Director's Report to the National Advisory Mental Health Council

September 15, 2006

I am pleased to welcome members of the National Advisory Mental Health Council (NAMHC) and other participants and guests to our 213th Council meeting. Since our last meeting in May, the National Institute of Mental Health (NIMH) has made progress on several fronts, which I share with you in this report.

In light of recent events, I would first like to offer a few words in memory of Dr. Wayne S. Fenton. On September 3, 2006, we at NIMH tragically lost one of our most committed and talented colleagues. A research psychiatrist, Dr. Fenton had been at NIMH since 1999, where he provided leadership for a number of important research initiatives regarding the pathophysiology and treatment of serious mental illness. One of his more recent initiatives was the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). This was part of a concentrated NIMH effort to develop new treatments to improve cognitive impairment for people with schizophrenia, to enable them to live and work in the community. For the past two years, Dr. Fenton served as both Director of the Division of Adult Translational Research and Treatment Development (DATR), as well as Associate Director for Clinical Affairs. He also maintained a private practice expressly for treating those with the most serious mental illnesses, in addition to supporting both local and national advocacy efforts. Throughout his professional career, Dr. Fenton was known as a psychiatrist dedicated to caring for and advocating for the most severely mentally ill patients, often meeting them in their homes or halfway houses rather than his office. He received many national awards for his dedication to the treatment of schizophrenia, including regular recognition in Best Doctors in America.

Dr. Fenton's death is a profound loss not only for his many friends and family and for his colleagues at NIMH, but for people with serious mental illness everywhere.

NIH-Wide Update

NIH Office of Portfolio Analysis and Strategic Initiatives (OPASI) Solicits Input for Roadmap

Now in its third year of implementation, the National Institutes of Health (NIH) Roadmap is beginning to yield accessible resources for biomedical researchers, training programs in interdisciplinary and multidisciplinary sciences, and scientific advances that may help improve the health of the nation. These successes, along with recognition of the ongoing need for a medical research "incubator space," have led to the institutionalization of the NIH Roadmap process within the Division of Strategic Coordination (DSC) in the new NIH OPASI. OPASI's strategic initiatives will address critical roadblocks and knowledge gaps that constrain rapid progress in biomedical research. Focused specifically on areas of research that cut across or fall between the missions of individual NIH Institutes and Centers (ICs), these initiatives synergize the work of separate ICs and address issues that are the responsibility of NIH as a whole.

In July, NIH began convening consultation meetings and soliciting ICs and Program Offices in the Office of the Director (OD) to identify ideas for a new cohort of strategic initiatives that address major, cross-cutting, biomedical research challenges. Input from the science and lay communities will also be solicited using a web-based Request for Information.

DSC staff will review all idea nominations according to the following criteria:

- Is the proposed initiative truly transforming—could it dramatically affect how biomedical and/or behavioral research is conducted over the next decade?
- Will the outcomes from proposed initiatives synergistically promote and advance the missions of individual ICs to benefit health?
- Does the proposed initiative require participation from NIH as a whole and/or does it address an area(s) of science that does not clearly fall within the mission of any one IC or OD Program Office?
- Is the proposed initiative something that no other entity is likely or able to do, and is there a public health benefit to having the research results in the public domain?

After all nominations have been collected, the IC Directors will meet in late November to prioritize ideas for review and selection by the NIH Director. Selected ideas will then proceed into concept development phases, and in 2007, initiative finalists will be identified for implementation in Fiscal Year (FY) 2008.

NIH Roadmap – Selected Updates

The NIH Roadmap is an integrated vision to deepen the understanding of biology, stimulate interdisciplinary research, and reshape clinical research to accelerate medical discovery and improve public health. A full summary of Roadmap activities can be found at http://www.nihroadmap.nih.gov/. Here I will summarize just a few highlights where NIMH served as the lead Institute.

Molecular Libraries Roadmap

The Molecular Libraries Screening Centers Network, or MLSCN (http://mli.nih.gov), in the initial year of its three-year funding period, has made significant progress toward its goal of finding biologically active compounds that can be developed for medical uses. As of May, MLSCN advances include a novel chemical probe that can boost or block the passage of substances through the body's protective barriers[1] and two innovative, molecular screening technologies.[2,3] These advances will have high impact on the fields of chemical biology and biomolecular screening. In July, *NIH News* and *NIH Research Matters* collectively published four articles on MLSCN research discoveries, including:

- "New Tool Can Boost or Block the Body's Protective Inner Barriers," July 13, 2006
- "Researchers Uncover Genetic Clues to a Common Form of Age-Related Dementia," July 17, 2006
- "Probing the Body's Protective Inner Barriers," July 21, 2006
- "New Paradigm Will Help Identify Leads for Drug Discovery: NIH Roadmap Initiative Develops More Precise Method for Rapidly Screening Chemical Compounds," July 24, 2006

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[1] Sanna MG, Wang SK, Gonzalez-Cabrera PJ, Don A, Marsolais D, Matheu MP, Wei SH, Parker I, Euijung J, Cheng WC, Cahalan MD, Wong CH, Rosen H. Enhancement of capillary leakage and restoration of lymphocyte egress by a chiral $S1P_1$ antagonist in vivo. *Nat Chem Biol*. 2006 Aug;2(8):434–41.

[2] Edwards BS, Young SM, Oprea TI, Bologa CG, Prossnitz ER, Sklar LA. Biomolecular screening of formylpeptide receptor ligands with a sensitive, quantitative, high-throughput flow cytometry platform. *Nat Protoc*. 2006 Jun;1(1): 59–66.

[3] Inglese J, Auld DS, Jadhav A, Johnson RL, Simeonov A, Yasgar A, Zheng W, Austin CP. Quantitative high-throughput screening: a titration-based approach that efficiently identifies biological activities in large chemical libraries. *Proc Natl Acad Sci U S A*. 2006 Aug 1;103(31):11473-8.

Currently, the centers are implementing 74 assay applications from the research community, and all 10 centers have added data to the PubChem BioAssay database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pcassay). Comprising 10 of 19 BioAssay contributors, the centers have deposited screening data for 962,380 substances, which were tested in 49 assays. The Molecular Libraries technologies made it possible to efficiently screen these nearly 1 million substances, out of which 3,936 bioactive compounds have been identified. All are ripe for further research and development.

Translational Research

The reviews for Institutional Clinical and Translational Science Awards (CTSAs) and Planning Grants for CTSAs took place in July. At this time, no official information on awards is available for dissemination, pending the meeting of the National Center for Research Resources (NCRR) Council. A new Request for Applications (RFA) for FY 2007 CTSA applications was released in August 2006.

Clinical Outcomes Assessment

The Patient Reported Outcomes Measurement Information System (PROMIS) initiative seeks to develop a publicly accessible, computerized, adaptive testing system based on item-response theory that can measure patient-reported symptoms across a wide variety of chronic diseases and conditions. At the completion of its second year of a five-year contract agreement, the PROMIS team has established a domain framework, with five domains chosen for initial development: physical functioning, pain, fatigue, emotional distress (depression, anxiety, anger, and alcohol use/abuse), and social role participation. More than 7,000 items were initially generated from a review of these domains and their measurement, and a combination of evaluation methods resulted in approximately 760 revised items. These items are currently being tested in approximately 8,000 general population samples and 4,000 disease group samples for further calibrations. Testing will be completed in early 2007.

NIH Blueprint for Neuroscience Research

The Neuroscience Blueprint (http://braininfo.us/blueprint/index.html) is a framework to enhance cooperation among the 16 NIH ICs that support research on the nervous system. In FY 2006, Blueprint funds were used to both expand existing activities and create new tools and resources and to support the following initiatives:

- Neuroscience Blueprint Interdisciplinary Center Core Grants – This initiative will support centralized resources and facilities shared by neuroscience investigators. It is anticipated that up to four projects will be awarded in FY 2006.
- New Ways to Image Neural Activity – This initiative addresses the need to develop technologies that can visualize neural activity with greater spatial and temporal resolution than is currently possible. It is anticipated that up to six projects will be awarded in FY 2006.
- Clearinghouse for Neuroimaging Software and Data – This initiative will establish a clearinghouse for neuroimaging tools and databases to facilitate wider dissemination and use of these resources. It will initially focus on functional magnetic resonance imaging (fMRI). It is anticipated that one project will be awarded in FY 2006.

  Many neuroimaging tools and databases are underutilized because they are not user-friendly or easily adoptable.

