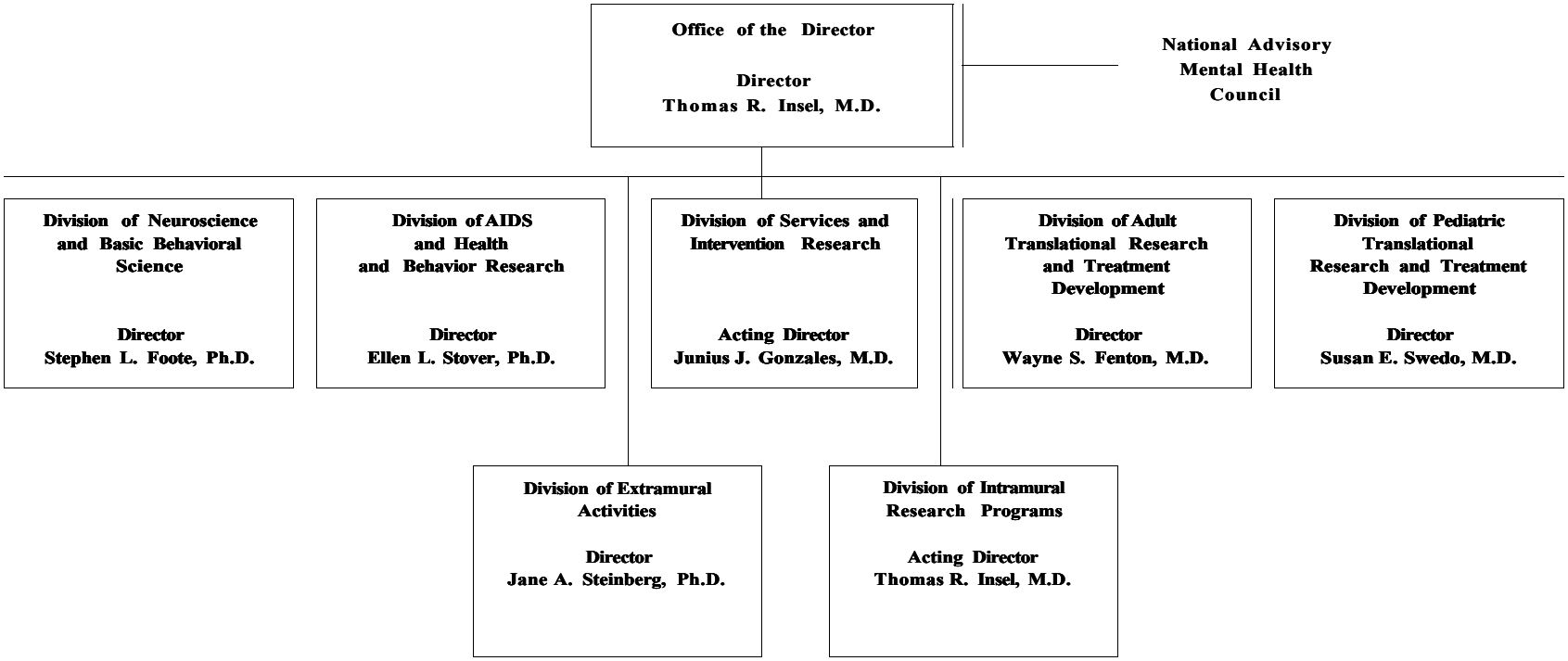
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Mental Health

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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 $1,423,609,000, *[$1,417,692,000]*.

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

National Institutes of Health
National Institute of Mental Health

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$1,390,714,000	$1,423,609,000	$1,417,692,000
Enacted Rescissions	(8,940,000)	(11,676,000)	0
Subtotal, Adjusted Appropriation	1,381,774,000	1,411,933,000	1,417,692,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	(2,549,000)	0	0
Comparative transfer to NIBIB for Radiology Program	(102,000)	0	0
Comparative transfer to Buildings and Facilities	(406,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	2,549,000	0	0
Subtotal, adjusted budget authority	1,381,266,000	1,411,933,000	1,417,692,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,381,266,000	1,411,933,000	1,417,692,000
Unobligated balance lapsing	0	0	0
Total obligations	1,381,266,000	1,411,933,000	1,417,692,000

V Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $3,735,000; FY 2005 - $3,800,000; FY 2006 - $3,800,000
Excludes $256,570 in FY 2005 and $256,570 in FY 2006 for royalties.

Justification

National Institute of Mental Health

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

Budget Authority:

FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
690	$1,381,266,000	716	$1,411,933,000	716	$1,417,692,000	—	$5,759,000

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

INTRODUCTION

The National Institute of Mental Health (NIMH) supports research on mind, brain, and behavior with the aim of reducing the public health burden of mental and behavioral disorders. Armed with new scientific discoveries and powerful new tools, researchers stand poised to elucidate long-standing mysteries about the mechanisms involved in the pathophysiology of mental disorders. This is a vital step in the development of more effective strategies to manage, treat, and even prevent these debilitating disorders. NIMH's ultimate goal is to generate research that will transform the prevention of, and recovery from, mental disorders.

The landmark report of the President's New Freedom Commission: Achieving the Promise - Transforming Mental Health Care in America defined the challenge. The burden of these disorders is staggering, in terms of both morbidity and mortality. Mental illness represents four of the top six sources of disability from medical causes for Americans ages 15-44[1]; suicide accounts for more deaths each year than either homicide or AIDS[2]. Recent estimates put the economic costs of treating mental disorders at $150 billion, with elements of these costs increasing beyond 20 percent per year[3]. The President's Commission report called for a

[1] The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020 by Christopher J. L. Murray, Alan D. Lopez, Harvard School of Public Health, World Health Organization, World Bank.

[2] World Health Organization, World Report on Violence and Health. Geneva, 2002.

[3] New Freedom Commission on Mental Health, Achieving the Promise: Transforming Mental Health Care in America. DHHS Pub. No. SMA-03-3831. Rockville, MD, 2003.

transformation of mental health care, with a focus on consumers and families, with increased access to science-based treatments, and with recovery as a goal.

NIMH is now faced with the challenge of continuing a remarkable period of scientific achievement brought about during a time of major budgetary expansion that is scheduled to diminish. In light of the increasing burden of mental illness coupled with slowing fiscal growth, NIMH worked this past year to seek creative ways in which to optimize its impact on public health; the Institute and its major stakeholders endeavored to reevaluate priorities for funding research. To help with this process, two workgroups of the National Advisory Mental Health Council were formed: one to review the NIMH extramural clinical treatment portfolio and one to review the basic sciences research portfolio.

The goal of the clinical treatment workgroup was to help NIMH focus strategically in its support of therapeutics and interventions research, which includes more than 100 treatment studies addressing clinical questions that go beyond the scope and mission of the trials conducted by the private sector. The workgroup's report: *Treatment Research in Mental Illness: Improving the National's Public Mental Health Care Through NIMH-funded Interventions Research* describes clinical areas where more study is essential, such as treatment adherence, and urges increased innovation as well as a sharpened focus on amplifying the impact on clinical practice. The report also cites the need for an expansion of core resources and clinical trials infrastructure in order for NIMH to enhance its treatment development capacity. The workgroup reviewing the basic sciences research portfolio evaluated priorities using three major criteria: (1) *relevance*—whether proposed activities pertain to the NIMH mission of reducing the burden of mental and behavioral disorders; (2) *traction*—which research areas are poised for rapid progress because of access to new research tools or recent scientific advances; and (3) *innovation*—emphasizing "discovery" science that may lack extensive pilot data, but which is extremely relevant and could provide an enormous pay-off.

In its report *Setting Priorities for the Basic Sciences of Brain and Behavior* (2004), the workgroup outlines specific tools and areas of research particularly ripe for increased investment, such as the pathophysiology of mental disorders and the translation of basic science discoveries into biomarkers, diagnostic tests, and new treatments. Translation of basic science to clinical issues and integration of behavioral advances with brain sciences is now a major focus of the Institute, as it will be imperative to reduce the growing burden of mental disorders.

To facilitate this essential translation and integration, NIMH reorganized its extramural programs into five research divisions (from three): basic science, translational research for adults, translational research for children and adolescents, behavioral effects on health (including HIV/AIDS spread and prevention), and psychiatric services and interventions. A key aim of the reorganization is ensuring and accelerating translation of the best ideas in neuroscience research into the clinics and out to the community.

This is a time of great excitement in mental health research. Rapid advances are revealing the biological and environmental components of major mental illness. The science for recovery will require the translation of discoveries on brain and behavior into better diagnostic tests (genetics), biomarkers of disease (imaging), and personalized treatments (clinical trials). These discoveries

hold great promise for achieving the ultimate goal of recovery for every American struggling with mental illness.

SCIENCE ADVANCES AND STORY OF DISCOVERY

GENETICS

In this "golden age of neuroscience," genetics is the bedrock science of the complex processes of the brain and behavior. Still in its infancy, genetic science holds the key to therapies that can address not just the symptoms of mental disease but its root causes as well. Numerous advances were made in the field of genetics this year. Below is a compilation of some of the highlights from the past year.

In December 2003, *Science* magazine named the collective identification of genes that control risk for mental disorders such as schizophrenia, depression, and bipolar disorder, as one of the year's most significant scientific breakthroughs, second in importance only to advances in understanding the cosmos. The NIMH funded most of the research that led to these key discoveries in genetics, as well as studies of environmental influences suspected of increasing individuals' risk for psychiatric illness and disorders of the brain. Since then, NIMH-funded researchers have replicated the dramatic early findings and gone on to add new discoveries that expand our understanding of the genetic risk architecture for mental disease.

For example, several new discoveries were made in schizophrenia research this year. NIMH intramural scientists have identified a relationship between a gene called GRM3, which governs the activity of glutamate, and a group of traits known to be associated with schizophrenia. Glutamate is a key neurotransmitter in the brain. Neurotransmitters are critical in communication between neurons, which is important for various processes including learning, memory, and mood regulation. Glutamate has long been thought to play a role in schizophrenia, as it has an impact on brain physiology and cognition. Many of the genes previously identified as likely candidates for the disorder have been thought to affect the glutamate system.

Another recent genetic investigation into schizophrenia identified three variations on the TRAR4 region of chromosome 6 as likely causes of susceptibility for the disorder. Although the precise details of how TRAR4 works are not yet understood, its identification suggests that the disorder may be influenced by a dopamine malfunction, as many have long suspected, and opens up new avenues for schizophrenia research. Another dopamine-related gene, the PPP3CC gene, was also found to be a potential vulnerability gene for schizophrenia. PPP3CC codes for a substance called calcineurin, which helps regulate dopamine. In other investigations, NIMH researchers identified potential genetic markers for schizophrenia on the CAPON gene on chromosome 1, using a detailed genetic map of 24 families with the disease over several generations. Together, these investigations are helping to identify neural regions and pathways that can be targeted for more intensive neurobiological studies. The goal is to eventually develop new medications with lower risks of unwanted side effects.

NIMH genetic investigations have also revealed that mutations in the human serotonin transporter gene, hSERT, appear to be associated with obsessive compulsive disorder (OCD) and

obsessive compulsive personality disorder, and possibly with anorexia nervosa (AN), Asperger's syndrome, social phobia, tic disorder, and alcohol or other substance abuse/dependence.

Progress has also been made in bipolar disorder. Using genetic profiles of families with bipolar disorder, Japanese researchers found an alteration in a gene called XBP1, involved in the cellular response to stress. The gene was highly expressed in the prefrontal cortex (the area of the brain responsible for higher thinking and which also affects the ability to express emotions). Preliminary data suggest that valproate, one of the mood stabilizers, can ameliorate the effects of an altered XBP1 gene, warranting a large scale clinical trial to establish whether treatment for mood disorders can be customized according to each person's genetic risk.

This growing roster of genes implicated in mental disease brings us ever closer to diagnostic tests for early detection, better strategies for prevention, and new targets for treatment. Yet until fairly recently, researchers lacked sufficient data to begin to identify many of the genetic and molecular mechanisms leading to mental illness. Recognizing this fundamental problem, in 1989 the NIMH launched the *NIMH Human Genetics Initiative* (HGI) to collect data on families with a history of mental illness and to distribute that data to the scientific community worldwide. As the discoveries described above confirm, the HGI's massive dataset has already demonstrated its tremendous value as a community resource for mapping vulnerability genes, studying the interaction between genes and their environment, and identifying the neural circuits and pathways associated with different disorders - all of which are necessary to develop more effective therapeutic drugs. The initial focus of the HGI was on schizophrenia, bipolar disorder, and Alzheimer's disease. In the years since, it has expanded to include early-onset recurrent depression. The HGI has now collected comprehensive clinical information from more than 800 individuals and 300 families with early-onset, recurrent depression, a variant whose genetic mechanisms should be easier to map because it is highly heritable. Initial analyses of the HGI data confirmed that it is a chronic condition often associated with other mental problems, such as panic disorder, social phobias, and suicidal behavior. The dataset will continue to be broadly distributed to the neuroscience community.

Story of Discovery: Epigenetics and Mental Health

Since Watson and Crick identified the double-helix of DNA in the 1950s, the study of genetics has become increasingly central in biomedical research. But while DNA contains the blueprints for the manufacture of all the proteins needed for life, biological development is also shaped by a variety of other influences - among them "epigenetic" factors, which provide additional instructions on how, where, and when the genetic information should be used.

Epigenetics is a relatively new field of study, brought to the foreground with recent developments in the search to understand the causes of disease. Many people credit the biologist Conrad Waddington with coining the term in 1942 when he used it to describe his theory on developmental biology. At the time, many scientists thought that throughout development the genome constantly changed as cells differentiated. But Waddington suggested instead that genes remained structurally stable, merely turning on and off to produce the many types of cells in the body. In the 1950s, a number of experiments helped prove his idea, that the genes themselves were not altered in development.