- Neuromouse – This topic includes two initiatives:
    - Development of Recombinase-Expressing ('Driver') Mouse Lines for Studying the Nervous System to study gene function in distinct cell types and/or useful temporal and spatial patterns in the nervous system. It is anticipated that up to four projects will be awarded in FY 2006.
    - Distribution or "Repatriation" of Existing Mouse Lines – This initiative involves creating repositories of existing mouse lines for wider use by the scientific community. To date approximately 220 mouse lines have been targeted for the repository.
- Development of the NIH Toolbox for Assessment of Neurological and Behavioral Function – This initiative will develop a set of neurological and behavioral measures of cognitive, sensory, and/or motor aspects of neural functioning appropriate for a variety of projects, including longitudinal epidemiologic studies and prevention and intervention trials. It is anticipated that up to two projects will be awarded in FY 2006.
- Training Initiatives – This topic involves three initiatives to ensure the training of a new generation of neuroscientists in translational research, computational neuroscience, and neuroimaging:
    - Training in Translational Research in Neurobiology of Disease. It is anticipated that up to five projects will be awarded in FY 2006.
    - Training in Computational Neuroscience: From Biology to Model and Back Again. It is anticipated that up to six projects will be awarded in FY 2006.
    - Training in Neuroimaging: Integrating First Principles and Applications. It is anticipated that up to four projects will be awarded in FY 2006.

The Blueprint ICs have also projected the following plans for FY2007:

- Neurodegeneration Project Team
  Based on recommendations that emerged from a March 2006 workshop, this team is developing initiatives relevant to the following topics:

  1. New methods for delivering biologically active molecules into the brain or sensory organs with emphasis on blood-brain barrier transport
  2. Biomarkers/biosignatures for early detection of neurodegeneration (including imaging)
  3. Interdisciplinary postdoctoral training requiring fellows to have mentors in two, traditionally distinct areas that may contribute new insight for understanding and treating neurodegenerative disorders
  4. A similar interdisciplinary program for senior investigators providing short-term awards for research training in a different discipline that would foster new approaches

  In addition, internal Blueprint working groups will develop and implement administrative strategies to address these additional recommendations:

  1. Encourage and facilitate the use of existing biological materials for neuroscience research.
  2. Coordinate and publicize existing NIH programs in translational research that would be applicable to neurodegeneration.
  3. Develop and distribute tools to collect, analyze, and integrate large and diverse data sets.

The initiative concepts were reviewed and approved by the National Institute of Neurological Disorders and Stroke (NINDS) Advisory Council and will be posted on the NIH Blueprint for Neuroscience Research website at http://neuroscienceblueprint.nih.gov/.

NIMH Update

Update on Electronic Submission

The planned conversion of all R01s to electronic submission is on track for 2/1/2007. NIH will issue a "parent" R01 Funding Opportunity Announcement for R01 applications that are not responding to a specific initiative from a particular Institute. Since all applicants will be required to respond to announcements electronically, the parent announcement will accommodate any investigator-initiated R01 applications that previously would not have cited an announcement. The Institutes will also re-issue new R01 announcements for specific research areas. The NIH Guide to Grants and Contracts (http://grants1.nih.gov/grants/guide/index.html) and the Electronic Submission website (http://era.nih.gov/ElectronicReceipt/) will post the latest news on this continuing process.

To prepare extramural grant applicants for the transition of R01s to electronic format, NIH will hold two training sessions on December 5, 2006. In addition, there will be hands-on computer lab sessions in December to give applicants the opportunity to practice with eSubmission experts. Please see http://era.nih.gov/ElectronicReceipt/training_12052006.htm for more details. General training videos are now currently available online at http://era.nih.gov/ElectronicReceipt/training.htm#4.

Public Reviewer Training and Orientation Session

Input from public members adds important perspectives to the review process and helps to ensure public health relevance is discussed during peer review. As such, NIMH has included public reviewers as full voting members on committees reviewing intervention and services research applications for the past six years. In June, the Review Branch hosted a public reviewer workshop for 37 individuals who were selected for their involvement with mental health care as consumers, family members, mental health professionals, advocates, educators, or other related roles. The attendees learned about NIMH-supported research and the role of the peer review process. Throughout the day, the attendees heard from NIMH OD and Division of Extramural Activities (DEA) staff, review committee chairpersons, and past public participants and participated in a mock study section review. Participant feedback indicated that the workshop was highly informative and that the vast majority of attendees felt willing to serve as public reviewers.

Council Member Elected Chairman of the National Mental Health Association

The National Mental Health Association's (NMHA) Delegate Assembly unanimously elected Council member Sergio Aguilar-Gaxiola, MD, PhD, as its new Chairman of the Board of Directors, beginning in June 2006. Dr. Aguilar-Gaxiola, the first Latino to serve as board chair, will provide direction and leadership to the country's largest mental health organization, with more than 340 affiliates nationwide.

Science of Note

Experimental Medication Kicks Depression in Hours Instead of Weeks

Current antidepressants routinely take eight weeks or more to exert their effect in treatment-resistant patients and four to six weeks in more responsive patients—a major drawback of these medications. To help find better treatments, Carlos A. Zarate Jr. and colleagues at NIMH randomly assigned 18 treatment-resistant, depressed patients to receive either a single intravenous dose of ketamine (Ketalar®) or a placebo. Ketamine, a medication used in higher doses as an anesthetic in humans and animals, blocks a brain protein called the N-methyl-D-aspartic acid (NMDA) receptor. Previous studies have shown that blocking this protein reduces depression-like behaviors in animals. In this

preliminary clinical study, depression improved within one day in 71 percent of those who received ketamine, and 29 percent of these participants became nearly symptom-free within one day. Thirty-five percent of those who received ketamine still showed benefits seven days later. None of the participants, all of whom received a low dose, had serious side effects from ketamine, which can produce hallucinations and euphoria at higher doses. The authors suggest that such findings may help scientists understand how and why depression occurs, reveal biological markers that may one day aid in diagnosis, and point the way to more precise targets for new medications.

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006 Aug;63(8):856-64.

Job Performance Deficits Due to Depression

A newly published study, conducted by researchers led by David Adler at Tufts-New England Medical Center, compared depressed employees with two groups: those with rheumatoid arthritis, which is a condition associated with work disability, and depression-free healthy employees. The study enrolled 572 patients who were recruited from February 2001 and March 2003 from primary care physician offices. Participants were followed for 18 months. When compared, the depression group was far more vulnerable to job loss, absenteeism, and impaired productivity while at work. Furthermore, the researchers noted that even when depressed subjects received treatment and experienced improvement in their clinical symptoms, their work productivity was still impaired.

Adler DA, McLaughlin TJ, Rogers WH, Chang H, Lapitsky L, Lerner D. Job Performance Deficits Due to Depression. Am J Psychiatry. 2006 Sep 1;163 (9):1569-1576.

Adult Children of Depressed Parents Have Higher Risk of Mental and Physical Illness

Recent findings from a prospective, 20-year follow-up study by Myrna Weissman and colleagues at Columbia University showed that adult offspring (mean age 35) of parents with moderate to severe depression, compared to those of parents without depression, have a three-fold increased risk of lifetime mood and anxiety disorders, particularly major depression and phobic disorders. Offspring of depressed parents also have higher rates of panic disorder, alcohol dependence, and drug dependence than offspring of non-depressed parents, although differences are not statistically significant. Consistent with previous findings, the age of onset of anxiety disorders peaks prior to puberty, and the peak onset of depression and substance dependence follow in mid-to-late adolescence (between ages 15–20). In addition to the increased risk for psychopathology, offspring of depressed parents also reported poorer functioning in some social domains and increased risk for physical illnesses, with elevated (but nonsignificant differences in) rates of cardiovascular disease and neuromuscular disorders. This is the first study to follow children at high risk for the development of psychopathology from childhood (ages 6–23) to adulthood and to directly examine the continued risk of parental depression on offspring health.

Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H. Offspring of depressed parents: 20 years later. Am J Psychiatry. 2006 Jun;163(6):1001-8.