Over the years, researchers have learned that two epigenetic mechanisms can cause prolonged differences in gene expression. The first is methylation - the process by which the addition of a methyl group to DNA can silence genes, be it briefly or for substantial portions of a lifetime. Conversely, when a methyl group is removed from the

gene (i.e., the DNA is demethylated) it usually leads to a significantly increased expression of the gene's protein product.

In the last 5-7 years, researchers have clearly demonstrated a second method that influences gene expression: the way in which long strands of DNA are packaged into the nucleus of the cell. The DNA is firmly wound around proteins called histones, like thread around a spool. The DNA and proteins together are called chromatin, which is folded over and over upon itself into a tight package. However, for the cellular machinery to reach the DNA and activate a gene or repair DNA damage, segments of the chromatin must be unraveled. The unraveling is achieved by different enzymes that slightly modify the chemical structure of the histones. For example, one type of enzyme adds acetyl groups to histones, decreasing the ability of histones to bind to DNA. As a result, the DNA unwinds from the histones, making the DNA available for other cellular machinery to come in and do its vital work.

Scientists studying mental disorders have been investigating the implications of epigenetic influences in both normal and disease processes: learning, memory, response to stress, mood and anxiety disorders, autism, and bipolar disorder, to name a few. Three recent studies have paved the way toward further understanding some of these areas. For instance, NIMH grantees have recently found that the addition of acetyl groups to histones is critical for long-term memory formation. When rats are trained on behavioral tasks that stimulate learning and memory formation, certain types of histones become acetylated. They also discovered that mice lacking the enzymes that cause acetylation have impaired long-term memory. As a result of this enzyme deficiency, presumably chromatin cannot unravel, and the genes involved in memory consolidation cannot be activated. In addition, the scientists demonstrated that memory can be enhanced by administering a drug that promotes endurance of acetyl groups surrounding histones—thereby slowing their re-spooling with DNA, so the genes needed for memory formation can be further activated.

In another study, this time using sea slugs as a model, researchers supported by NIMH worked with an enzyme called PARP1, which also facilitates the unraveling of chromatin by chemically modifying histones, and which is activated in response to DNA damage—presumably to allow the cellular machinery to access and repair the DNA. The researchers found that PARP1 may also permit activation of genes responsible for the consolidation of long-term memories. Because PARP1 has a dual role in memory formation and DNA repair, the scientists hypothesize that learning might have evolved as a cell's response to stress or injury.

Taken together, these results suggest that therapeutics that selectively unravel segments of chromatin could be used to treat some types of cognitive impairment or to enhance long-term memory.

In a third epigenetic study, this one in rats, scientists showed for the first time how behavioral events—in this case early maternal care—actually can lead to activation (via demethylation) of the genes regulating their offspring's ability to withstand stress throughout the lifespan.

The researchers found that mothers with a "caring" style of nurturing, involving pup licking, grooming, and arched-back nursing, increased the number of glucocorticoid receptors. (Glucocorticoids are stress hormones and the receptors are involved in the regulation of these hormones.) Nurtured pups had better control and a more modest response to stress than the pups raised by "non-caring" mothers. This improved stress response emerged in the first week of life and persisted into adulthood. But if the rat pups of caring mothers were switched to non-caring foster mothers within 12 hours of birth, the pups' later responses to stress reflected the style of the foster mother rather than the biological mother.

The mechanism driving this change was the demethylation of a key area on the gene coding for the glucocorticoid receptor, in response to the caring mother's grooming. Pharmacological tests then confirmed that maternal behavior was indeed the factor responsible for producing the stable alterations of DNA methylation and chromatin structure - showing that behavior can mold gene expression.

These experiments tell us that early experience can have lifelong consequences, from the molecular to the behavioral level - and such changes appear to be reversible within a certain window of time. Understanding the mechanisms by which we might provide treatments to enhance the effect of early life experiences will be an important avenue for future investigation of mental and other disorders.

BASIC SCIENCE FOR TRANSLATION

Brain Development

Imaging Study Reveals Slow Maturation Timeline for the Cortex. NIMH intramural researchers in collaboration with grantees have conducted a decade-long MRI study of normal brain development from ages 5 to 20. The study shows that the prefrontal cortex, responsible for reasoning and problem solving, does not develop fully until young adulthood. A time-lapse 3-D movie that compresses 15 years of human brain maturation into just seconds shows gray matter - the working tissue of the brain's cortex—diminishing in a back-to-front wave, likely reflecting the pruning of unused neuronal connections during the teen years. Cortex areas can be seen maturing at ages in which relevant cognitive and functional developmental milestones occur. It was long believed that a spurt of overproduction of gray matter during the first 18 months of life was followed by a steady decline as unused circuitry is discarded. Then, in the late l990s, the co¬ author of the current study and his colleagues discovered a second wave of overproduction of gray matter just prior to puberty, followed by a second bout of pruning during the teen years. The new study finds that the first areas to mature (e.g., extreme front and back of the brain) are those with the most basic functions, such as processing the senses and movement. Areas involved in spatial orientation and language (parietal lobes) follow. Areas with more advanced functions—integrating information from the senses, reasoning, and other "executive" functions (prefrontal cortex)—mature last. These findings on normal brain development help shed light on previous research showing brain changes that occur in neurodevelopmental disorders such as schizophrenia and autism. Research with teenagers with a rare form of schizophrenia that develops prior to puberty showed that they lost four times the normal amount of gray matter in their frontal lobes—suggesting that childhood onset schizophrenia may be an exaggeration of a normal maturation process. By contrast, research in children with autism showed an abnormal *increase* in gray matter, rather than a decrease. Further studies on neurodevelopmental processes will help us understand the causes, treatment or prevention of mental illness.

Developmental Processes During Puberty Regulate Stress Responses. Adolescence is marked by increased susceptibility to mental disorders and drug use, conditions that appear to be exacerbated by stress. When confronted with stress, certain organs in the body secrete hormones that initiate a cascade of reactions, such as a rush of energy and alertness, allowing an individual to respond quickly to a perceived threat. Normally, these organs provide each other feedback, indicating whether hormone release should be shut off. For reasons that are unclear, sometimes the floodgates do not close and hormone levels stay too high. Previous studies have suggested that male juvenile rats show exaggerated and prolonged hormonal responses to stress compared with adults. Since testosterone decreases stress responses, NIMH grantees questioned whether the exaggerated stress response could be due to lower testosterone levels in juvenile animals. To test this hypothesis, the researchers induced stress in adult or juvenile male rats by restraining their movement, and then measured concentrations of stress hormones in the blood. The researchers confirmed that following exposure to stress, higher levels of stress hormones were released for a prolonged duration in juvenile rats. These data suggest that the body's mechanism for controlling stress responses continues to develop during adolescence. Therefore, the juvenile brain may be more vulnerable to the physiological effects of stress than the adult brain. This work highlights the importance for future research to clarify the impact of stress hormones on the

nervous system during puberty and to determine whether chronic or acute stress during puberty will alter physiology and behavior in adulthood.

Riding the CREST of Neural Development And Plasticity. As the human brain develops and matures, it must maintain a certain degree of malleability—or neuronal plasticity—in order to constantly adapt to and learn from the myriad of new experiences encountered throughout the lifespan. One form of neuronal plasticity is to change the strength of connections between neurons, which can be achieved by altering the number of dendrites on a neuron. Dendrites are short, highly branched extensions that emanate from a neuron and are responsible for receiving and integrating signals from other neurons. The structure and branching of dendrites influence how a neuron integrates the signals it receives, and it is thought that neuronal signaling events—specifically those that involve calcium—mediate the growth, rearrangement, and pruning of dendrites. An NIMH grantee has made a critical advance in the understanding of how calcium-induced gene activation affects dendrite growth and neuronal plasticity. The scientists identified a new molecule called CREST (Calcium-Responsive Transactivator), a protein that interacts with gene-activating proteins in response to neuronal activity (and calcium influx) to increase the expression of the genes involved in dendrite growth. In mice that were bred to lack CREST, many dendrites in the cerebral cortex did not develop normally—they were shorter and less branched. The researchers also discovered that CREST is normally expressed in the adult mouse hippocampus, a brain region important for learning and memory that exhibits neuronal plasticity throughout the lifespan. These results suggest that CREST function is required for dendrite growth in response to neuronal activity—findings that increase our understanding of how neuronal activity creates and maintains the circuitry necessary for learning and memory.

Gender Differences in the Brain Influenced by Cell Death. Mental disorders, such as ADHD and depression, affect males and females differently; some of these disorders are more prevalent in one sex than another, or may even cause different symptoms. These gender differences may be explained by sexual dimorphism—a physical distinction between the sexes, which exists in many species. For example, male mammals are usually larger than females, while male birds are often more brightly colored than their female counterparts. Similarly, sexual dimorphism can exist in the brain. The establishment of male or female characteristics in the brain is directed, in part, by the influence of reproductive hormones on cell survival during development. The developing brain generates many more cells than it needs, but once the brain is wired, surplus cells and faulty cells are eliminated by a process called programmed cell death. Recent studies by NIMH grantees suggest that a protein called Bax, which is involved in programmed cell death, controls developmental events that establish sexual dimorphism in specific nuclei, or groups of neurons in the mouse forebrain. Normally, one nucleus, designated AVPV, contains more neurons in females, while another nucleus, called BNSTp, has more neurons in males. The researchers discovered that eliminating, or "knocking-out," the Bax gene abolished these gender differences. These results suggest that deletion of the Bax gene rescued neurons that would have otherwise been eliminated by programmed cell death as the animals matured. These studies will increase our understanding of the gender differences in the brain that may confer susceptibility to mental disorders, hopefully facilitating the development of better therapies.

Learning. Memory, and Cosnition

Imaging Reveals Human Brain Regions Involved In Extinguishing Fear. Effective treatment for post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and other anxiety disorders requires an understanding of the brain systems that control fear. "Extinction" refers to a reduction of fear following repeated exposure to a fearful event without unpleasant consequences. For example, if a child falls when learning to ride a bike, he or she may be afraid to try again. However, this fear will eventually dissipate when the child later rides without falling. Studies in both animals and humans indicate that the extinction of a previously learned fear represents a new form of learning rather than the forgetting of the original fear. In a recent study supported by NIMH, researchers used functional magnetic resonance imaging (fMRI) to examine the brain activation patterns in humans during the acquisition and extinction of fear responses. The scientists found that activity in the amygdala, a region critical for emotion, correlated with the acquisition and early extinction of the initial fear. In contrast, activity in the ventral medial prefrontal cortex (vmPFC), a region associated with the regulation of higher cognitive function, correlated with longer-term extinction of the fear. Activity in the vmPFC was predictive of how well the subjects remembered the extinction training. While previous studies in animals have implicated the vmPFC in the long-term extinction of fear responses, this translational study is the first to demonstrate the importance of this brain region for fear extinction in humans. The knowledge of how fears are acquired and diminished will provide important contributions to the understanding and treatment of anxiety disorders.

Understanding Proteins that Control Different Types of Learning. The cellular basis of learning and memory relies on the strengthening of connections between signaling neurons. In recent years, studies to understand the cellular processes underlying learning and memory have focused on changes in neurons that *receive* signals, rather than the neurons that *transmit* signals. NIMH funded researchers are the first to demonstrate that eliminating a protein called RIM 1a in the transmitting neuron can cause deficits in certain cognitive functions, while sparing motor coordination and other behaviors. The researchers showed that mice lacking RIM1a are deficient in several forms of long-term potentiation (LTP) —the strengthening of the connection between two neurons for an extended period of time. LTP is thought to be important for learning and memory. In addition, mice lacking RIM1a exhibit severe behavioral impairments in associative learning—a process in which discrete concepts or situations that are experienced together become linked. For example, if a mouse hears an auditory tone at the same time that it receives a foot shock, the mouse will become fearful of the tone because it associates the sound with pain. Mice deficient in RIM1a, however, do not learn this type of associated fear. The deletion of RIM1a may compromise some forms of neuronal signaling and thus, specific types of learning.

Brain Signal Predicts Working Memory Prowess. Some people are better than others at remembering what they have just seen, i.e., holding mental pictures in mind from moment to moment. An individual's capacity for such visual working memory can be predicted by his or her brainwaves, according to new NIMH supported research. A key brain electrical signal leveled off when the number of objects held in mind exceeded a subject's capacity to accurately remember them, while it continued to soar in those with higher capacity. Neural activity of subjects with poorer working memory scores leveled off early, showing little or no increase

when the number of objects to remember increased from two to four, while those with high capacity, who correctly remembered more objects, showed large increases. Since working memory capacity is strongly predictive of performance on a broad array of cognitive abilities—reasoning, language, flexible problem solving—investigators foresee the physiological measure may be used in applications assessing individuals who are behaviorally or verbally impaired, such as in cases of stroke or paralysis. The technique has also been used to study development of cognitive abilities in pre-verbal children.

Rare Deficit Reveals Thinking Circuitry. Using brain imaging, NIMH neuroscientists have pinpointed the site of a defect in a brain circuit associated with a specific thinking deficit. Their study demonstrates how a rare genetic disorder, Williams Syndrome, can offer clues on how genetic flaws may translate into cognitive symptoms in more common and complex major mental disorders. The study focused on the inability to visualize an object as a set of parts and then construct a replica, as in assembling a puzzle - a key cognitive deficit experienced by people with Williams Syndrome. Researchers used magnetic resonance imaging (MRI) to trace the thinking deficit to a circuit at the back of the brain that processes locations of objects in the visual field. In addition to this visuospatial construction deficit, people with Williams Syndrome also tend to be overly friendly and anxious and often have mental retardation and learning disabilities. Compared to most mental disorders, which are thought to involve complex interactions between multiple genes and environmental triggers, the genetic basis of Williams Syndrome is remarkably well understood. People with the disorder lack about 21 genes in a particular part of chromosome 7. According to the researchers, Williams Syndrome offers a unique opportunity to study how genes influence our ability to construct our social and spatial worlds. Studying people with this disorder can help investigators discover how genetic mutations change molecular and cellular processes and lead to differences in the brain circuitry for complex aspects of cognition.