Bipolar Disorder Exacts Twice Depression's Toll in Workplace

Major depression is six times more prevalent than bipolar disorder, but bipolar disorder costs twice as much in lost productivity—65.5 lost workdays per year per worker—and nearly half as much in dollars—a disproportionately high $14.1 billion annually—according to a study by Ronald Kessler, Philip Wang, and colleagues at Harvard University. Based on the National Comorbidity Survey-Replication (NCS-R) study population, the researchers measured the persistence of the disorders by asking respondents how many days during the past year they experienced an episode of mood disorder. They judged the severity based on symptoms during a worst month. Lost work days due to

absence or poor functioning on the job, combined with salary data, yielded an estimate of lost productivity due to the disorders. The researchers traced the higher toll mostly to bipolar disorder's more severe depressive episodes rather than to its agitated manic periods. The bipolar-associated depressive episodes were much more persistent, affecting 134–164 days compared to 98 days for major depression. The bipolar-associated depressive episodes were also more severe. All measures of lost work performance were consistently higher among workers with bipolar disorder who had major depressive episodes than those who reported only manic or hypomanic episodes. The latter workers' lost performance was on a par with workers who had major depressive disorder.

Kessler RC, Akiskal HS, Ames M, Birnbaum H, Greenberg P, Hirschfeld RMA, Jin R, Merikangas KR, Simon GE, Wang PS. Prevalence and Effects of Mood Disorders on Work Performance in a Nationally Representative Sample of U.S. Workers. Am J Psychiatry. 2006 Sep 1;163 (9):1561-1568.

Fear Circuit Flares as Bipolar Youth Misread Faces

Children with bipolar disorder may misread neutral facial expressions as hostile and have heightened reactions to emotional indicators in neutral faces, thus revealing some of the underlying workings of mania and depression that can disrupt the lives of up to one percent of children. Ellen Leibenluft, Brendan Rich, Daniel Pine, and colleagues at NIMH's Mood and Anxiety Disorders Program studied brain scans of the left amygdala—a fear hub—and related brain structures in youth with bipolar disorder. They found that youth with the disorder more often misinterpreted neutral faces as hostile—and their amygdala flared accordingly—than youth without the disorder. This face-processing deficit could account for the poor social skills, aggression, and irritability that children with bipolar disorder often exhibit.

Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, Fromm SJ, Pine DS, Leibenluft E. Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. Proc Natl Acad Sci USA. 2006 Jun 6;104(23):8900-5.

New Factors Identified for Predicting Violence in Schizophrenia

Violent behavior by people with schizophrenia is uncommon. However, when it occurs, it is of concern. The causes of such behavior have been poorly understood. This study, conducted by Jeffrey Swanson (Duke University), Jeffrey Lieberman (Columbia University), and colleagues, analyzed data from the NIMH-funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) to understand the factors that increase risk of violent behavior in this population. Results identified clusters of contributing factors, including specific types of schizophrenia symptoms, co-occurring substance abuse, specific interpersonal and social factors, presence of depressive symptoms, childhood conduct problems, and recent victimization. These findings will be useful in developing services and interventions to manage and reduce violent behavior by persons with schizophrenia.

Swanson JW, Swartz MS, Van Dorn RA, Elbogen EB, Wagner HR, Rosenheck RA, Stroup TS, McEvoy JP, Lieberman JA. A national study of violent behavior in persons with schizophrenia. Arch Gen Psychiatry. 2006 May;63(5):490-9.

Activating Nicotinic Receptor Combats Cognitive Deficits of Schizophrenia

Current antipsychotic medications can improve the delusions and hallucinations of schizophrenia, but do not reverse cognitive impairments responsible for long-term disability. A study by Robert Freedman and colleagues at the University of Colorado offered a direct demonstration that activating the alpha-7 nicotinic acetylcholine receptor improved neurocognition in people with schizophrenia. In a small, placebo/control study, the investigators enhanced the receptor's activity with the compound DMBX-A. Compared to placebo, DMBX-A resulted in significant neurocognitive improvement and decreased inhibition of P50, a biomarker for the gene that encodes the receptor. Nicotine is a low-potency agonist of the receptor, and the researchers suggest that

nicotine use among the more than 80 percent of schizophrenia patients who smoke may in part be an effort to reverse attentional impairments. Because of rapid receptor desensitization, however, nicotine has no clinical value. Pending further research, other agents that act on the receptor may be found to be useful.

Olincy A, Harris JG, Johnson LL, Pender V, Kongs S, Allensworth D, Ellis J, Zerbe GO, Leonard S, Stevens KE, Stevens JO, Martin L, Adler LE, Soti F, Kem WR, Freedman R. Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. Arch Gen Psychiatry. 2006 Jun;63(6):630-8.

Variation in Gene Raises Schizophrenia Risk

A variation in a gene essential to development of cells that form myelin, the axonal insulating material that increases the conduction of electrical signals, appears to raise risk of schizophrenia. The variation in the gene, *OLIG2*, appears to raise risk of schizophrenia by itself, and in interaction with other genes implicated in schizophrenia (*CNP* and *ERBB4*, but not *NRG1*) disrupts the function of oligodendrocytes, the myelin-forming cells. This finding by Kenneth L. Davis and colleagues at Mt. Sinai School of Medicine, Bronx Veterans Affairs (VA) Medical Center, and Cardiff University adds to recent evidence that abnormalities in cells that support neurons, such as oligodendrocytes, rather than in neurons themselves, may be a primary site of schizophrenia pathology. The variation in the *OLIG2* gene may cause problems in the myelin sheath formed by oligodendrocytes, potentially disrupting neurons' ability to communicate with one another, thus resulting in some of the symptoms of schizophrenia. The study was conducted using human DNA samples and brain tissue and mouse brain tissue.

Georgieva L, Moskvina V, Peirce T, Norton N, Bray NJ, Jones L, Holmans P, Macgregor S, Zammit S, Wilkinson J, Williams H, Nikolov I, Williams N, Ivanov D, Davis KL, Haroutunian V, Buxbaum JD, Craddock N, Kirov G, Owen MJ, O'donovan MC. Convergent evidence that oligodendrocyte lineage transcription factor 2 (OLIG2) and interacting genes influence susceptibility to schizophrenia. Proc Natl Acad Sci USA. 2006 Aug 15;103(33):12469-74.

Gene Signaling Contributes to Reduced NMDA Function in Schizophrenia

An important development in schizophrenia research is the concept that reduced function in the biology of excitatory amino acid transmitters, such as NMDA, is central to the pathology of the disorder. New findings suggest that enhanced signaling by the protein NRG1 may contribute to reduced function of NMDA in schizophrenia. The gene that encodes NRG1 has been linked to schizophrenia, but how alterations in the gene and in NRG1 receptors (erbBs) lead to increased risk of the disorder is unknown. Showing how relevant pathways are altered has been difficult, because studies can be conducted only through human neuroimaging and/or with postmortem brain tissue. Using a novel approach in which postmortem tissue could be stimulated, Chang-Gyu Hahn from the University of Pennsylvania and colleagues found striking changes in signaling by NRG1 and one of its receptors, erbB4, in tissue from the prefrontal cortex of schizophrenia patients. NRG1-induced erbB4 activation was dramatically enhanced and association of erbB4 coupling with NMDA receptors was significantly altered. In brain tissue stimulated with NRG1 and NMDA, suppression of NMDA receptor activation was greater in tissue from schizophrenia patients than in tissue from controls, adding to evidence that dysregulation of NRG1-erB4 signaling is involved in the reduced NMDA function implicated in schizophrenia.

Hahn CG, Wang HY, Cho DS, Talbot K, Gur RE, Berrettini WH, Bakshi K, Kamins J, Borgmann-Winter KE, Siegel SJ, Gallop RJ, Arnold SE. Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. Nat Med. 2006 Jul;12(7):824-8.

Males with Autism Have Fewer Cells in Amygdala

Males with autism have significantly fewer cells in the amygdala, an area of the brain that processes social and emotional information, compared to males without the disorder, reported Cynthia Mills

Schumann and David G. Amaral of the University of California, Davis. The investigators compared brain tissue from nine males with autism and 10 males without the disorder, all of whom had died of natural causes, using a modern (stereological) technique. There were no differences between the two groups in the average size of the neurons in the amygdala or in the overall volume of the amygdala or its subregions. The scientists did, however, find a reduced number of cells in the amygdala and a subregion called the lateral nucleus. The results of this study are important for understanding the pathophysiology underlying autism, of which causes remain unknown.
Schumann CM, Amaral DG. Stereological analysis of amygdala neuron number in autism. J Neurosci. 2006 Jul 19;26(29):7674-9.