Newly Discovered Molecules Provide Clues to Biology of Learning. Before researchers can design medications that enhance brain function and correct cognitive deficits, they must first understand the molecular mechanisms at work in a living brain. Learning and memory, for instance, are believed to be controlled by changes in the strength of connections between neurons, known as synaptic plasticity. To relay a signal in the brain, neurons communicate with each other using chemical messengers called neurotransmitters. To initiate a signal, a neuron releases neurotransmitters into the synapse—the gap between neighboring neurons. After crossing the synapse, neurotransmitter molecules bind to receptors on the surface of the neighboring neuron, creating a cascade of molecular changes that alter the neuron's function. Because the interactions between neurotransmitters and their receptors ultimately determine the strength of neuronal connections, the number of receptors on the cell surface must be carefully regulated. NIMH-funded researchers are teasing apart the intricate molecular processes that control the behavior of receptors for the neurotransmitter glutamate. Unlike many neurotransmitter receptors that reside stably at the cell surface, some glutamate receptors continuously cycle in and out of the neuronal membrane. This dynamic behavior of glutamate receptors is thought to be an important mechanism for regulating synaptic plasticity. Several years ago, NIMH grantees discovered the stargazin family of proteins and demonstrated that stargazins help to escort glutamate receptors to the cell surface. Recently, the investigators further characterized the relationship between stargazins and glutamate receptors, demonstrating

that upon binding with glutamate, the receptors dissociate from their stargazin chaperones. As a result, the glutamate receptor disappears inside of the cell, leaving stargazins behind on the surface. While the role of glutamate receptor cycling in synaptic plasticity is unclear, this study brings researchers a step closer to understanding the molecular control of learning and memory.

Memory, **Receptor Trafficking, and Endosomes.** Learning and memory is thought to be partly controlled by a process in the brain called long-term potentiation (LTP)—the strengthening of the connection between two neurons—an effect that can last anywhere from days to months. LTP occurs when neurons signal frequently or strongly, and as a result, their connections are strengthened to facilitate future communication. During LTP, signaling strength can be changed by adding more neurotransmitter receptors to the surface of a neuron. NIMH grantees have shown that AMPA receptors—a type of receptor that is necessary to strengthen signaling during LTP—are shuttled to the surface of the neuron by bubble-shaped structures called endosomes. Endosomes are formed when pieces of the cell membrane pinch off inside the cell, taking anything that is on the cell surface—like AMPA receptors—with them. Endosomes are continuously recycled and can later fuse with the cell membrane, restoring the AMPA receptors to the cell surface. The NIMH-funded researchers demonstrated that triggering LTP accelerates the recycling of endosomes and the insertion of AMPA receptors into the cell membrane. However, when endosome recycling is blocked, the AMPA receptors are trapped within the endosomes and cannot migrate to the cell membrane. In addition, blocking the transport of AMPA receptors out of endosomes completely abolishes LTP. These findings provide us with a better understanding of the cellular changes that control the neuronal signaling important for learning and memory. They provide guidance for future studies directed at developing drugs that could improve cognitive deficits in mental disorders.

BIOMARKERS

Panic Disorder Patients Deficient in Emotion-Regulating Receptor. In people with panic disorder, it appears that three brain areas are lacking in a key component of a chemical messenger system that regulates emotion, according to a study by NIMH intramural researchers. Brain scans using a new type of tracer revealed that a type of serotonin receptor is reduced by nearly a third in three structures of the brain that mediate anxiety in patients with panic disorder. The finding is the first in living humans to show that the 5-HT1A receptor, which is pivotal to the action of anti-anxiety medications, may be abnormal in the disorder, and may help to explain how genes might influence vulnerability for panic and anxiety disorders in general. Previous research with animals had found that a strain of gene "knockout" mice, engineered to lack the receptor during a critical period in early development, exhibits anxiety traits in adulthood, such as a reluctance to begin eating in an unfamiliar environment. More recent experiments with the knockout mice show that a popular SSRI (selective serotonin-reuptake inhibitors) drug produces its anti-anxiety effects by stimulating the formation of new neurons in a brain area called the hippocampus via the serotonin 5-HT1A receptor. Noting the recent discovery of a variant of the 5-HT1A receptor gene linked to major depression and suicide, the researchers suggest that reduced expression of the receptor may be a source of vulnerability in humans, and that abnormal function of these receptors appears to specifically impact the cortical circuitry involved in the regulation of anxiety.

Depression Traced to Overactive Brain Circuit. Studies over the last 30 years have linked major depression to abnormally reduced function in serotonin systems. A recent study by NIMH intramural scientists using positron emission tomography (PET) brain imaging shows that an emotion-regulating brain circuit is overactive in people prone to **depression**—even when they are not depressed. Researchers discovered the abnormality in the brains of those whose depression relapsed when serotonin, a key chemical messenger, was experimentally reduced. Even when in remission, most subjects with a history of mood disorder experienced a temporary recurrence of symptoms when their brains were experimentally sapped of tryptophan, the chemical precursor of serotonin and the neurotransmitter that is boosted by antidepressants. Neither a placebo procedure in patients nor tryptophan depletion in healthy volunteers triggered the mood and brain activity changes. Brain scans revealed that a key emotion-processing circuit was overactive only in patients in remission—whether or not they had re-experienced symptoms—and not in controls. The finding suggests that tryptophan depletion unmasks an inborn trait associated with depression. This adds to evidence that a genetic predisposition that renders some people vulnerable to inadequate serotonin activity may be at the root of the mood disorder.

Perception Failures Illuminate Neural Flaws Behind Schizophrenia Symptoms. Abnormal visual processing of motion has been implicated as a possible basis for the disturbed perception and thinking that characterize schizophrenia. A series of targeted tests revealed that in a substantial proportion of people with schizophrenia—and their near relatives—eye-tracking was abnormal. Humans track moving objects by looking at the object itself (local tracking) and in context (global tracking), with each tracking method controlled by a different set of neurons. Suspecting that eye-tracking problems reflect abnormalities in areas of the brain responsible for processing motion signals, the researchers designed tests to find out exactly which neurons are involved. Schizophrenia patients, they found, react normally in the local processing task but are slow to detect the direction of coherent motion. These results implicate malfunctions in the extrastriatal cortex as a possible neurological explanation for certain schizophrenia symptoms. In doing so, they suggest that learning practices designed to correct perception deficits might also prove an effective new tool for correcting some of the disturbed thinking that characterizes schizophrenia.

Imaging Pinpoints Brain Area That Directs "Cognitive Control." In this fast-paced world, people rapidly adjust their behavior in response to changing circumstances. Scientists believe that the brain adjusts behavior by a highly regulated process called cognitive control. Cognitive control can be exercised as one drives a car while also talking on a cell phone or crossing a busy street. These situations require a person to pay attention to the right information at the right time. In addition, cognitive control helps a person to overcome highly practiced and automatic behavior—such as when traveling in England—one must overcome the urge to look to the left when traffic comes from the right. Because cognitive control requires a lot of physiological effort, the brain needs to know when such exertion is necessary. Previous research has suggested that the prefrontal cortex (PFC) in the front of the brain executes cognitive control, but it has been unclear how the PFC is activated during this process. To determine what part of the brain initiates cognitive control, NIMH grantees used functional magnetic resonance imaging (fMRI) to scan the brains of subjects performing cognitive tasks. The tasks required subjects to adjust their behavior quickly in response to conflict—a counterintuitive situation that requires focus—

such as naming the color of a word printed in green ink when that word is "RED." During the experiment, the researchers found increased brain activity in the anterior cingulate cortex (ACC) in the middle of the brain. The increase in ACC activity was shortly followed by increased activity in the PFC. This study suggests that the ACC detects conflict, and then initiates cognitive control in the PFC. Similar experiments could be used to study deficits in cognitive control in individuals with mental disorders, such as those with schizophrenia, who have an underactive ACC that may result in chaotic and disorganized behavior.

DIAGNOSIS

Breakthroughs Offer Ways to Detect Alzheimer's Disease. Alzheimer's disease (AD) affects almost 10 percent of those over age 65 and almost half of those over age 85[4]. There is no known way to prevent the disease. Characterizing the brain changes associated with AD would help immensely toward developing primary prevention therapies. The optimal goal would be to thwart the disease at a very early age, decades before the onset of cognitive decline. Today, two groundbreaking discoveries put the promise of noninvasive early detection closer within reach. Tracking early Alzheimer's neurological effects, researchers in the NIMH-funded Human Brain Project compared brain activity in 13 healthy adults and 13 age-matched subjects diagnosed with mild dementia. Affected individuals showed reduced activity in the brain's inferior parietal lobes, which control mathematical and spatial tasks. Together with the posterior cingulate cortex, which also monitors spatial input and mediates between memories and emotion, this part of the brain forms a network that is largely inactive except during periods of rest (eyes closed) or in the performance of the simplest cognitive tasks. The researchers therefore hypothesized that these areas act as the brain's "default mode." Brain images revealed that metabolic changes in the "default mode" network triggered similar changes in the hippocampus, the brain's memory storehouse. Since abnormal function in the "default mode" network occurs even in the disease's mildest stages, they proposed brain imaging of these areas as a noninvasive way to screen for incipient Alzheimer's disease.

Combining imaging with genetics, a different team of NIMH-funded researchers recently identified a possible genetic marker for the disease—a variant of the gene that codes for APOE, a protein involved in metabolizing cholesterol. PET scans of apparently normal individuals in their fifties and sixties who carry this variant showed decreased activity in brain regions known to be affected by the disease. The researchers then scanned normal APOE variant carriers aged 20-39 and found lowered metabolism in the same brain areas. This groundbreaking work suggests that the pathological processes at work in Alzheimer's disease start decades before memory deficits become apparent. In discovering clinical markers for detection, NIMH researchers not only advanced understanding of this fearful disease, they also eliminated a key obstacle to the development of more effective treatments, management, and prevention.

Advances in Characterizing Early-stage Schizophrenia. The last decade has seen growing interest in the possibility of preventive treatment during the earliest, pre-psychotic stages of schizophrenia. Yet there is relatively little data on the key symptoms and deficits that

[4] Evans, D.A., Funkenstein, H. H., Albert, M. S., Scherr, P. A., Cook, N. R., Chown, M. J., Herbert, L. E., Hennekens, C. H. & Taylor, J. O. Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. J. Am. Med. Assoc. 262, 2551-2556, 1989.

characterize this early stage. In an attempt to address this, NIMH grantees examined 82 adolescents and young adults seeking treatment for mild schizophrenia symptoms. The most common complaint was social isolation. Patients also reported other symptoms not specific to schizophrenia such as declining performance at school, depressed mood, or anxiety. Almost as frequently, subjects reported "positive" symptoms such as magical beliefs or paranoid thinking. The pattern of presenting symptoms suggests the existence of three psychosis subgroups that differ according to nonspecific behavioral difficulties, type of mild positive symptoms, and signs of emerging psychosis. Thus, it may be that different interventions are needed at differing stages of symptom progression. Antidepressants, neuroprotective agents, cognitive enhancement strategies, and psychosocial treatment are likely worth further study for treating symptoms and even preventing progression to psychosis and schizophrenia.

An Emerging Type of Late-Life Depression. The causes of depression in the elderly and the factors affecting its course are not well understood. However it is known that genetic factors are less significant in people who become depressed for the first time in later life. Other factors, such as cerebral ischemia, are believed to play a role in the development of late-life depression. Ischemia occurs when blood flow to the brain becomes restricted because of a narrowed or blocked artery. This can occur for various reasons, such as a hemorrhage, a blood clot, cardiac disease, or vasoconstriction associated with migraine. Various MRI studies over the past 10 years suggest that ischemic changes leading to lesions in the white matter in the brain's frontal regions and basal ganglia may significantly contribute to the development of depression. In a recent study it was proposed that the term "subcortical ischemic depression" (SID) be used to describe vascular depression due to ischemic changes in the subcortex of the brain. In a recent NIMH funded study of 139 depressed elders, investigators sought to show that individuals with SID differ in clinical presentation from those depressed individuals without SID. The major finding was that more than half of elderly depressed community-dwelling subjects treated in tertiary care settings met the criteria for SID. Subjects with SID were significantly more likely to report a later age of depression onset, have a history of hypertension, and exhibit lassitude (slowness in initiating and performing everyday activities). Such subjects were significantly less likely to describe a family history of depression and less inclined to experience loss of libido. The authors conclude that this clinical syndrome description should be seen as part of a continuum of neuropsychiatric conditions associated with subcortical ischemic disease. These results contribute to the field's growing ability to improve prognosis and guide treatment in late-life depression.

The Hidden Epidemic of Depression in New Mothers. As much as 10 percent of all new mothers suffer from postpartum depression, which can leave enduring psychological scars on both families and children[5]. However, it frequently goes undetected in the typical 4-6 week obstetrical follow-up visit. Recognizing this failure, a large pediatric primary care practice offered all new mothers a short questionnaire at each well-child visit during the child's first year, beginning with the 2-week visit. Approximately half of all mothers completed the screening, with 27 percent of these reporting high levels of depressive symptoms. The fact that mental health referrals increased significantly after the initiation of the screening procedure suggests that well-child visits offer a favorable setting for the detection of postpartum depression. Treating

[5] Kumar R., Robson, K. A prospective study of emotional disorders in childbearing women. Br J Psychiatry; 144:35-47, 1984.

depression in new mothers, however, poses the added danger of exposing nursing infants to antidepressant drugs. NIMH researchers therefore developed a simple assay system to measure the breast milk concentrations of the twelve most commonly prescribed antidepressants (including the SSRIs and tricyclics). The simple, routine methodology they designed allows one technician to process 30 breast milk specimens a day and will allow researchers to develop the data required to set clinical guidelines regarding the exposure for infants of breastfeeding mothers who are being treated with antidepressant medications during the post-partum period.

TREATMENTS FOR RECOVERY

Combination Treatment Most Effective in Adolescents with Depression. Major depressive disorder in adolescence is common and is associated with significant morbidity and family burden. It is an important risk factor for suicide, the third leading cause of death among adolescents[6]. Depression in adolescence is also a major risk factor for long-term psychosocial impairment in adulthood. In the face of this enormous public health challenge, it is critical that safe and effective treatments are identified. At present, fluoxetine (Prozac) is the only FDA-approved medication for depression in children and adolescents—and there are conflicting results regarding its benefits and risks. In adults, studies indicate that fluoxetine in combination with cognitive behavioral therapy (CBT), is more effective against depression than either alone. But it was not known whether the same is true for adolescents. This is especially important in light of evidence that depression manifests quite differently in adolescents than in adults. To clarify the usefulness of treating adolescent depression with CBT, fluoxetine, or both, NIMH funded a multi-site, randomized, clinical trial involving 439 depressed adolescents at 13 sites nationwide. Results of the first 12 weeks of the Treatment for Adolescents with Depression Study (TADS), found that a combination of medication and CBT was the most effective treatment, with 71 percent responding to the combination of fluoxetine and CBT. Of the other three treatment groups, fluoxetine alone, with a 60.6 percent response rate, but not CBT (43.2 percent response) was significantly better than placebo (34.8 percent response). Clinically significant suicidal thinking, which was present in 29 percent of the participants at the beginning of the study, improved significantly in all four treatment groups, with those receiving medication and therapy showing the greatest reduction (below 8 percent). This is the first large, federally funded study using an antidepressant medication and CBT to successfully treat adolescents suffering with moderate to severe depression.

Brain Imaging Reveals How Different Therapies Work for Depression. Talk therapies and medications have both proven successful against depression. Yet until recently little was known about the neurological events in the brain that account for their therapeutic effect. Studies of medications suggest a "bottom up" series of events, in which the drug reduces feelings of depression by affecting metabolic activity in the lower parts of the brain (limbic region) that drive basic emotional behavior. By contrast, cognitive behavioral therapy (CBT), is thought to work "top down" by focusing on the cortical area, helping patients adopt healthier patterns of thought. In an effort to trace the neurological patterns behind therapeutic success, researchers took PET scans of the brains of 17 unmedicated depression patients before and after 15-20 sessions of CBT. These were then compared with scans of 13 outpatients on the antidepressant

[6] Arias, E., MacDorman, M. F., Strobino, D. M., Guyer, B. Annual summary of vital statistics - 2002. Pediatrics 112 (6pt1): 1215-1230, 2003.

paroxetine (Paxil). By study's end, both groups had improved and both showed changes in brain function. Significantly, the pattern of change differed with the type of therapy received. The researchers observed that patients who received cognitive behavioral therapy showed increased blood flow and metabolic activity in the hippocampus and dorsal cingulate—areas associated with memory and motivation—and decreased activity throughout the frontal cortex, an area associated with thinking and worry. These changes matched with clinical improvement in patients' feelings of hopelessness, views of self, and overall mood, suggesting that CBT had enabled them to pay attention to what was personally relevant and stop over-processing information that was not. By contrast, when paroxetine was used, researchers found that blood flow decreased in the bottom regions and increased in the cortical (top), "thinking" areas. By defining the way different therapies affect the brain, this study took the first essential step toward the devising successful combination strategies to fight depression.

Improvement in Imaging Helps in Treatment of Depression. Serotonin is a neurotransmitter that helps nerve cells communicate with one another. The most commonly used antidepressants (SSRIs) help increase the amount of serotonin available to neurons in the brain. To initiate communication, serotonin is released from the neuron into the synapse between neighboring neurons. Serving as the cleanup crew, the serotonin transporter (SERT) then shifts into gear, acting as the molecular pump responsible for the reuptake of the serotonin from the synapse for later use. Antidepressants work by binding to the SERTs and blocking their ability to recycle the serotonin, allowing more of it to remain available to neurons. NIMH-funded researchers can now visualize this process at work, using an improved imaging technique that tracks SERTs in the living brain. This could allow scientists to observe the actions of antidepressant drugs in real¬ time, facilitating the treatment of depressed patients - even revealing who will respond to antidepressants and who will not. To detect SERTs in a living organism, researchers use radioligands—radioactively labeled molecules that can recognize and bind to the SERT receptor. After the radioligand is injected into the bloodstream, a scanner detects the radioactive material and produces an image depicting the distribution of SERTs in the brain. In the past, however, creating the optimal radioligands for SERTs posed several challenges to scientists. Many radioligands are not ideal for imaging because the compounds do not bind to SERTs tightly, or the molecules attach to additional receptors in the brain. However, NIMH-funded researchers have discovered that by modifying a new class of radioligands, they can greatly enhance the labeling of SERTs. The new method also allows detection of very low levels of SERTs in the brain. Further studies testing these new SERT radioligands in humans will determine their utility for understanding antidepressant drug action and treatment responses.

Depressed Elderly Reduce Suicidal Thoughts With Help of "Care Managers." Suicide is a major public health issue, with about 30,000 people in the United States dying from it each year - far more than die than from homicide[7]. Older Americans account for 18 percent of all suicides, though they comprise just 13 percent of the population. Those at the very highest risk for suicide

[7] Arias, E., Anderson, R. N., Kung, H. C., Murphy, S. L., Kochanek, K. D. Deaths: Final Data for 2001: National Vital Statistics Reports 52(3). Hyattsville, Md: National Center for Health Statistics. DHHS publication (DHS) 2003-1120.

are elderly men; the major risk factor is depression[8]. Despite the availability of effective treatments, late-life depression often remains improperly diagnosed and inadequately treated. Research shows that the majority of older adults who die by suicide have seen their primary care physician within months of their death. Thus, NIMH approached suicide risk reduction from a public health perspective, funding PROSPECT—Prevention of Suicide in Primary Care Elderly: Collaborative Trial. The PROSPECT researchers set out to demonstrate that by educating physicians and providing standardized screening, diagnosis, and treatment, a social worker, nurse, or masters-level psychologist (e.g. care managers) in a primary care setting could treat depression well enough to significantly improve outcomes and even save lives. Depressed patients who received the PROSPECT intervention were offered anti-depressant (SSRI) medications and/or interpersonal therapy (a specific form of "talk" therapy), from a care manager who also followed up patients and monitored their symptoms, drug side effects, and treatment adherence. Suicidal thinking resolved more quickly in patients who received the intervention compared to those who received regular care. Also, patients who received the intervention had less severe symptoms, a better response to treatment, and longer remissions. Without this kind of structured formal screening and diagnosis, patients are less likely to get treatment. Results indicate that quality treatment of depression in primary care can be a prevention strategy to reduce the risk for suicide in later life.

Drugs vs. Talk Therapy as Treatments for Social Phobia. Anxiety, embarrassment and even panic are typical reactions to speaking in public. But for people with generalized social phobia, even minor daily interactions with other people can trigger these self-destructive emotions. General social phobia is a persistent and disabling mental disorder that affects some 14 percent of Americans throughout their lives[9]. It is typically treated with antidepressant drugs (SSRIs). To test the efficacy of talk and drug therapies in dealing with social phobia, NIMH grantees conducted a randomized double blind placebo-controlled trial using cognitive-behavioral group therapy (CBT) alone and in combination with SSRIs. The researchers followed 295 outpatients undergoing 14 weeks of therapy at two academic outpatient centers. Five types of therapy were tested. One group received fluoxetine (Prozac), another received weekly sessions of comprehensive CBT; a third received a placebo, a fourth received both CBT and fluoxetine, and a fifth received CBT and placebo. Participants reported that all treatments were well tolerated, although both fluoxetine and the placebo produced higher rates of nausea, insomnia, and headache than CBT, and several patients dropped out rather than be treated with drugs alone. While all active treatments proved better than placebo, even at the end of treatment most patients still had substantial symptoms. At four weeks, fluoxetine was significantly more effective at alleviating social phobia than any other treatment. But by week 14, all active therapies, alone and in combination, had produced equivalent results. The study proves that active treatment can alleviate general social phobia symptoms, that SSRIs are more effective in the short term, and that talk therapy—which produces no side effects—works for most people over time just as well medication. Recent evidence suggests that individual CBT works better for treating general social phobia and might be more effective if preceded by a short course of SSRIs to reduce anxiety from the start.

[8] Office of Statistics and Programming, NCIPC, CDC. Web-based Injury Statistics Query and Reporting System (WISQARS™): http://www.cdc.gov/ncipc/wisqars/default.htm.

[9] Kessler, R. C., Stein, M. B., Berglund, P. Social phobia subtypes in the National Comorbidity Survey. Am J Psychiatry 155:613-619, 1998.

Removing Poverty Reduces Adolescent Conduct Disorder - Not Anxiety or Depression. There has long been a link between mental illness and poverty. However, there are two competing theories about the role of poverty in the origins of mental illness. One emphasizes social causation, or the adversity and stress associated with low social status; the other, called social selection, claims that genetically predisposed people drift down into, or fail to rise out of, poverty, and thus into environments that increase risk for mental illness. The distinction between the two can be important in suggesting different strategies for prevention or treatment. An NIMH-supported study tested these competing models in 1,420 rural children, aged 9-13 at intake, who were given annual psychiatric assessments for 8 years. One-quarter of the children in the sample were American-Indian, and the rest predominantly white. Halfway through the study, a casino happened to open on the Indian reservation, which gave every American-Indian an income supplement that increased annually. This moved 14 percent of Indian families out of poverty, while 53 percent remained poor, and 32 percent were never poor. Incomes of white families were unaffected. Psychiatric diagnoses and symptoms were compared for the four years before and after the casino opened. Before the casino, the persistently poor and ex-poor children had more psychiatric disorders and symptoms than the never-poor; but after the casino opened, levels among the ex-poor fell to those of the never-poor, while levels among the persistently-poor remained high. The effect was specific to conduct and oppositional defiant disorder. Other psychiatric disorders, including depression and anxiety, were unaffected. Similar results were found in white children whose families moved out of poverty during the same period. Results support social causation explanations for conduct and oppositional disorder, but not for anxiety or depression. This finding underscores the importance of targeting psychosocial factors in the treatment and prevention of common disruptive behavior disorders.

NIH ROADMAP INITIATIVE

The NIH Roadmap is a set of progressive initiatives that seek to transform all of biomedical research and accelerate its discoveries. These initiatives by design have the potential to advance our understanding of the brain and to discover novel ways to diagnose, prevent and treat mental illness. The Roadmap initiatives are organized into three themes. The first is "New Pathways to Discovery" and within this theme is contained the "Molecular Libraries and Imaging" initiative, for which NIMH has assumed a lead role. The goal of this initiative is to provide organic chemical compounds, known as "small molecules," to scientists to use as tools to improve our understanding of biological pathways in health and disease. This is important because presently, very few small molecules are known to be biologically active and few are being used for research and drug development. The task of collecting and screening all small molecules that are potentially biologically active is too large and costly for any academic institution to undertake. Because it is unlikely to result in the development of marketable products, this undertaking has not appealed to the private sector either. NIH, because of its mission, has vested interest in identifying as many biologically relevant molecules as possible and providing them to the private and public sector for further research and development. The potential of scientific discoveries of clinical relevance is enormous. This is of particular interest for NIMH because of the astonishingly small number of molecules studied in psychiatric disorders and targeted for their treatment. The NIMH mission can be advanced by the identification of even one novel small molecule with biological activity in the brain. The development of highly sensitive brain imaging

probes will likely provide invaluable information about brain circuits involved in mental illness and those that are altered by treatment. In the past year, NIH awarded Discovery Partners International a multi-year contract to set up and maintain a Small Molecule Repository to collect and manage up to one million chemical compounds and provide them to multiple NIH Screening Centers. A national network of up to 10 screening centers will be funded at academic institutions and other locations to provide researchers with a broad range of promising small molecules. This will allow biologists in the public sector for the first time to take advantage of small molecules as biological probes.

A major thrust of the second NIH Roadmap theme "Research Teams of the Future," is to encourage an interdisciplinary approach to biomedical research that will enhance the translation of basic research into clinically relevant discoveries. One of the initiatives issued this year was "Exploratory Centers for Interdisciplinary Research" with the goal of planning centers that overcome barriers to conducting biomedical research in an interdisciplinary fashion. Of the 21 centers to be funded, eight focused on problems such as cognitive phenotyping for neuropsychiatric therapeutics, genetics of complex traits, and behavioral epidemiology, all directly relevant to the mission of NIMH.

Similarly, a training initiative entitled "Interdisciplinary Health Research Training: Behavior, Environment and Biology" answers the need for research training that integrates three broad, scientific areas: biology, behavior, and social environment. Through formal coursework and research training, the three applications funded will support training interdisciplinary researchers who will focus on neurobehavioral development, autism, and neurodevelopmental toxicology—all within the NIMH mission.

Initiatives within the third theme, "Re-engineering the Clinical Research Enterprise," are focused on improving clinical research through facilitating translational research, developing technologies to measure patient-reported symptoms, adopting a systematic infrastructure and policies that will better serve the evolving field of scientific discovery, and preparing the future clinical research workforce. NIMH is participating in all of these efforts.