Genetically Engineered Mice Allow Scientists to Watch Nerve Cells in Action
The brain's ability to change in response to experience is essential for healthy brain function, and abnormalities in this process are known to contribute to a variety of psychiatric disorders. To better understand the ways in which nerve cells react to an animal's experience requires the ability to monitor the activity of a given set of cells, over a prolonged period of time, in the live animal. However, current tools do not have sufficient resolution to observe individual nerve cells and do not allow repeated observation of the same cells over a period of days. Kuan Hong Wang at the Howard Hughes Medical Institute at MIT and colleagues engineered mice that have a genetically encoded, optical reporter in certain nerve cells. The fluorescent reporter protein is linked to a gene that is activated by neuronal stimulation, so that the cells light up when that region of the brain responds to a stimulus. This allowed the investigators to observe individual nerve cells in a mouse's brain under a microscope and to watch the same cells over several days as they changed in response to experience. Neurons in the visual cortex of these mice changed after exposure to visual stimuli, which were similar to changes detected by traditional electrophysiology. The genetically engineered mice provide neuroscientists with the ability to literally watch individual nerve cells as they change, and represent a powerful new approach to better understanding the relationship between genes and cognition.
Wang KH, Majewska A, Schummers J, Farley B, Hu C, Sur M, Tonegawa S. In Vivo Two-Photon Imaging Reveals a Role of Arc in Enhancing Orientation Specificity in Visual Cortex. Cell. 2006 Jul 28;126(2):389-402.

Advances in Research On Fear Learning and Related Research
Among the findings on molecular and cellular mechanisms generated by Joseph LeDoux's Conte Center for the Neuroscience of Fear and Anxiety:

- Raphael Lamprecht of New York University and colleagues focused on the role of two molecular components of the neuronal cytoskeleton (the physical scaffolding of neurons) in synaptic plasticity and fear learning. The neuronal cytoskeleton controls developmental processes thought to be involved in memory formation. Fear conditioning in rats lead to movement of prolifin, a protein that promotes cytoskeletal formation, into structures called dendritic spines in the lateral amygdala, the locus of fear conditioning. The spines underwent enlargement in specialized membrane protein structures. These actions could provide the physical basis for enhanced synaptic response in the lateral amygdala. In another study, Lamprecht and colleagues showed that inhibition of myosin light chain kinase (MLCK), a cytoskeletal protein that regulates cellular events related to synaptic transmission, plays an important role in regulating synaptic plasticity underlying fear learning in the lateral amygdala. Normally, MLCK appears to suppress fear learning and may be important for preventing fear responses to nonthreatening stimuli. Disrupting this

mechanism may contribute to the development of pathological fear and anxiety.
Lamprecht R, Farb CR, Rodrigues SM, LeDoux JE. Fear conditioning drives profilin into amygdala dendritic spines. Nat Neurosci. 2006 Apr;9(4):481-3.

Lamprecht R, Margulies DS, Farb CR, Hou M, Johnson LR, LeDoux JE. Myosin light chain kinase regulates synaptic plasticity and fear learning in the lateral amygdala. Neuroscience. 2006;139(3):821-9.

- Conor Liston, from The Rockefeller University, and colleagues provided the first direct evidence that dendritic remodeling in the prefrontal cortex may underlie functional deficits in attentional control symptomatic of stress-related mental illnesses. Chronic stress induced different structural effects in two areas of the brain that predicted severity of stress-related impairments in attention shifting. Stress selectively impaired extradimensional attention shifting, which depends on medial prefrontal cortex function, but not reversal learning, an orbital frontal cortex-dependent function.
Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, Morrison JH, McEwen BS. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. J Neurosci. 2006 Jul 26;26(30):7870-4.

- Research on consolidated memories (memories strengthened through molecular processes) has raised a key question as to whether reactivation makes associated memories labile in a way that requires reconsolidation. Jacek Debiec, of New York University, and colleagues found that directly reactivated memories become labile, but indirectly reactivated (i.e., associated) memories do not. This suggests that memory reactivation produces content-limited changes in a memory and its associations. It may be possible to use disruption of reconsolidation to reduce fear-arousing aspects of emotional memory without radically altering personality via widespread changes in the associative structure of memory.
Debiec J, Doyere V, Nader K, Ledoux JE. Directly reactivated, but not indirectly reactivated, memories undergo reconsolidation in the amygdala. Proc Natl Acad Sci USA. 2006 Feb 28;103(9):3428-33.

Molecular Target Identified for Selective Memory Erasure

Despite the wealth of recent data on molecules that influence the learning and memory process, identifying molecules specific to the retention of memories has proved to be a challenge. This is because none of the molecules tested thus far have been specific to the later stages of long-term potentiation (LTP), a sustained increase in synaptic transmission that is thought to play a role in information storage in the hippocampus. Todd Sacktor and colleagues at SUNY Downstate Medical Center in Brooklyn, New York, have now discovered that a potent inhibitor of the enzyme PKMzeta selectively reverses established late LTP without affecting the LTP induction process in rats. This inhibitor also produces a persistent loss of one-day-old spatial information without affecting the learning process. These results thus identify a molecular target for selectively erasing memory and substantially advance the case for LTP as a neural mechanism for memory. They are also of translational interest for the potential treatment of disorders resulting from aberrant or maladaptive memory, such as PTSD, neuropathic pain, and epilepsy.
Pastalkova E, Serrano P, Pinkhasova D, Wallace E, Fenton AA, Sacktor TC. Storage of spatial information by the maintenance mechanism of LTP. Science. 2006 Aug 25;313(5790):1141-4.

Receptor Knockout Yields an Adventurous Mouse

Mice altered to lack a particular type of receptor in the brain's executive hub are more prone to go where normal mice fear to tread. In choosing between the dueling impulses to seek novelty or avoid a threat, whether an animal tended to venture out or to play it safe hinged on the presence of serotonin 2A receptors in the brain's outer layer, or cortex. Jay Gingrich, Rene Hen, Noelia Weisstaub, and colleagues at Columbia University molecularly knocked out the gene that encodes

the receptor in the cortex to identify the neural underpinnings of such approach-avoidance conflict anxiety. While it was known that serotonin plays a key role in mediating such anxiety-related behavior, how and where this happens in the brain has been unclear. The findings confirm that the receptors in the brain's thinking hub, rather than in other areas, are critical for assessing risks. The results also suggest that anti-anxiety drugs work by chronically blocking and causing a reduction in expression of genes for the 2A receptors, a process that typically takes a few weeks. The new insights into the workings of this system may lead to improved treatments for anxiety disorders.

Weisstaub NV, Zhou M, Lira A, Lambe E, Gonzalez-Maeso J, Hornung JP, Sibille E, Underwood M, Itohara S, Dauer WT, Ansorge MS, Morelli E, Mann JJ, Toth M, Aghajanian G, Sealfon SC, Hen R, Gingrich JA. Cortical 5-HT2A receptor signaling modulates anxiety-like behaviors in mice. Science. 2006 Jul 28;313(5786):536-40.

Blood Pressure Medication Relieves Daytime PTSD Symptoms

Current treatments for post-traumatic stress disorder (PTSD) are reported to be only minimally effective in reducing both nighttime and daytime re-experiencing and intrusion symptoms; many people with PTSD self-medicate with drugs or alcohol. Recent studies have demonstrated that prazosin (Minipress®), a generically available alpha-1 adrenergic antagonist, can reduce nighttime PTSD symptoms. A new study by Fletcher B. Taylor, of the Veterans Affairs (VA) Puget Sound Health Care System and University of Washington, and colleagues suggests that daytime administration of prazosin also may bring relief from anxiety, nervousness, and fear. The results suggest that daytime administration will not interfere with routine daytime tasks and skills, indicating that prazosin may be an effective addition to current treatments.

Taylor FB, Lowe K, Thompson C, McFall MM, Peskind ER, Kanter ED, Allison N, Williams J, Martin P, Raskind MA. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. Biol Psychiatry. 2006 Apr 1;59(7):577-81.

Are Some People Primed to Develop PTSD?

Studies have shown that psychiatric illness is a risk factor for developing new PTSD after trauma exposure. Results from a study of patients being treated for bipolar disorder when the terror attacks of September 11, 2001, took place support these prior findings, report Mark Pollack of Massachusetts General Hospital and colleagues. Twenty percent of the patients reported new-onset PTSD. Those in a hypomanic state at the time of the attacks were at even greater risk for developing new PTSD, even after taking into account severity of trauma exposure. Sixty-two percent of patients in a hypomanic, manic, or mixed mood state at the time of the trauma developed PTSD. Although this finding does not rule out other risk factors, it offers a plausible and testable hypothesis about the role of arousal during trauma exposure among all persons exposed to extreme stress and their risk for new psychiatric illness. The majority of patients involved in this study experienced the 9/11 attacks indirectly, through television and other news reports. Whether this type of exposure is adequate for diagnostic exposure criteria is an open question, but the current study supports the idea that indirect exposure can be a significant issue among those who are most vulnerable to environmental stress.