NIMH NEW INITIATIVES

Develop biologically based markers of disease that could transform diagnosis, risk assessment, and treatment for disabling mental disorders, as well as provide information on timing of disease onset, severity or progress. A major goal for NIMH is to identify biological and behavioral markers of mental disorders in order to more precisely pinpoint targets for prevention and treatment. This means understanding the neural basis of the illness at all levels including the genetic, cellular, system, organismic, and environmental level processes that contribute to the development of disease or response to medications. In other fields of medicine, identification of disease-related genetic, cellular, and biochemical changes have provided relatively reliable biomarkers for diagnosis and predicting treatment response. In the mental health field, recent advances in neuroscience and neuroimaging are converging and are providing real opportunities to identify candidate genetic variations and brain circuits involved in aspects of mental disorder. Both approaches could yield new diagnostic tools and interventions as well as reveal the biomedical impact of existing treatments. This initiative would identify specific

combinations of biomarkers that are ready for validation in proof of concept studies; it would also bring together leaders in various disciplines to identify cognitive, behavioral, endocrine, and neuroimaging biomarkers underlying the pathways and circuits involved in the development of mental disorders.

Develop new treatments that will target the cognitive, social, and affective deficits seen in schizophrenia and schizophrenia spectrum disorders in childhood. In the last decade there have been significant advances toward understanding the early neuronal abnormalities and neurochemical changes preceding the onset of schizophrenia symptoms. New molecular and statistical tools are also allowing researchers to identify candidate susceptibility genes. These neurobiological advances must now be quickly translated into improved and novel interventions; pharmacologic and/or psychosocial treatments are desperately needed to address the social withdrawal and loss of motivation seen in schizophrenia. NIMH will develop and test the safety and efficacy of new preventive and ameliorative treatments for schizophrenia and other psychotic disorders. Specifically, NIMH will fund efforts to delineate the neural circuits that contribute to one or more subtypes of schizophrenia. Success will lie in human neuroimaging to determine progressive changes in schizophrenia; analysis of postmortem brain collections; and the interrogation of genes and their protein products in brain and peripheral tissue. In addition, NIMH will collaborate with the FDA, academic, and industry scientists to develop and test an assessment of neurocognition in schizophrenia, suitable for use as an endpoint in clinical trials of therapeutics targeting cognitive deficits. Novel compounds that target neurocognitive deficits in schizophrenia will also be evaluated in clinical trials. These efforts will be conducted through a network of six treatment units nationwide.

Develop and test new treatments for infants and children with autism spectrum disorders. Autism is one of a broader continuum of five disorders called autism spectrum disorders (ASD). Autism becomes apparent in early childhood, usually by the age of two or three, and may even appear earlier. Core deficits include difficulty in communicating, expressing emotion, and relating to others socially. Deficits are seen in learning, attention, and sensory processing. While there is yet no proven biological treatment, it is generally agreed that early behavioral intervention is beneficial. Behavioral methods can enhance social skills, language acquisition, and nonverbal communications, while reducing challenging behaviors. Yet outcomes are still variable, with some children making major progress and others advancing quite slowly. Behavioral approaches are most successful when they begin early, are intensive, and highly structured. More study is needed to determine which early interventions really can make a difference to long-term outcome. This initiative will develop and test the safety/efficacy of new psychosocial interventions for children with ASDs. Most of the evidence base is on applied behavior techniques for preschool age children. There is a need for *novel* treatments in that age group. And, as earlier diagnosis is becoming feasible, there is an urgent need for interventions for toddlers and even infants. NIMH sponsors ongoing working groups to address these issues. Future steps include development of sensitive outcome measures and pilot testing of promising interventions. Following these efforts, comparative treatment trials and effectiveness trials could be conducted. It is also critical to develop proactive, ethical guidelines for autism-related studies conducted with very young children. NIMH workshops will assist grantees in addressing these issues.

Develop tools to understand the impact of hormonal changes during life transitions on mood and cognitive function. Life transitions such as adolescence, pregnancy, menopause, and aging are associated with large hormonal shifts that impact not only the body but also brain function. These transitional periods can also be triggers for the onset of emotional and cognitive disorders in susceptible individuals. For example, while many processes such as sleep patterns and complex reasoning change as a normal consequence of adolescence, this is also when symptoms of depression, bipolar disorder, schizophrenia, eating disorders, and substance abuse disorders are often first reported. Evidence suggests that sex differences in hormonal activity contribute to differences in physiological and behavioral responses to stress and to the onset of some mental disorders. For example, females have a higher incidence of depression than males from puberty to menopause but a lesser severity of schizophrenia symptoms. Perinatal mood disorders are potentially devastating conditions that occur in some women during and after pregnancy. These include the (postpartum) blues, clinical mood and anxiety disorders, and postpartum psychosis. While hormonal changes are implicated in these disorders, no specific endocrine predictors of disorder or mechanisms have been identified. This is partly due to the very limited availability of specific molecular tools to assess neuroendocrine status in brain. This initiative supports the development of novel approaches to assess, visualize, and manipulate dynamic neuroendocrine signaling in brain that contributes to alterations in emotional and cognitive function during hormonal transition periods. Results may lead to the development of methods to identify at-risk individuals, to target early interventions, and to identify new treatment targets.

Reduce rates of adolescent depression and suicide. Major depressive disorder in adolescence is common and an important risk factor for suicide, the third leading cause of death among adolescents. It is critical that safe and effective treatments are identified to reduce the rate of adolescent suicidal behaviors and depression. NIMH will continue and expand an initiative to increase understanding of the clinical epidemiology of suicidal behavior and thinking in children and adolescents, with an emphasis on those who have received or are currently on SSRIs. Efforts will also focus on development and testing of antidepressant treatments that specifically target youths at increased risk for suicidal behavior - patients who are now excluded from entering depression clinical trials. Funded studies will aim to decrease the time to recovery from depressive episodes, reduce the rate of recurrence of depressive episodes, and decrease the rate of suicidal attempts. Also, studies will determine methods to assess long-term effects of antidepressant treatment, and whether it can change prognosis of the illness.

Increase the effective dissemination and implementation of treatment and services. Despite the proliferation of research studies on mental health treatments and services, there remain large gaps between research and practice and research and policy. Researchers estimate that it takes 17 years for the uptake of at least some of research advances into the 'real' world. More research is needed to better understand the reason for this lag and identify ways to improve and accelerate practice of evidence-based medicine. This initiative will increase the uptake of scientifically based treatments and services for mental disorders across diverse community settings in critical need of this information (health care, schools, social services) and to decrease the time required for uptake. Studies will be funded to pinpoint the effective dissemination and implementation mechanisms needed for successful use of evidence-based treatments and services. NIMH will also work to increase the number of community-based settings involved in academic research

partnerships to improve uptake of scientifically based treatments and services in community settings.

The NIH Neuroscience Blueprint

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

For fiscal year 2005, the Blueprint participants are developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. These initiatives, with the participation of all Blueprint Institutes, include an inventory of neuroscience tools funded by the NIH and other government agencies, enhancement of training in the neurobiology of disease for basic neuroscientists, and expansion of ongoing gene expression database efforts. The NIMH will be coordinating an expansion of training efforts by making available supplemental grants to existing Training awards to develop Neurobiology of Disease courses and/or to support post doctoral training efforts. There is a divide between basic neuroscience research and clinical research—few young neuroscientists with the most rigorous basic scientific training pursue research questions in the clinical neurosciences, and few clinicians conduct research. Encouraging research institutions involved with training future scientists to include Neurobiology of Disease courses in their training curriculum is an important step forward in bridging the divide between basic and clinical research, and across specialized disciplines. If we are to spur advances in neuroscience then we will need not only new tools, resources, and paradigms for studying molecules, cells, circuits and the whole organism, but also scientists skilled in communicating and integrating across and between different disciplines and levels of analysis. Providing supplements to current training awards builds on these resources, and allows us to address an important need for many ICs.

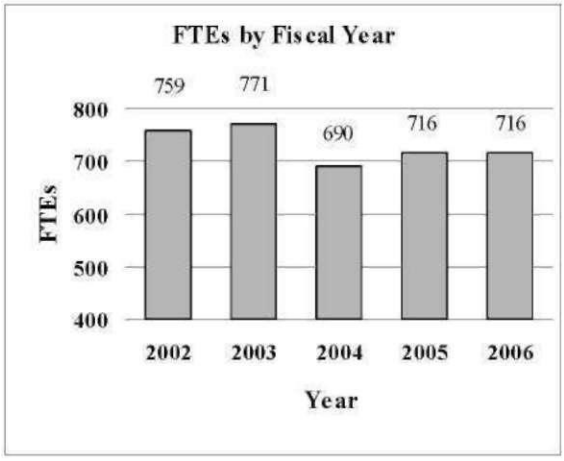
Advances in the neurosciences and the emergence of powerful new technologies offer many opportunities for Blueprint activities that will enhance the effectiveness and efficiency of neuroscience research. Blueprint initiatives for fiscal year 2006 will include systematic development of genetically engineered mouse strains of critical importance to research on nervous system and its diseases and training in critical cross cutting areas such as neuroimaging and computational biology. The NIMH will take the lead in coordinating the development of genetically engineered mouse strains important to nervous system research. This project, call ed the Neuromouse Project, will focus on genes of interest to neuroscientists, either because they have been identified within a putative functional circuit or they have been identified as candidate genes in studies of clinical populations with diseases of the nervous system. The structure of the targeted allele, gene expression pattern, and phenotype information collected for each mouse line will be captured in one or more widely accessible databases. It should be noted also that Tte

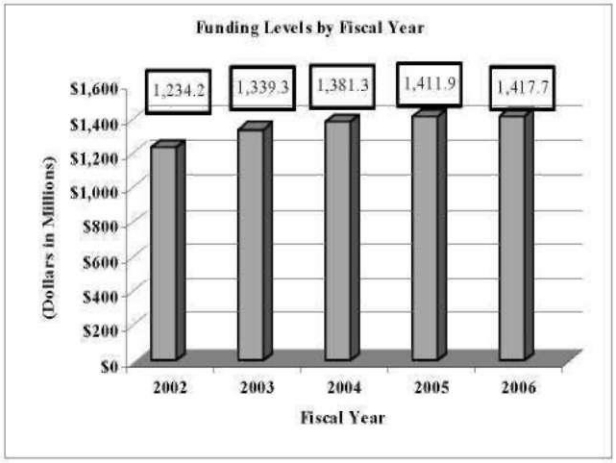
Neuromouse Project will form one element of a larger trans-NIH initiative to target all 27,000 genes in the mouse genome (Knock Out Mouse Project; KOMP). The Neuromouse Project will facilitate investigations by neuroscientists to determine the function of these genes by examining the anatomy, physiology, and behavior of mice in which this gene has been altered or deleted. Such an approach is critical if progress is to be made for understanding the causes and developing treatments for diseases of the nervous system, and is thus of interest to multiple ICs.

NIMH BUDGET POLICY

The Fiscal Year 2006 budget request for the NIMH is $1,417,692,000, an increase of $5,759,000 and 0.4 percent over the FY 2005 Appropriation. Also included in the FY 2006 request, is NIMH's support for the trans-NIH Roadmap initiatives, estimated at 0.89 percent of the FY 2006 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NIMH are shown in the graphs below.





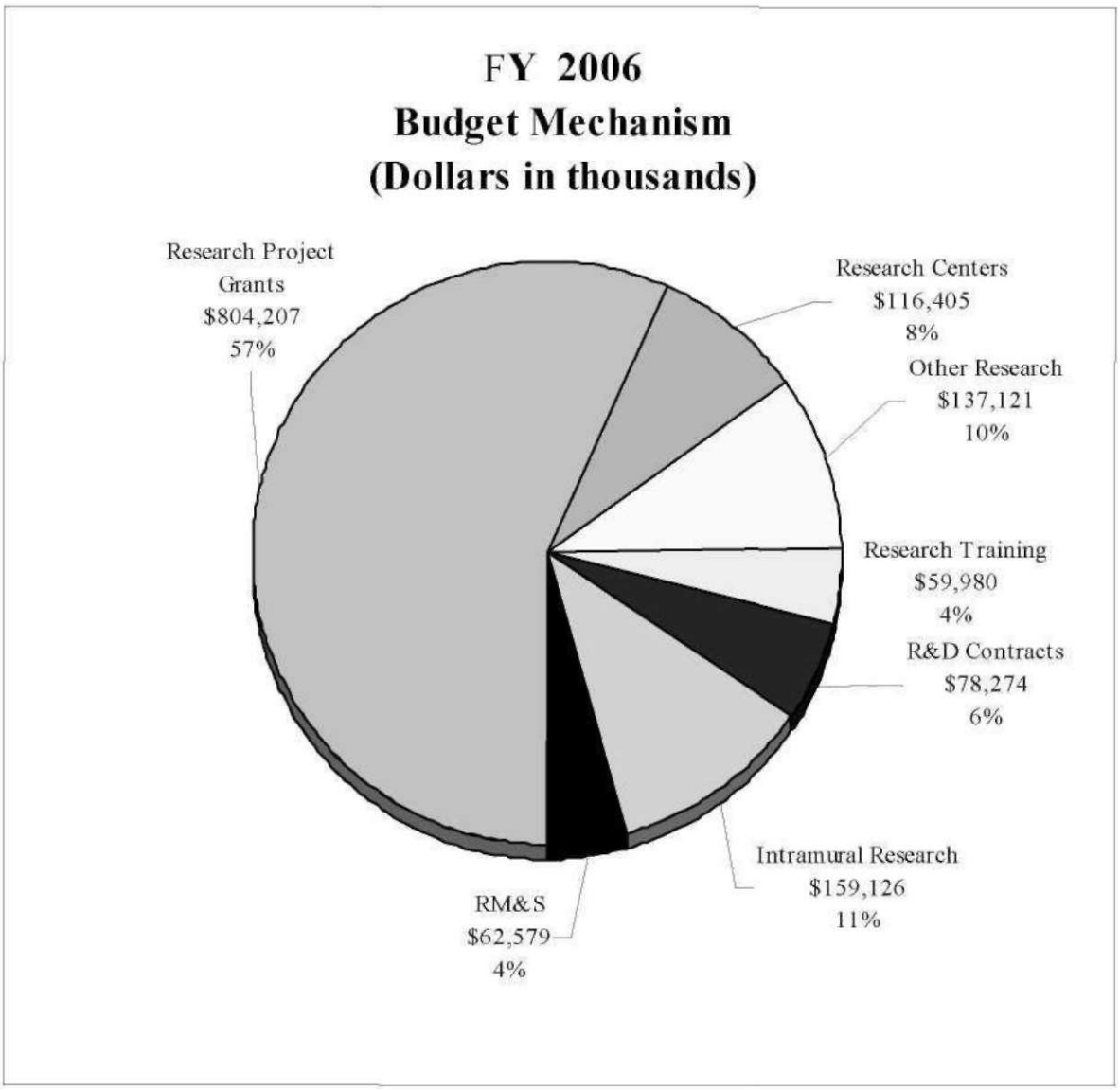
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. The average cost of competing RPGs will be held at the FY 2005 level. There will be no inflationary increases for direct, recurring costs in Noncompeting continuation RPGs.

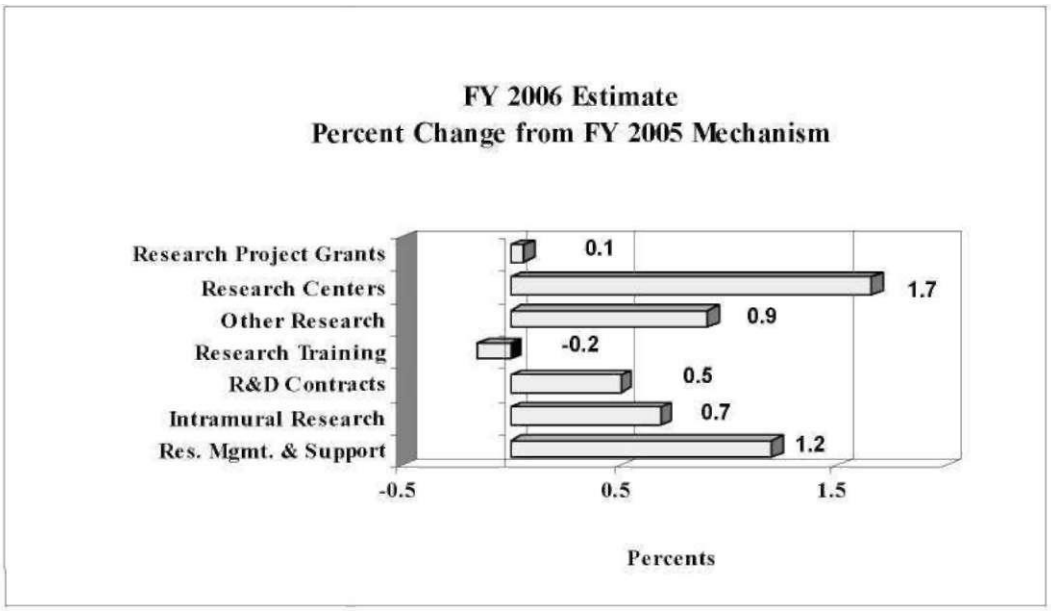
Advancement in medical research is dependent on attracting the best and the brightest to pursue careers in biomedical research. In the Fiscal Year 2006 request, stipend levels for post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will increase by 4.0 percent for those with 1-2 years of experience, with all other stipends remaining at the FY 2005 levels. NIH will also provide an increase of $500 per post-doctoral fellow for increased health insurance costs. This increase in stipends and health benefits is financed within the FY 2006 request by reducing the number of Full-Time Training Position by -13. NIMH will support 1,474 pre- and post-doctoral trainees in full-time training positions.

The Fiscal Year 2006 request includes funding for 72 research centers, 677 other research grants, including 515 clinical career awards, and 205 R&D contracts. Intramural Research and Research Management and Support receive increases of 0.5 percent, the same as the NIH total increase.

NIMH is participating in the NIH Neuroscience Blueprint. The FY 2006 request includes $4.1 million for a variety of Neuroscience Blueprint initiatives, including neuroscience cores, training initiatives, and the Neuromouse project.

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




FY 2006 Estimate
Percent Change from FY 2005 Mechanism
Research Project Grants
Research Centers
Other Research
Research Training
R&D Contracts
Intramural Research
Res. Mgmt. & Support
0.1
1.7
0.9
-0.2
0.5
0.7
1.2
-0.5
0.5
1.5
Percents

Budget Mechanism -Total

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 ontimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	1,621	$580,509,000	1,669	$603,644,000	1,615	$591,890,000
Administrative supplements	(52)	4,550,000	(67)	4,543,000	(66)	4,296,000
Competing:						
Renewal	145	52,823,000	129	48,592,000	138	51,982,000
New	476	131,616,000	421	120,557,000	453	129,618,000
Supplements	9	843,000	9	775,000	9	775,000
Subtotal, competing	630	185,282,000	559	169,924,000	600	182,375,000
Subtotal, RPGs	2,251	770,341,000	2,228	778,111,000	2,215	778,561,000
SBIR/STTR	88	25,431,000	86	25,610,000	84	25,646,000
Subtotal, RPGs	2,339	795,772,000	2,314	803,721,000	2,299	804,207,000
Research Centers:						
Specialized/comprehensive	66	100,631,000	70	113,157,000	7°	114,717,000
Clinical research	0	0	0	0		0
Biotechnology	1	577,000	1	901,000		1,245,000
Comparative medicine	0	443,000	0	443,000		443,000
Research Centers in Minority Institutions	0	0	0	0		0
Subtotal, Centers	67	101,651,000	71	114,501,000	72	116,405,000
Other Research:						
Research careers	517	74,026,000	515	74,615,000	515	75,170,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	22	21,435,000	22	21,578,000	23	221,578,000
Biomedical research support	0	26,000	0	33,000	0	38,000
Minority biomedical research support	0	0	0	0	0	0
Other	140	38,280,000	141	39,662,000	139	39,735,000
Subtotal, Other Research	679	133,767,000	678	135,888,000	677	137,121,000
Total Research Grants	3,085	1,031,190,000	3,063	1,054,110,000	3,048	1,057,733,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	329	12,001,000	327	12,160,000	324	12,160,000
Institutional awards	1,203	48,109,000	1,160	47,912,000	1,150	47,820,000
Total, Training	1,532	60,110,000	1,487	60,072,000	1,474	59,980,000
Research & development contracts	207	75,221,000	204	77,879,000	205	78,274,000
(SBIR/STTR)	(23)	(5,958,000)	(23)	(6,163,000)	(23)	(6,163,000)
	FTEs		FTEs		FTEs	
Intramural research	463	154,732,000	468	158,036,000	468	159,126,000
Research management and support	227	60,013,000	248	61,836,000	248	62,579,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, NIMH	690	1,381,266,000	716	1,411,933,000	716	1,417,692,000
(RoadMap Support)		(2,549,000)		(8,926,000)		(12,677,000)
(Clinical Trials)		(119,187,000)		(121,831,000)		(122,349,000)

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY2004 Actual		FY 2005 Appropriation		FY2005 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Extramural research and training		$1,166,521		$1,192,061		$1,195,987		$3,926
Subtotal, Extramural research		1,166,521		1,192,061		1,195,987		3,926
Intramural research	463	154,732	468	158,036	468	159,126		1,090
Research management & support	227	60,013	248	61,836	248	62,579		743
Total	690	1,381,266	716	1,411,933	716	1,417,692		5,759

Summary of Changes

FY 2005 Appropriation				$1,411,933,000
FY 2006 Estimated Budget Authority				1,417,692,000
Net change				5,759,000
	FY 2005 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$62,584,000		$864,000
b. Annualization of January 2005 pay increase		62,584,000		579,000
c. January 2006 pay increase		62,584,000		1,080,000
d. One less day of pay		62,584,000		(248,000)
e. Payment for centrally furnished services		28,071,000		140,000
f. Increased cost of laboratory supplies, materials, and other expenses		67,381,000		791,000
Subtotal				3,206,000
2. Research Management and Support:				
a. Within grade increase		27,195,000		464,000
b. Annualization of January 2005 pay increase		27,195,000		95,000
c. January 2006 pay increase		27,195,000		469,000
d. One less day of pay		27,195,000		(108,000)
e. Payment for centrally furnished services		9,014,000		45,000
f. Increased cost of laboratory supplies, materials, and other expenses		25,627,000		302,000
Subtotal				1,424,000
Subtotal, Built-in				4,630,000

Summary of Changes–continued

CHANGES	FY 2005 Appropriation Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	1,669	$608,187,000	(54)	($12,001,000)
b. Competing	559	169,924,000	41	12,451,000
c. SBIR/STTR	86	25,610,000	(2)	36,000
Total	2,314	803,721,000	(15)	486,000
2. Research centers	71	114,501,000	1	1,904,000
3. Other research	678	135,888,000	(1)	1,233,000
4. Research training	1,487	60,072,000	(13)	(92,000)
5. Research and development contracts	204	77,879,000	1	395,000
Subtotal, extramural				3,926,000
	FTEs		FTEs	
6. Intramural research	468	158,036,000	0	(2,116,000)
7. Research management and support	248	61,836,000	0	(681,000)
Subtotal, program		1,411,933,000		1,129,000
Total changes	716		0	5,759,000

Budget Authority bby Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	716	716	0
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	$146,980	$149,920	$2,940
Average GM/GS grade	11.6	11.6	0.0
Average GM/GS salary	$79,225	$82,394	$3,169
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$92,837	$96,550	$3,713
Average salary of ungraded positions	113,303	117,835	4,532

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$37,987,000	$39,605,000	$1,618,000
11.3 Other than Full-Time Permanent	22,807,000	23,659,000	852,000
11.5 Other Personnel Compensation	1,412,000	1,465,000	53,000
11.7 Military Personnel	1,350,000	1,400,000	50,000
11.8 Special Personnel Services Payments	9,622,000	9,781,000	159,000
Total, Personnel Compensation	73,178,000	75,910,000	2,732,000
12.0 Personnel Benefits	15,410,000	15,985,000	575,000
12.1 Military Personnel Benefits	00041,000	1,130,000	41,000
13.0 Benefits for Former Personnel	004,000	106,000	4,000
Subtotal, Pay Costs	**89,779,000**	**93,131,000**	**3,352,000**
21.0 Travel & Transportation of Persons	3,293,000	3,275,000	(18,000)
22.0 Transportation of Things	325,000	323,000	(2,000)
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	28,000	28,000	0
23.3 Communications, Utilities & Miscellaneous Charges	1,747,000	1,737,000	(10,000)
24.0 Printing & Reproduction	1,131,000	1,125,000	(6,000)
25.1 Consulting Services	2,102,000	2,090,000	(12,000)
25.2 Other Services	6,054,000	6,141,000	87,000
25.3 Purchase of Goods & Services from Government Accounts	122,065,000	121,293,000	(772,000)
25.4 Operation & Maintenance of Facilities	3,677,000	3,657,000	(20,000)
25.5 Research & Development Contracts	47,281,000	47,022,000	(259,000)
25.6 Medical Care	1,573,000	1,564,000	(9,000)
25.7 Operation & Maintenance of Equipment	0(12,000)	2,145,000	(12,000)
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**184,909,000**	**183,912,000**	**(997,000)**
26.0 Supplies & Materials	8,920,000	8,871,000	(49,000)
31.0 Equipment	7,615,000	7,573,000	(42,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	1,114,182,000	1,117,713,000	3,531,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	4,000	4,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	**1,322,154,000**	**1,324,561,000**	**2,407,000**

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$37,987,000	$39,605,000	$1,618,000
Other Than Full-Time Permanent (11.3)	22,807,000	23,659,000	852,000
Other Personnel Compensation (11.5)	1,412,000	1,465,000	53,000
Military Personnel (11.7)	1,350,000	1,400,000	50,000
Special Personnel Services Payments (11.8)	9,622,000	9,781,000	159,000
Total Personnel Compensation (11.0)	**73,178,000**	**75,910,000**	**2,732,000**
Civilian Personnel Benefits (12.1)	15,410,000	15,985,000	575,000
Military Personnel Benefits (12.2)	1,089,000	1,130,000	41,000
Benefits to Former Personnel (13.0)	102,000	106,000	4,000
Subtotal, Pay Costs	**89,779,000**	**93,131,000**	**3,352,000**
Travel (21.0)	3,293,000	3,275,000	(18,000)
Transportation of Things (22.0)	325,000	323,000	(2,000)
Rental Payments to Others (23.2)	28,000	28,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	1,747,000	1,737,000	(10,000)
Printing and Reproduction (24.0)	1,131,000	1,125,000	(6,000)
Other Contractual Services:			
Advisory and Assistance Services (25.1)	2,102,000	2,090,000	(12,000)
Other Services (25.2)	6,054,000	6,141,000	87,000
Purchases from Govt. Accounts (25.3)	77,258,000	76,263,000	(995,000)
Operation & Maintenance of Facilities (25.4)	3,677,000	3,657,000	(20,000)
Operation & Maintenance of Equipment (25.7)	2,157,000	2,145,000	(12,000)
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**91,248,000**	**90,296,000**	**(952,000)**
Supplies and Materials (26.0)	8,912,000	8,863,000	(49,000)
Subtotal, Non-Pay Costs	106,684,000	105,647,000	(1,037,000)
Total, Administrative Costs	**196,463,000**	**198,778,000**	**2,315,000**

National Institute of Mental Health

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

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

Item

Mental health *research* ***and the aging*** - 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 interested in supporting funding for late-life mental health research at NIMH. The committee encourages NIMH to strengthen the resources supporting aging research and to provide data on existing funds targeted toward geriatric mental health research. (p. 97)

Action taken or to be taken

NIMH agrees that the public health needs of an aging society require a vigorous program of geriatric mental health research. The NIMH Director and the National Advisory Mental Health Council (NAMHC) convened the Aging Research Workgroup in January 2003 to assess the Institute's extramural aging research and training portfolio and to identify strategies for developing: promising research areas in mental health and aging; researchers skilled in studying aging issues; NIMH program staff expertise in aging research; and collaborations with other stakeholders.