Pollack MH, Simon NM, Fagiolini A, Pitman R, McNally RJ, Nierenberg AA, Miyahara S, Sachs GS, Perlman C, Ghaemi SN, Thase ME, Otto MW. Persistent posttraumatic stress disorder following September 11 in patients with bipolar disorder. J Clin Psychiatry. 2006 Mar;67(3):394-9.

Behaviors, Not ADHD Diagnosis, Predict Adolescents' Initial Substance Use

NIH researchers found that specific behaviors in preadolescent children may help predict who will begin to use tobacco, alcohol, or marijuana. Monique Ernst of NIMH and colleagues at the National Institute of Drug Abuse (NIDA) studied 12-to-14 year-olds over four years and found that the children who were aggressive tended to use tobacco and marijuana in later years, while the children

who were impulsive tended toward alcohol use. However, a diagnosis of attention-deficit/hyperactivity disorder (ADHD) did not predict which youth would begin to use substances. The distinction may help pediatricians and other health care providers to better focus prevention efforts on the adolescents who are most vulnerable to substance use. Most studies of this age group have focused on substance use, abuse, and dependence already in progress. This study examined 78 adolescents before they had used any substances and followed them over a long period, providing a window on risk and opportunities for prevention.

Ernst M, Luckenbaugh DA, Moolchan ET, Leff MK, Allen R, Eshel N, London ED, Kimes A. Behavioral predictors of substance-use initiation in adolescents with and without attention-deficit/hyperactivity disorder. Pediatrics. 2006 Jun;117(6):2030-9.

Brain Changes Mirror Symptoms of ADHD

Researchers studying the brain scans of children found that the front part of the hippocampus (the brain's memory hub) tended to be larger in children with ADHD, especially those with fewer symptoms, compared to children without the disorder. Bradley Peterson, of Columbia University and the New York State Psychiatric Institute, and colleagues suggest that such brain changes develop to help the child cope with the impatience and stimulus-seeking problems associated with the disorder. They also found that the amygdala (emotion-processing hub) is smaller in ADHD children, and that there were poor connections between the amygdala and the pre-frontal cortex, which may contribute to impulse-control problems associated with ADHD. In a similar long-term study, NIMH researchers Philip Shaw and Judith Rapoport found that the outer cortex of brains among youth with ADHD—an area that controls attention—is thinner and remains thin in those whose ADHD symptoms do not improve. In youth who showed improvement as they aged, the cortex thickened on the right side, suggesting that brain changes accompany improvements in coping with ADHD. The disorder is thought to stem from brain-circuit abnormalities.

Plessen KJ, Bansal R, Zhu H, Whiteman R, Amat J, Quackenbush GA, Martin L, Durkin K, Blair C, Royal J, Hugdahl K, Peterson BS. Hippocampus and Amygdala Morphology in Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry. 2006 Jul;63(7):795-807.

Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, Giedd J, Castellanos FX, Rapoport J. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2006 May;63(5):540-9.

Shy Temperament Associated with Heightened Brain Activity

NIMH intramural researcher Monique Ernst and colleagues found that children with extremely shy temperaments have heightened brain activity in response to any prominent event, whether it is positive or negative. The researchers studied the brain scans of 32 adolescents—13 of whom were considered to have a shy temperament and 19 of whom were not—and found that even when faced with an event that had rewarding implications, the shy children's brains overreacted, compared to the those of children who were not shy. Having a shy temperament early in life is a risk factor for developing certain mental disorders later. The findings help to fill in a growing map of potential links among functions of brain areas, behaviors, and risk of mental disorders.

Guyer AE, Nelson EE, Perez-Edgar K, Hardin MG, Roberson-Nay R, Monk CS, Bjork JM, Henderson HA, Pine DS, Fox NA, Ernst M. Striatal functional alteration in adolescents characterized by early childhood behavioral inhibition. J Neurosci. 2006 Jun 14;26(24):6399-405.

Antipsychotic Prescriptions Rise Sharply for Children and Adolescents

The number of antipsychotic medication prescriptions for children and adolescents increased six-fold from 1993 to 2002, according to a study of visits made by people 20 years old and younger to doctors' offices. Analyzing data from the National Ambulatory Medical Care Surveys, by the

National Center for Health Statistics, NIMH investigator Gonzalo Laje and colleagues from Columbia University reported that prescriptions increased from 201,000 to 1.2 million during that time. The researchers also found that 92 percent of the prescriptions were for newer antipsychotic medications—the "second-generation" antipsychotics—during the period from 2000 to 2002. These medications are approved for adults by the Food and Drug Administration (FDA), but there is not yet enough data on their long-term safety and efficacy in children and adolescents for FDA to consider approval for this age group. Only two older antipsychotic medications are FDA-approved for youth. In the analysis of data from 2000 to 2002, the prescription rate for antipsychotic medications was significantly higher for white, non-Hispanic, male youth than for female youth and youth of other racial and ethnic groups. Among the disorders studied, the antipsychotic medications were prescribed most frequently for disruptive behavior disorders, followed by mood disorders and developmental disorders.

Olfson M, Blanco C, Liu L, Moreno C, Laje G. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. Arch Gen Psychiatry. 2006 Jun;63(6):679-85.

Brain Link Identified in Strep-Triggered OCD

A likely mechanism by which a bacterial infection triggers obsessive compulsive disorder (OCD) in some children has been demonstrated by NIMH researcher Susan Swedo, Christine Kirvan of California State University, and colleagues. Their research suggests that an antibody triggered by strep throat acts on a brain enzyme, disrupting neuronal communications and triggering pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS), which is marked by tics and OCD symptoms. Three fourths of blood samples from acute, symptomatic PANDAS cases boosted the enzyme to significantly higher levels than samples from recovering, non-symptomatic patients. Similarly, nearly three-fourths of the samples from symptomatic cases contained antibodies for strep, compared to only 23 percent of samples from recovering, non-symptomatic patients. Notably, cerebrospinal fluid (CSF) from PANDAS patients contained highly elevated levels of the suspect strep-triggered enzyme while CSF of non-PANDAS subjects showed no such activation.

Kirvan CA, Swedo SE, Snider LA, Cunningham MW. Antibody-mediated neuronal cell signaling in behavior and movement disorders. J Neuroimmunol. 2006 Jul 26; [Epub ahead of print]

Impact of Hurricane Katrina on Mental Illness and Suicidality

From 2001–2003, residents of regions later struck by Hurricane Katrina were interviewed regarding mental health and suicidality as part of the NCS-R. After the hurricane, Ronald Kessler, of Harvard University, and colleagues asked the same questions of residents that had been asked in the earlier, pre-Katrina NCS-R, to assess the disaster's impact. They found that estimated prevalence of serious mental illness rose from 6.1 percent before Katrina to 11.3 percent after Katrina. Mild-to-moderate mental illness rose from 9.7 percent to 19.9 percent. However, prevalence of suicidal ideation and plans for suicide dropped among residents estimated to have mental illness, from 8.4 percent to 0.7 percent for suicidal ideation, and from 3.6 percent to 0.4 percent for plans for suicide. The researchers cited post-traumatic personal growth, which also was assessed in the survey, as a potential reason for the drop in suicidality, pending further investigation.

Kessler RC, Galea S, Jones TR, Parker HA, on behalf of the Hurricane Katrina Community Advisory Group. Bulletin of the World Health Organization. Article ID: 06-033019; Article DOI: 10.2471/BLT.06.033019.

Suicidal Thinking in Teens Predicts Mental Illness and Poorer Functioning Later in Life

In this study, Helen Reinherz and colleagues at Simmons College found that suicidal ideation at age 15 was associated with increased risk for an Axis I disorder at age 30, particularly anxiety disorder, and for much higher odds of having suicidal ideation and suicide attempts compared to subjects

without suicidal ideation at age 15. Those with suicidal ideation as adolescents were 15 times more likely to have suicidal ideation at age 30. Although less than 29 percent of subjects with suicidal ideation attempted suicide between ages 15 and 30, they were 12 times more likely to do so than were adolescents without suicidal ideation. Additionally, those with suicidal ideation had more problem behaviors and poorer overall functioning; their self-perceptions of coping ability, self-esteem, and interpersonal relations were also lower. These findings underscore the importance of considering suicidal ideation in adolescence as a marker of severe distress and as a predictor of compromised functioning as adolescents move into adulthood.