The Workgroup's report, "Mental Health for a Lifetime: Research on the Mental Health Needs of Older Americans," was issued in 2004 and is available to the public on the NIMH website (http://www.nimh.nih.gov/council/agingreport.cfm). Recognizing the public health significance of mental disorders in old age, the report charts a path for NIMH to develop research that will promote mental health for the growing proportion of older Americans. In addition, this report identifies research required to understand the needs of individuals living with mental illness as they move toward later life. NIA staff contributed to the development of the Report because of the mutual interest of the two Institutes in several areas of basic and translational neuroscience and behavioral science research.

The recommendations contained in the report were adopted by the NAMHC and were used to structure a new Geriatrics Research Branch that has been charged with implementing the recommendations.

Item

Down syndrome - The Committee encourages NIMH to research the mental health symptoms of persons with Down syndrome and to investigate risk factors and possible treatments for autism, obsessive-compulsive disorder, attention deficit disorder, anxiety and depression. The Committee urges NIMH to include Down syndrome in its studies on related disorders and to coordinate its work with the National Center on Birth Defects and Developmental Disabilities at

the Centers for Disease Control and Prevention. The Committee encourages NIMH to work closely with NINDS, NICHD, NIA and NHGRI to establish a research initiative to fund Down syndrome research relating to cognition and behavior through biomedical interventions. (p. 97)

Action taken or to be taken
NIMH supports research designed to better recognize mental illness, such as anxiety, depression, attention deficit disorder and obsessive-compulsive disorder, in persons with intellectual disabilities, including persons with Down syndrome. NIMH has established ongoing collaboration with NICHD, NINDS, and NIDCD in the area of mental retardation, including, for example, co-sponsorship of a large international meeting in this area. In FY04, NIMH released a program announcement entitled "Research on Psychopathology in Intellectual Disabilities (Mental Retardation)" designed to solicit grant applications to address these important issues. Though primarily an NIMH effort, the program announcement has garnered further collaboration with these institutes via the proposal of projects relevant to each of the other institutes.

The NIMH is a member of the External Partners Group of the National Center on Birth Defects and Developmental Disabilities (NCBDDD) and as such, remains informed of its activities relevant to the Institute's work on Downs syndrome and related disorders. In addition, NIMH contributes towards the NCBDDD's "Learn the Signs. Act Early" campaign, which is an effort to increase awareness of all social-emotional/communication problems early in development.

Item
Parkinson's disease - The Committee encourages NIMH to enhance its research on the role of depression in Parkinson's disease. Depression may be a very early symptom of Parkinson's, sometimes appearing before other traditional symptoms. NIMH should also continue its ongoing research into the proper treatment of depression and other serious mental disorders that often co-occur with Parkinson's, such as dementia and anxiety. (p. 97)

Action taken or to be taken
NIMH has long recognized the importance of co-occurring mental disorders with Parkinson's disease. The Institute's commitment to this area is evidenced by its significant investment in research support, its participation in numerous trans-NIH activities, as well as collaborations with advocacy groups, and the support 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 regards to trans-NIH activities, NIMH continues to function as the co-leading institute with NINDS on the Parkinson's disease Matrix activity, "Clinical Trials of Non-Motor Symptoms." Similarly, NIMH continues to solicit research proposals addressing cognitive deficits in Parkinson's disease through its collaboration with other NIH institutes on a program announcement entitled "Basic and Translational Research on the Cognitive Sequelae of Parkinson's Disease" designed to solicit proposals addressing this important issue. Additionally, the Institute has worked with NINDS to convene an expert panel to discuss diagnosing depression in Parkinson's disease; a publication from this meeting is currently in preparation. Finally, NIMH staff interact regularly with Parkinson's disease patient advocate groups to support and educate their members. For example, NIMH staff participated in a recent meeting of the Parkinson's Action Network Research and Education Forum.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 108-345)

Item

Aging and Mental Health - The Committee continues to be concerned that NIMH has not provided substantial resources to promote aging research or provide data on existing funds targeted toward geriatric mental health research. Therefore, the Committee encourages NIMH to significantly expand research in this area extramurally through all available mechanisms to advance the geriatric mental health research agenda. (p. 149)

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 geriatric mental health.

Item

Alzheimer's Disease - Recently, NIMH launched a five-site trial of antidepressant medications designed to help identify the best medication regimen for treating the behavioral problems that often occur in Alzheimer patients. Initial results should be available in late 2004. In addition, NIMH intramural researchers identified a promising new method for early detection of Alzheimer's disease. Long-term studies now underway will determine whether this biomarker can be used as a predictive and diagnostic tool. The Committee encourages NIMH to continue to place significant priority on studies of Alzheimer's disease. (p. 149)

Action taken or to be taken

NIMH continues to pursue an active research portfolio concerning the causes, diagnosis and treatment of Alzheimer's disease. This work spans all phases of research, from basic neuroscience studies to treatment and services research. Over recent years, NIMH led the field in developing consensus criteria for diagnosing a specific syndrome of depression in Alzheimer's disease. These criteria are currently being validated within the context of a five-site trial that is examining the effectiveness of anti-depressant medications in treating depression in Alzheimer's disease. This trial was funded in 2003, and results are expected to be available in 2008.

In addition, since 1999 the Institute has supported the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) studies, one of which examines the effectiveness of the newer, "atypical" antipsychotic medications in the management of behavioral symptoms in Alzheimer's disease. The Alzheimer's disease trial is a 35-site study to compare the effectiveness of several antipsychotic medications and determine the best medication regimen for treating the agitation and related behavioral problems that occur in Alzheimer's disease. Data collection for this study is nearly completed and results will be published in mid 2005.

NIMH will continue to support a variety of studies to improve understanding of and care for Alzheimer's disease, and will collaborate with other NIH institutes on joint efforts in this area, as appropriate.

Item

Down Syndrome - The Committee encourages NIMH to research the mental health symptoms of persons with Down syndrome and to investigate risk factors and possible treatments for autism,

obsessive-compulsive disorder, attention deficit disorder, anxiety, and depression. The Committee urges NIMH to include Down syndrome in its studies on related disorders and to coordinate its work with the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention. The Committee further urges NIMH to work closely with NINDS, NICHD, NIA and NHGRI to establish a new, multi-year research initiative to fund Down syndrome research relating to cognition and behavior through biomedical interventions. (p. 149)

Action taken or to be taken
Please refer to Page 35 of this document for NIMH's response to this significant item regarding the importance of addressing Down Syndrome.

Item
FragileX- 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 working with FRAXA Research Foundation to spearhead three focused research meetings devoted to identifying critical research needs, in November 2001, January 2003, and a planned meeting in 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 that 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. (p. 149)

Action taken or to be taken
NIMH continues to work closely with The Fragile X Research Foundation (FRAXA) and other NIH institutes on issues surrounding Fragile X and its relationship to autism and other neuropsychiatric disorders. Research has consistently demonstrated neuroanatomical and behavioral similarities in individuals with autism and Fragile X, with perhaps 25-40 percent of Fragile X individuals meeting the diagnostic criteria for autism. Arguments have been made that there are etiological and pathophysiological mechanisms shared between Fragile X children and at least a subgroup of children with autism. Recognizing the importance of these findings, NIMH, together with NINDS, NICHD, and FRAXA, jointly sponsored a workshop entitled, "At the Crossroads: Common Pathways in Fragile X and Autism" on July 7-8, 2004. This workshop brought together leaders in the field of autism and Fragile X to develop future directions for neurobiological research on Fragile X. Recommendations from the workshop were to identify shared etiological mechanisms at the level of cellular processes (e.g., activation of receptors in cortical neurons), underlying circuits (e.g., GABA receptor-mediated inhibition) and neuroanatomy (e.g., information integration and underconnectivity among brain regions involved in language processing). NIMH, NINDS, NICHD, and FRAXA will develop and support a Program Announcement to solicit state-of-the-art research applications to address many of the recommendations of this workshop. This public-private partnership is expected to support research that will greatly accelerate progress in understanding the neurobiological basis of Fragile X and in identifying key molecular targets for designing new therapeutic compounds.

Item

Frontier Mental Health Needs - The Committee commends NIMH on its outreach efforts to determine the differences in mental health needs that may exist in remote frontier communities. The Committee encourages NIMH to expand its research efforts into these communities, which are often ignored in research projects, but which continue to suffer from high incidences of mental health problems including depression, suicide and co-occurring disorders with substance abuse. (p. 150)

Action taken or to be taken

Through its Office of Rural Mental Health Research (ORMHR), as well as other programs, NIMH continues to expand its research efforts in frontier mental health needs. ORMHR supports several grants that focus on remote frontier communities that have poor access to mental health care. For example, one project is currently studying American Indians and Alaskan Natives in rural and frontier populations to: determine their prevalence of mental illness; assess their service utilization; and, develop primary preventive intervention programs for children and adolescents. Another is studying cultural protective factors (e.g., traditional practices, spirituality, and Ojibwe identity) to determine their effect on the resiliency (and avoidance of high-risk behavior) of children and adolescents. And a third is studying rural and frontier Native American populations to determine: the amount of mental health care provided by non-specialty mental health care providers; and, Native American youth's access and use of mental health services, regardless of the kind of provider.

In addition the ORMHR conducted a workshop "A Rural Mental Health Research Agenda: Building on Success by Planning for the Future." Meeting participants noted that rural and frontier communities offer self-contained environments that provide unique opportunities to study the effectiveness of interventions (both treatment and prevention) and other issues in "real world" settings. One recommendation, currently underway, was to conduct a meta-analysis of databases to inform the systematic identification of rural and frontier communities at high risk for increased prevalence of mental illness and/or underutilization of mental health services. The ORMHR is encouraging investigators to study the socio cultural and economic factors involved.

One area of great interest is the use of telecommunications technology as a means of delivering mental health care to rural and frontier populations. This technology may offer an opportunity to reduce the many barriers (including lack of culturally competent care) to effective mental health care delivery and may well enhance the quality of care. Further, until there is evidence that services can be effectively delivered via telemedicine to frontier populations, third-party payers are unlikely to adequately reimburse for such services. ORMHR recently conducted an e-mental health workshop to stimulate studies to determine whether individuals in frontier populations with various mental disorders can be as effectively diagnosed and treated via telemedicine versus care delivered face-to-face.

Item

Major Depression and Bipolar Disorder - The prevalence, economic consequences, and systemic nature of major depression is alarming. Depression is now recognized as a multi-system disorder affecting not only the brain, but the entire body. It has been associated with alterations in endocrine, cardiovascular, and immune systems as well as changes in bone metabolism.

Researchers funded by NIMH found that the prevalence for major depression for lifetime was 16.2 percent; in any given year, more than 20 million children and adults in the Nation are affected by major depression or bipolar disorder. Depression has been shown to be a leading cause of disability worldwide. The Committee urges the NIMH to continue its efforts to understand depression, to develop new treatments, to decrease the impact of depression on co-morbid illnesses, and—because depression and bipolar disorders are prominently associated with suicide—to reduce suicide. The Committee is pleased with NIMH's leadership in the public education campaign entitled 'Real Men. Real Depression' and encourages the Institute to continue these education and information dissemination efforts. (p. 150)

Action taken or to be taken

NIMH appreciates the Committee's recognition of its work while it continues to address the crippling problem of major depression through its extensive research and dissemination efforts. The Institute supports research on all aspects of depression, from basic research on its etiology and its neurological underpinnings, to the development of preventive and treatment interventions and their widespread application. In addition, the Institute ensures effective communication with the public of research results through its efforts in information dissemination. Some examples of NIMH's investments in this research include the following.

Effectiveness research. While most treatments for mood disorders were developed in narrowly-defined, uncomplicated cases, in reality many patients suffer from multiple conditions. Large-scale trials supported by NIMH - *Sequenced Treatment Alternatives to Relieve Depression* (STAR*D) and *Systematic Treatment Enhancement Program for Bipolar Disorder* (STEP-BD)—studying thousands of patients with broad inclusion criteria, are seeking to better characterize the long-term course of depression and bipolar disorder and evaluate the best treatments, including the best "next step" if initial treatments produce inadequate response, and the preferred treatment approach to the vexing problem of bipolar depression. Particular attention is paid to understanding the special treatment needs of understudied and vulnerable populations, including pregnant and postpartum women, minorities, and those with co-morbid physical and mental disorders.

Relapse prevention / treatment development. Major depression and bipolar disorder are characterized by recurrent episodes over time. While most treatment research has focused on acute episodes, NIMH-supported researchers are now addressing the critical next step: prevention of relapse following recovery from an acute depressive or manic episode. Ongoing studies support a role for psychosocial interventions, alone or in combination with antidepressant medication, for this purpose. Other investigators are evaluating the benefit of treating residual insomnia persisting after recovery from a depressive episode as a means of forestalling relapse. Treatment development advances include a new multi-site trial aimed at optimizing the use of a noninvasive somatic treatment for depression, transcranial magnetic stimulation (TMS).

Suicide prevention. NIMH, in collaboration with NIAAA, NIDA, and the American Foundation for Suicide Prevention, funded four new centers in FY04 focused on suicide prevention. A primary mission of these centers will be the development of new treatment approaches for persons with depression and at high risk for suicidality. The centers will also

assist in finding new approaches to assessing the safety of antidepressant medications among depressed persons.

Information Dissemination. NIMH distributes research-based information on depression and bipolar disorder for the general public; a new series of publications aimed at informing young adults about recognizing depression and seeking appropriate help for themselves or others, is being readied for publication. Launched in the spring of 2003, the NIMH *Real Men, Real Depression* program—featuring real people with the disorder, not actors—is the first national public education campaign aimed at raising awareness about depression in men and encouraging them to seek treatment. The campaign's extensive reach has touched an audience of more than 318 million.

Item

Outreach - The Committee commends NIMH on its outreach efforts to determine the differences in mental health needs that may exist in remote rural communities. The Committee encourages NIMH to expand its research efforts toward the unique needs of the Native Hawaiian community. (p. 150)

Action taken or to be taken

NIMH continues to expand its efforts towards the unique needs of the Native Hawaiian community. For example, the Department of Psychiatry of the John A. Burns School of Medicine, University of Hawaii at Manoa hosted a staff visit by the NIMH Office for Special Populations and Grants Management Branch. The NIMH visit and additional staff collaborations have resulted in a submission of a competing research center grant application to NIMH for funding of an Advanced Center on Mental Health Research from an institution in Hawaii. The application is pending review.

Access to quality mental health care for the Native Hawaiian community is being addressed by NIMH through an ongoing workgroup focusing on research in using telecommunications in rural locations. The workgroup, which includes broad representation from the research, medical and telecommunications communities, is exploring how telecommunications technology may offer ways to reduce the many impediments (including lack of culturally-competent care) to delivering mental health care to the Native Hawaiian community. Furthermore, until research provides the evidence that services can be effectively delivered via telecommunications and across various racial and ethnic minority groups, adequate reimbursement by third-party payers remains unlikely. Research grant applications that result from this initiative are expected to have considerable benefit for the Native Hawaiian community.

Item

Parkinson's Disease - The Committee encourages NIMH to increase its research on the role of depression in Parkinson's disease. Particularly, depression may be a very early symptom of Parkinson's, sometimes appearing before other traditional symptoms. NIMH should also continue its ongoing research into the proper treatment of depression and other serious mental disorders that often co-occur with Parkinson's, such as dementia and anxiety. (p. 150)

Action taken or to be taken

Please refer to Page 36 of this document for NIMH's response to this significant item concerning NIMH's recognition of the importance of developing effective treatments of depression and other serious mental disorders that often co-occur with Parkinson's disease.

Item

Portfolio Review - The Committee is pleased with recent NIMH efforts to set priorities with an eye toward achieving maximum impact against mental disorders. A balanced NIMH research portfolio ranges from the most basic molecular research to complex clinical and health services research—all of which contributes to the body of knowledge that will enable science to develop targeted and highly effective treatment interventions that can then be implemented through services that reach every individual who is in need. In this regard, the Committee understands that Working Groups of the National Advisory Mental Health Council [NAMHC], convened by the NIMH Director—including NAMHC members and outside scientific experts—have scrutinized the current NIMH portfolio related to clinical trials, to basic neurobiological research, and to basic behavioral research. The Committee favors these efforts at careful portfolio management, and looks forward to seeing the resulting recommendations of the Workgroups as to how the NIMH can best focus its efforts in areas that are relevant to the tremendous public health burden of mental disorders while at the same time promising the greatest opportunity for scientific advancement. (p. 150)

Action taken or to be taken

NIMH appreciates the Committee's recognition of its efforts in portfolio review. During the past year the Institute convened a workgroup of the National Advisory Mental Health Council (NAMHC) to examine its portfolio in the basic sciences in behavioral and biological arenas. The workgroup's report, "Setting Priorities for Basic Brain and Behavioral Science Research at NIMH," re-affirmed the importance of basic science and the very high quality of the research portfolio. However, it noted that "Basic brain and behavioral research should be undertaken in the service of the public health mission of NIMH. Basic science questions that are most central to understanding the potential causes, treatment, and prevention of mental illness and behavioral disorder should be the highest priority." The report goes on to outline specific tools and areas of research particularly ripe for increased investment, areas ready for refocus, and areas better served by other Institutes.

The Institute also convened a second NAMHC workgroup to examine research priorities in clinical trials research. In its report entitled "Treatment Research in Mental Illness: Improving the Nation's Public Health Care through NIMH Funded Interventions Research," the workgroup reaffirmed NIMH's crucial role in fostering treatment research in mental disorders, and highlighted examples in which the Institute had succeeded in promoting innovative studies with high impact. Nevertheless, the workgroup put forth a number of recommendations to strengthen the clinical treatment portfolio at NIMH, organized in three areas: creating the optimal treatment research portfolio; building clinical trials capacity and expertise; and, improving the operation, efficiency and productivity of clinical trials.

Taking these reports into account, as well as solicited input from various stakeholders, NIMH has re-organized its extramural program structure. The new structure emphasizes our continued

support for basic science discovery, our growing commitment to translational research that can enhance the application of basic science to clinical issues, and continued priorities for research on clinical trials and improving mental health services.

In addition, NIMH is implementing several of the recommendations of the working groups by re- setting funding priorities and developing new funding initiatives.

Item
Prader-Willi Syndrome - The Committee commends the NIMH for its efforts to further the understanding and description of the mental health components of Prader-Willi Syndrome. The Committee recommends that NIMH expand its programs to develop practical treatment protocols, including pharmaceutical options, for the severe anxiety, obsessive-compulsive disorder, oppositional-defiant disorder and psychotic mental illness aspects of Prader-Willi Syndrome. (p. 151)

Action taken or to be taken
Prader-Willi Syndrome, a rare neurodevelopmental disorder, is of relevance to the NIMH because of the frequency with which psychiatric symptoms manifest among individuals with the syndrome. As part of the research being conducted by the NIMH-sponsored Research Units on Pediatric Psychopharmacology (RUPPs), treatment paradigms are being developed and tested for a variety of childhood psychiatric symptoms, including severe anxiety, obsessive-compulsive disorder (OCD), oppositional symptoms and psychosis. Both pharmacological and psychosocial modalities are utilized, alone and in combination. Several of the treatment studies conducted by the RUPPs have included children and adolescents with developmental disabilities, including Prader-Willi syndrome and autistic spectrum disorders, as research subjects. Their inclusion in the trials will ensure that the results are applicable not only to typically developing children and adolescents, but also to those with neurodevelopmental disabilities.

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. 151)

Action taken or to be taken
NIMH continues to conduct and support research relevant to the psychobiological and behavioral consequences of exposure to violence, including terrorism and war. The focus of this research spans and integrates basic and clinical sciences to identify markers of resilience and of posttraumatic distress and disorder that will lead to improved prediction, prevention, and treatment. NIMH has recently taken several steps to enhance its efforts including issuing and collaborating on several research announcements including three program announcements, the first of which is entitled "Mental Health Consequences of Violence and Trauma"; the second being "Research on Emergency Medical Services for Children"; and the third, "Informatics for

Disaster Management"; Also the NIMH collaborated on a request for applications entitled "Developing Translational Research on Mechanisms of Extinction Learning."

In addition, the Institute has initiated funding for several new research projects and provided support to increase research capacity. For example, three new projects have been funded under a program entitled "Developing Disaster Mental Health Research Capacity Through Education." In addition, several grants are now supporting novel cutting edge research on predictors, prevention and treatment of post-traumatic stress disorder (PTSD).

Other relevant activities include organizing a multi-agency effort with CDC, SAMHSA, VA/NCPTSD to develop, test and deploy a program for national surveillance and assessment of local community mental and behavioral health needs before and after major traumatic events, and launching new scientific studies relevant to biodefense in the immediate aftermath of unforeseen events.

Beyond encouraging and supporting new research, NIMH has been actively collaborating with other DHHS agencies (CDC, SAMHSA, HRSA) and other departments of the U.S Government (VA, DOD, DHS) to pursue novel research collaborations, conduct scientific reviews, and to generate and disseminate guidance on enhancing the Nation's preparedness and response to the psychological consequences of terrorism and other traumatic events. For example, NIMH contributed to the following efforts to develop and disseminate research and practice guidance:

- Mental Health and Mass Violence: Evidence-Based Early Psychological Intervention for Victims/Survivors of Mass Violence. A Workshop to Reach Consensus on Best Practices (NIMH (DHHS), U.S. Departments of Defense, Justice, and Veterans Affairs, and the American Red Cross) http://137.187.63.95/publicat/massviolence.cfm
- Ethical Issues Pertaining to Research in the Aftermath of Disasters (NIMH (DHHS), New York Academy of Medicine) _http://www.nimh.nih.gov/scientificmeeting_s/disaster.cfm
- Eighteenth Annual Rosalynn Carter Symposium on Mental Health Policy in 2002. Status Report: Meeting the Mental Health Needs of the Country in the Wake of September 11, 2001 http _://www._cartercenter.org/news/programresults47. htm
- Institute of Medicine report Responding to the Psychological Consequences of Terrorism http://www.iom.edu/proj_ect.asp?id=3_895
- National Advisory Committee on Children and Terrorism http://www.bt.cdc.gov/children/recommend.asp

Item

Selective Serotonin Reuptake Inhibitors - The Committee urges the NIMH, in collaboration with the NICHD and other appropriate Institutes, to develop and conduct studies to examine the safety and efficacy of selective serotonin reuptake inhibitors [SSRIs] in children and adolescents. SSRIs are prescribed to millions of American children each year, and that number continues to increase dramatically. Yet there is conflicting information about the benefits and possible risks of using SSRIs to treat youth suffering from depression. Therefore, the Committee recommends that studies be designed to conclusively answer questions about the safety and efficacy of SSRIs in youth suffering from depression. The Committee further recommends that these studies focus

on original research to the extent that existing data prove insufficient to answer such questions, (p. 152)

Action taken or to be taken

Research on the safety and efficacy of antidepressant medications in children continues to be a high priority at NIMH, as it has for some time. In the early 1990s, NIMH funded one of the first placebo-controlled studies of fluoxetine (Prozac), an SSRI, in childhood depression.

More recently, a much larger NIMH study, conducted at 13 sites across the country, the Treatment of Adolescents with Depression Trial (TADS), was completed and the results published in August of this year. TADS demonstrated that fluoxetine is an effective treatment for adolescents with major depressive disorder. When fluoxetine is combined with a particular type of psychotherapy, "cognitive-behavioral therapy" (CBT), it is even more effective. There is concern that SSRI medications, including fluoxetine, can increase the risk for suicidal behaviors, such as suicidal threats and attempts. The TADS data add to data from other industry-funded studies that suggest that this may be case for a few subjects, but for the large majority of patients treatment decreases the risk for suicidal behavior. Thus, the TADS study provides strong evidence that there is a favorable balance between risks and benefits for fluoxetine as a treatment for adolescent depression. It also demonstrates the importance for careful monitoring of depressed patients during treatment because suicidal behavior is a risk intrinsic to depression and because treatment itself can, in rare cases, increase the risk for possible suicide related events.

NIMH is now funding an extended follow-up of the youth that participated in TADS in order to determine long-term benefits and risks associated with treatment. Results should become available within the next year. In addition to TADS, NIMH is funding other multi-site trials in adolescent depression that will contribute new data on the safety and effectiveness of antidepressants.

NIMH, in collaboration with NIAAA, NIDA and the American Foundation for Suicide Prevention, funded 4 developing centers in FY04 focused on suicide prevention. These centers will be asked to assist in finding new approaches to assessing the safety of SSRIs among depressed persons.

NIMH is also convening expert groups to help the Institute determine which further studies would be most informative and if systematic studies of naturalistically treated patients in the community may provide useful information about the safety of medications.

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Institute of Mental Health	Section 464R	42§285p	Indefinite	$1,351,861,000	Indefinite	$1,357,712,000
National Research Service Awards	Section 487(d)	42§288	a/	60,072,000	b/	59,980,000
Total, Budget Authority				1,411,933,000		1,417,692,000

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

b/ Reauthorizing legislation will be submitted.

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1997	589,187,000 2/	701,247,000	589,187,000 2/	701,107,000 3/
1998	628,739,000 2/	744,235,000	759,956,000	750,241,000
1999	699,679,000 2/4/	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/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

3/ Excludes enacted administrative reductions of $478,000.

4/ Reflects a decrease of $2,111,000 for the budget amended for bioterrorism.

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	93	93	93
Division of Neuroscience and Basic Behavioral Science	26	30	30
Division of AIDS and Health and Behavior Research	19	24	24
Division of Services and Intervention Research	25	28	28
Research and Treatment Development	15	16	16
Division of Pediatric Translational Research and Treatment Development	12	13	13
Division of Extramural Activities	37	44	44
Division of Intramural Research Programs	463	468	468
Total	690	716	716
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2002	11.1
2003	11.2
2004	11.6
2005	11.6
2006	11.6

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	7	7	7
Total - ES Salary	$1,008,690	$1,028,864	$1,049,441
GM/GS-15	51	51	51
GM/GS-14	88	88	88
GM/GS-13	65	65	65
GS-12	80	81	81
GS-11	87	88	88
GS-10	1	1	1
GS-9	55	58	58
GS-8	29	33	33
GS-7	21	31	31
GS-6	4	8	8
GS-5	4	4	4
GS-4	3	4	4
GS-3	2	2	2
GS-2	1	1	1
GS-1	0	0	0
Subtotal	491	515	515
Grades established by Act of July 1,1944 (42 U.S.C. 207):			
Assistant Surgeon General	0	0	0
Director Grade	13	13	13
Senior Grade	1	1	1
Full Grade	1	1	1
Senior Assistant Grade	0	0	0
Assistant Grade	0	0	0
Subtotal	15	15	15
Ungraded	179	179	179
Total permanent positions	475	512	512
Total positions, end of year	692	716	716
Total full-time equivalent (FTE) employment,end of year	690	716	716
Average ES salary	$144,099	$146,980	$149,920
Average GM/GS grade	11.6	11.6	11.6
Average GM/GS salary	$76,325	$79,225	$82,394