Reinherz HZ, Tanner JL, Berger SR, Beardslee WR, Fitzmaurice GM. Adolescent suicidal ideation as predictive of psychopathology, suicidal behavior, and compromised functioning at age 30. Am J Psychiatry. 2006 Jul;163(7): 1226-32.

New Research Addresses Suicidal Behaviors in the African American Community

There has been little research on suicide in African American communities. A special issue of the *Journal of Black Psychology* examined the current trends, culturally relevant theories, and prospects for treating suicide among African Americans. Sean Joe, assistant professor of social work at the University of Michigan and an NIMH mentored research career awardee, used advanced methods in his research to examine cohort effects. His results indicated that, among both males and females, younger generations of Blacks are at higher risk, which may be further interpreted to suggest the recent decline in Black suicide rates will reverse. There are also differences noted in suicidal beliefs between African Americans and European Americans; for example, African Americans were less likely to attribute suicide to interpersonal problems and were more likely to report that God is responsible for life, as opposed to the individual or the government. Religiosity and spiritual beliefs appear to be essential, culturally relevant constructs for developing effective interventions to prevent suicide among African Americans.

Cosby AE, Molock SD. Introduction: Suicidal behaviors in the African American community. J Black Psychol. 2006 Aug 1;32(3):253-261.

Joe S. Explaining changes in the patterns of Black suicide in the United States from 1981 to 2002: An age, cohort, and period analysis. J Black Psychol. 2006 Aug 1;32(3):262-284.

Walker RL, Lester D, Joe S. Lay Theories of Suicide: An Examination of Culturally Relevant Suicide Beliefs and Attributions among African Americans and European Americans. J Black Psychol. 2006 Aug 1;32(3):320-334.

Molock SD, Puri R, Matlin S, Barksdale C. Relationship between religious coping and suicidal behaviors among African American adolescents. J Black Psychol. 2006 Aug 1;32(3):366-389.

Targeted Therapy Shows Promise in Treating Borderline Personality Disorder

Marsha Linehan of the University of Washington and her colleagues found that patients with borderline personality disorder responded better to a special type of psychotherapy called dialectical behavior therapy (DBT) than to other types of psychotherapy. DBT, a variation on cognitive behavior therapy, specifically targets suicidal behavior, behaviors that interfere with treatment, and risky social behaviors often associated with borderline personality disorder. DBT focused on improving patients' coping skills and motivation, and helped reinforce functional behaviors and positive emotions. The researchers found that DBT reduced suicide attempts by half, reduced use of emergency room and inpatient services, and reduced the rate of patient discontinuation of therapy. Borderline personality disorder is a difficult-to-treat mental illness affecting up to two percent of adults, mostly young women.

Linehan MM, Comtois KA, Murray AM, Brown MZ, Gallop RJ, Heard HL, Korslund KE, Tutek DA, Reynolds SK, Lindenboim N. Two-Year Randomized Controlled Trial and Follow-up of Dialectical Behavior Therapy vs Therapy by Experts for Suicidal Behaviors and Borderline Personality Disorder. Arch Gen Psychiatry. 2006 Jul;63(7): 757-766.

Antidepressant Does Not Reduce Risk Of Relapse of Anorexia Nervosa
The antidepressant medication fluoxetine (Prozac®) is no more effective than placebo in preventing relapse among patients with anorexia nervosa who had achieved a healthy weight during inpatient or day-program treatment. The results of the study, conducted by B. Timothy Walsh and colleagues from Columbia University and University of Toronto, are particularly relevant because 30 to 50 percent of patients with anorexia nervosa who achieve a healthy weight during initial hospitalization relapse and may need to be hospitalized again. Often, patients with anorexia nervosa are prescribed antidepressant medications for coexisting psychiatric symptoms of OCD, depression, or anxiety.
Walsh BT, Kaplan AS, Attia E, Olmsted M, Parides M, Carter JC, Pike KM, Devlin MJ, Woodside B, Roberto CA, Rockert W. Fluoxetine after weight restoration in anorexia nervosa: a randomized controlled trial. JAMA. 2006 Jun 14;295(22):2605-12.

College Women at Risk for Eating Disorder May Benefit From Online Intervention
Over the course of a lifetime, up to 4.2 percent of girls and women will develop bulimia nervosa, and up to 3.7 percent will develop anorexia nervosa, one of the top psychiatric illnesses that lead to death. However, a long-term, large-scale study led by C. Barr Taylor, of Stanford University, found that an Internet-based program may prevent some high-risk, college-age women from developing an eating disorder. The eight-week, online, cognitive-behavioral intervention called "Student Bodies," which has been effective in small, short-term studies, aims to reduce concerns about body image and to promote healthy habits through assignments, such as keeping a body-image journal, and participating in a discussion group moderated by clinical psychologists. The intervention appeared to be most successful among women with body mass indexes (BMIs) of 25 or more at the start of the program; among these women in the intervention group, none developed an eating disorder after two years, compared to 11.9 percent in the control group. The program also appeared to help women who had symptoms of an eating disorder at the start of the program, such as self-induced vomiting; laxative, diet pill, or diuretic use; or excessive exercise. Of those in the intervention group, 14 percent developed an eating disorder within two years, compared to 30 percent in the control group. The authors suggest that relatively inexpensive options, such as Internet-based interventions, can have lasting effects on high-risk women, helping them become less concerned about their weight and shape, while also helping them understand healthier eating and nutrition practices.
Taylor CB, Bryson S, Luce KH, Cunning D, Doyle AC, Abascal LB, Rockwell R, Dev P, Winzelberg AJ, Wilfley DE. Prevention of eating disorders in at-risk college-age women. Arch Gen Psychiatry. 2006 Aug;63(8):881-8.

HIV/AIDS

Adherence to HIV Medications is Higher in Africa than in North America
Patients infected with human immunodeficiency virus (HIV) in sub-Saharan Africa show substantially higher rates of adherence to HIV medications than do patients in North America. This finding emerges from a recent meta-analysis conducted by an international team of research colleagues, including NIMH-funded investigator David R. Bangsberg of the University of California San Francisco. The team synthesized the results of 59 prospective studies conducted with samples of HIV/AIDS patients taking antiretroviral medications in Africa or North America; 13 of these studies acknowledged support from NIMH. Pooled estimates show that the proportion of patients achieving high levels of medication adherence was greater in Africa (77 percent) than North America (55 percent). Even after controlling for a number of covariates, African patients remained 2.5 times more likely than North American patients to adhere closely to their medication regimens. The authors concluded that expectations that resource-limited African settings will foster

poor adherence are not an evidenced-based reason to delay expansion of HIV treatment programs in Africa. They also emphasized the importance of efforts to support and maintain strong HIV treatment adherence in Africa, as well as initiatives to increase and sustain adherence in North America.

Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, Rachlis B, Wu P, Cooper C, Thabane L, Wilson K, Guyatt GH, Bangsberg DR. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA. 2006 Aug 9;296(6):679-90.

HIV Treatment Advances Have Saved at Least 3 Million Years of Life in the U.S.

Although HIV disease has claimed over half a million lives in the U.S. and more than 20 million lives worldwide, results from a new study quantify how treatment advances have dramatically extended survival time for people living with AIDS. NIMH-funded investigator David Paltiel, of Yale School of Medicine, and colleagues marked the 10th anniversary of the introduction of highly active antiretroviral therapy (ART) by modeling the impact of treatment advances through a computer simulation. They found that improved HIV treatment through ART and other methods have increased the projected survival time following an AIDS diagnosis from an estimated 1.6 years without treatment to 14.9 years for those diagnosed after 2003. By compounding this increase across yearly estimates of adults with new AIDS diagnoses who were receiving care, the researchers conservatively estimated that 3 million years of life have been saved through improved HIV treatment. The results also indicated that nearly 2,900 infant infections have been prevented through the introduction of medicines to help prevent mother-to-child HIV transmission. The study underscored the importance of advancing domestic efforts to identify HIV-infected individuals and bring them into medical care, as well as the urgent need to expand treatment access within developing countries.

Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, Weinstein MC, Freedberg KA. The survival benefits of AIDS treatment in the United States. J Infect Dis. 2006 Jul 1;194(1):11-19.

Rho Protein May Affect Blood-Brain Barrier Integrity in CNS Disorders

Immune cells called monocytes circulate through the blood to prevent infection. Monocyte migration across the blood-brain barrier (BBB) is a key event in the pathophysiology not only of HIV-1 associated dementia, but also of several other acute and chronic central nervous system (CNS) disorders. Researchers led by Yuri Persidsky, from the Nebraska Medical Center, found that the migration of HIV-infected monocytes across the BBB resulted in the breakdown of tight junctions between cells. The breakdown of tight junctions was associated with the disruption of immunoreactivity of critical tight-junction proteins, such as occludin and claudin-5. The authors demonstrated that, during monocyte migration through the BBB, a type of protein called Rho phosphorylates claudin-5 and occludin, resulting in the breakdown of BBB integrity. More importantly, inhibitors of Rho markedly attenuated the phosphorylation of both occludin and claudin-5. These studies provide the foundation for future studies on effective treatment of CNS disorders that involve the disruption of the BBB. The effectiveness of Rho inhibitors in protecting against disruption of tight junctions may help to develop treatments to prevent monocyte trafficking into the CNS.

Persidsky Y, Heilman D, Haorah J, Zelivyanskaya M, Persidsky R, Weber GA, Shimokawa H, Kaibuchi K, Ikezu T. Rho-mediated regulation of tight junctions during monocyte migration across the blood-brain barrier in HIV-1 encephalitis (HIVE). Blood. 2006 Jun 15;107(12):4770-80.

Progress on NIMH Initiatives

NIMH Human Genetics Initiative

This initiative seeks to support timely access to primary data and biomaterials for human genetic studies. By doing so, NIMH seeks to stimulate research and development and to maximize the benefits from genetics studies afforded to individuals affected by these disorders. The sample and data repository at the Center for Collaborative Genetics Studies (CCGS) continues to expand, with more than 57,000 samples of patients and controls with associated phenotypes stored in its DNA and cell bank repositories as of July 31, 2006. In the first seven months of this year, the repository received 5,287 new samples from existing NIMH-supported projects; since May, one new project on bipolar disorder has been added to the repository, bringing the total number of projects to five. NIMH granted access to 29 research projects for sample and data access between January–July 2006. The scientific research community is making wide use of existing samples, demonstrated by the more then 50,000 DNA samples sent by CCGS to investigators between January 1 and July 31, 2006.

Pediatric Brain Development Imaging Project

Blueprint funds were awarded to a trans-NIH, longitudinal, multisite pediatric neuroimaging project to support the transfer of data from the study database at Montreal Neurological Institute to the NIH campus in preparation for release of the data to investigators outside of the project. The database will ultimately provide multimodal imaging and comprehensive clinical and/or behavioral data on more than 500 typically developing infants, children, and adolescents, each of whom are studied three or more times in a six-year period. Transferring the database to NIH makes use of the infrastructure created by the Biomedical Informatics Research Network (BIRN), sponsored by NCRR, and thus builds on existing NIH informatics initiatives.

NIMH-Administered RFAs

- *Implicating Noncoding RNAs in the Genetics of Mental Disorders*
  NIMH is seeking applications for research that characterize the role of microRNAs (miRNAs) and other noncoding RNAs in the etiology of mental disorders. The data generated by this effort will contribute to the disaggregation of the molecular machinery underlying mental disorders by integrating sequence-specific modulators of post-transcriptional gene expression into a theoretical framework of disease pathophysiology. This initiative is being funded under two mechanisms, R01 and collaborative R01.
  Release Date: May 11, 2006; Expiration Date: July 22, 2006
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-07-040.html
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-07-041.html
  Scientific Program Director: Thomas Lehner, PhD, MPH, Office of Human Genetics & Genomic Resources, Division of Neuroscience and Basic Behavioral Science (DNBBS), NIMH

Collaborative RFAs

- *Membrane Protein Production and Structure Determination*
  This Roadmap RFA is calling for applications that will increase understanding of the structure, function, and mechanisms of integral membrane proteins, which has been previously limited by the paucity of available high-resolution structures. Applications are requested for the development of innovative methods for producing membrane proteins in sufficient quantities for functional and structural studies. Innovations are also needed in methods for structure determination, including crystallization, phasing, isotopic labeling, and

collection of x-ray crystallographic, nuclear magnetic resonance (NMR), and other relevant data.
Release Date: August 31, 2006; Expiration Date: October 28, 2006
http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-003.html
Scientific Program Director: John C. Norvell, PhD, Division of Cell Biology and Biophysics, National Institute of General Medical Sciences (NIGMS)

- *Institutional Clinical and Translational Science Award*
  The purpose of this initiative is to assist institutions in forging a uniquely transformative, novel, and integrative academic home for clinical and translational science. NIH Roadmap resources will give institutions flexibility to develop their existing resources and talent and to propose ways to increase the efficiency and speed of clinical and translational research. The academic home is expected to include faculty who conduct original research, develop graduate and postgraduate training curricula, and lead programs that integrate clinical and translational science across multiple departments, schools, research institutes, and hospitals.
  Release Date: August 22, 2006; Expiration Date: January 18, 2007
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-07-002.html
  Scientific Program Director: Anthony Hayward, MD, PhD, Division for Clinical Research Resources, NCRR

- *Assay Development for High-Throughput Molecular Screening*
  High-throughput molecular screening (HTS) is the automated, simultaneous testing of thousands of distinct chemical compounds in models of biological mechanisms. Active compounds identified through HTS can provide the starting point in the design of powerful research tools that allow pharmacological probing of basic biological mechanisms, and which can be used to establish the role of a molecular target in a disease process or its ability to alter the metabolism or toxicity of a therapeutic agent. This funding opportunity is a component of the NIH Molecular Libraries and Imaging Roadmap Initiative and seeks to facilitate the discovery of new molecular probes for investigating biological function by funding the development and adaptation of biological assays for automated HTS.
  Release Date: July 13, 2006; Expiration Date: September 23, 2006
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-07-001.html
  Scientific Program Director: Mark Scheideler, PhD, Molecular Libraries Technology Development, NINDS

- *Using Metabolomics to Investigate Biological Pathways and Networks*
  The general aim of metabolomics is to identify, measure, and interpret the complex time and condition-dependent concentration, activity, or flux of metabolites in cells, tissues, and other biosamples, such as blood, urine, and saliva. This Roadmap initiative seeks to encourage the use of innovative technologies to establish methods and model systems for advancing the understanding of biological pathways and networks; their temporal and spatial resolution; and their regulation in health and disease states.
  Release Date: June 20, 2006; Expiration Date: October 21, 2006
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-06-010.html
  Scientific Program Director: Arthur L. Castle, PhD, Division of Diabetes, Endocrinology and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- *Building Interdisciplinary Research Careers in Women's Health (BIRCWH)*
  The Office of Research on Women's Health (ORWH), the focal point for women's health research at NIH, and its cosponsors are inviting institutional career development award applications for BIRCWH programs. These programs will support mentored research career development of junior faculty members who have recently completed clinical training or postdoctoral fellowships and who will be engaged in interdisciplinary basic, translational, behavioral, clinical, or health services research relevant to women's health or sex/gender

factors. The goal of this initiative is to increase the number and skills of investigators through a mentored research and career development experience leading to an independent scientific career that will benefit the health of women.
Release Date: June 13, 2006; Expiration Date: September 15, 2006
http://grants1.nih.gov/grants/guide/rfa-files/RFA-OD-06-004.html
Scientific Program Director: Charisee Lamar, PhD, MPH, RRT, Interdisciplinary Research and Reproductive Biology Research Programs, Center for Population Research, National Institute of Child Health and Human Development (NICHD)

- *Specialized Centers of Interdisciplinary Research on Sex and Gender Factors Affecting Women's Health*
  ORWH and cosponsors aim to promote interdisciplinary research in sex/gender factors through these specialized centers. The ORWH published *An Agenda for Research on Women's Health for the 21st Century* (http://orwh.od.nih.gov/research/resagenda.html) that provides an outline of research needs identified through national taskforces. The ORWH website also provides the FY 2006 research priorities identified by the ICs at http://orwh.od.nih.gov/research/priorities.html.
  Release Date: June 12, 2006; Expiration Date: September 15, 2006
  http://grants1.nih.gov/grants/guide/rfa-files/RFA-OD-06-003.html
  Scientific Program Director: Madeline Turkeltaub, RN, PhD, CRNP, FAAN, Extramural Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

NIMH Public Outreach

Summer Alliance for Research Progress Meeting

NIMH is committed to maintaining an active dialogue with its stakeholders and to developing a research agenda that is responsive to the needs of its constituents. As part of this effort, the Institute convened the NIMH Alliance for Research Progress summer meeting in July 2006 in Rockville, Maryland. The theme for the meeting was creating partnerships to transform research and services. Former Council member Renata Henry discussed *The Road Ahead: A Report by the NAMHC's Workgroup on Services and Clinical Epidemiology*, presented at the May Council meeting; and David Chambers, Associate Director for Dissemination and Implementation Research, Division of Services and Intervention Research (DSIR), described NIMH's activities in response to the workgroup recommendations. Gregory H. Reaman, Chairman of the Children's Oncology Group, was invited to describe the group's multicenter cooperation model for National Cancer Institute (NCI)-sponsored pediatric cancer research. Other presentations, by Richard McKeon, of the Substance Abuse and Mental Health Services Administration (SAMHSA); NIMH grantee Gregory K. Brown; and Steven E. Pflanz, of the U.S. Air Force, focused on partnerships to prevent suicide. A meeting report will be posted on the NIMH Web site at http://www.nimh.nih.gov/outreach/alliancemenu.cfm.

NIMH Outreach Partnership Program Competing Outreach Partners

The NIMH Outreach Partnership Program, which enlists 51 outreach partners representing every state and the District of Columbia, is a nationwide educational outreach initiative that brings together national and state organizations to help bridge the gap between research and clinical practice. The program receives support from NIDA and works in cooperation with SAMHSA. Organizations that conduct statewide outreach on mental illness and/or substance abuse disorders were invited to submit proposals to become outreach partners. The program is currently evaluating

proposals from organizations and anticipates making awards prior to the end of 2006. A description of the benefits of becoming an NIMH outreach partner is available at http://www.nimh.nih.gov/outreach/partners/index.cfm.

Research Conferences and Workshops

NIMH/National Business Group on Health Roundtable on Medication Management in Employer-Based Behavioral Health Systems

DSIR's Services Research and Clinical Epidemiology Branch held this one-day meeting in July 2006 in Washington, DC, to identify relevant research findings for employers and to discuss new opportunities to bridge the gap between research and practice. The meeting brought together mental health services researchers with representatives of employer-based behavioral health care, including pharmacy benefit managers, managed behavioral-health organization managers, consultants, and senior benefit managers. The attendees discussed current and future efforts to implement strategies to manage psychopharmacological prescribing and monitoring in Fortune 500 health systems. *For more information, please contact David Chambers at dchamber@mail.nih.gov.*

2006 American Psychological Association (APA) Convention

NIMH staff divisions organized several sessions at the APA convention held in August, in New Orleans, Louisiana. At these sessions, NIMH highlighted pediatric translational research, research training opportunities, priorities, psychiatric epidemiology, and health disparities. Given the location, special sessions by NIMH grantees on trauma and mental health were particularly relevant. The session entitled "*Translating Pediatric Anxiety Treatments From the Clinic to Real-World Settings*" involved collaboration between Division of Pediatric Translational Research and Treatment Development (DPTR) and DSIR grantees and staff to highlight examples of translational research on anxiety among child and adolescent populations. *For more information, please contact Cheryl Boyce at cboyce@mail.nih.gov or Ellen Stover at estover@mail.nih.gov*

NCDEU Meeting

Named after the original NIMH New Clinical Drug Evaluation Unit clinical trials program, the NCDEU meeting has grown and evolved over the years to include a broad range of academic and industry investigators, along with practitioners and NIMH and FDA staff. The 46th annual NCDEU meeting, held in June 2006 in Boca Raton, Florida, was sponsored by NIMH and cosponsored for the first time with the American Society of Clinical Psychopharmacology. Attendance at this year's meeting, cochaired by Mayada Akil and Matthew Rudorfer, exceeded 1,200 individuals, including 15 winners of the competitive New Investigators' Award. With a theme of *Large Clinical Trials and Evidence-Based Practice*, the latest advances in clinical treatment research, with an emphasis on methodology, were presented and discussed in a series of panels, workshops, and other oral and poster sessions. NIMH-sponsored research and research support were highlighted in the plenary session, *The Value and Limitations of Large Practical Clinical Trials in Informing Practice*, which featured investigators representing four, large, practical trials answering questions by stakeholders and explaining the significance of these studies to "real world" clinical practice. Other sessions featured NIMH staff describing aspects of Institute funding programs and the peer review process. Concluding with the FDA symposium, the meeting continues to offer a valuable opportunity for NIMH/FDA discussion and collaboration. *For more information, please contact Matthew Rudorfer at mrudorfe@mail.nih.gov.*

Federal Partnership on the Transformation of Mental Health Care in the United States
Led by SAMHSA's Center for Mental Health Services, NIMH's participation in this Federal effort to improve the quality of mental health care delivered to US citizens has increased with the creation, in 2006, of five workgroups to focus on priority areas related to transformation. These workgroups include Financing, Emergency Response, Suicide Prevention, Employment, and the Integration of Primary Care and Mental Health Care. Each has NIMH staff representation, whose goal is to influence the development of service initiatives based on strong research findings. A sixth priority group, chaired by NIMH and the Agency for Healthcare Research and Quality (AHRQ), will focus on the development of research initiatives to complement existing demonstration projects funded by Department of Health and Human Services agencies and other government departments. This effort is a direct response to the recent Advisory Council Workgroup Report, *The Road Ahead*, which called for efforts to work across Federal agencies to develop timely, policy-relevant research studies. *For more information, please contact David Chambers at dchamber@mail.nih.gov.*

Mapping the Landscape of Deployment Related Adjustment and Mental Disorders: A Working Group to Inform Research
In May, NIMH joined the VA Office of Research and Development and the United States Army Medical Research and Materiel Command for a meeting in Rockville, Maryland, to discuss progress and challenges in addressing deployment-related adjustment and mental disorders. The goals of the meeting were to identify major scientific questions that needed answers; areas where science was ahead of practice (or behind public health demand/need); whether research currently underway was adequate; and opportunities to coordinate across the relevant Federal research programs. Presentations and discussion revolved around the following five broad and overlapping topics: causes, correlates, and risk for PTSD; early detection and intervention; co-occurring health conditions; occupational, family and social adjustment/functioning; and healthcare services. *For more information, please contact Farris Tuma at ftuma@nih.gov.*

All-Hazards Behavioral Health Preparedness and Response Building on the Lessons of Hurricanes Katrina, Rita, and Wilma
Several NIMH staff participated in this SAMHSA organized behavioral health summit in May in New Orleans. The meeting brought together interagency teams from all states and territories to coordinate ongoing response efforts to the 2005 Gulf coast hurricanes, communicate research-based knowledge about behavioral responses to disaster and effective intervention, and assist states and territories in all-hazards preparedness for future disasters. NIMH organized and conducted plenary and breakout sessions on the likely course of mental health and substance abuse needs over time and in response to ongoing events; evidence-based approaches for early intervention and later treatment; psychological functioning of children in the aftermath of Hurricane Katrina; opportunities for advances in Federal, state, and local research and evaluation efforts; and how extreme stress and fear impact the brain and body to shape emotion, cognition, and behavior, including risk and resilience to behavioral health disorders. *For more information, please contact Farris Tuma at ftuma@nih.gov.*

Prevention of Traumatic Stress Disorders in High-Risk Occupations: Current Knowledge and Research Opportunities
In June, the NIMH Office of Prevention and DATR's Traumatic Stress Disorders Research Program held a meeting in Bethesda, Maryland, involving trauma researchers, prevention scientists, and subject-matter experts responsible for preparing civilian and military personnel for disaster response, mass casualty events, and combat. The goals of the meeting included determining whether

current knowledge of the stress-response process (such as risk and protective factors, presumed mechanisms of impairment, and longitudinal course) supports the notion of preventive intervention and aids in the identification of potential strategies for preventing a broad range of short-term, intermediate, and long-term adjustment difficulties following trauma exposure. Discussions centered on pretrauma characteristics that may buffer against acute and long-term stress reactions, how knowledge of risk and protective factors might translate into selective prevention strategies, and optimal methods for evaluating and implementing potential interventions. *For more information, please contact Robert Heinssen at rheinsse@mail.nih.gov or Farris Tuma at ftuma@nih.gov.*

Early Psychological Intervention Following Mass Trauma: Present and Future Directions
NIMH partnered with the New York Medical College and School of Public Health and the Uniformed Services University of the Health Sciences, Center for Study of Traumatic Stress, for a June meeting of trauma and early intervention experts, in New York. The goal was to review the available evidence on early intervention and to disseminate guidance to the field. Presentations focused on the roles of government, clinicians, and communities in effective early intervention following mass trauma; workforce and community resilience; the role, rationale, and challenges associated with primary care as an intervention opportunity; psychological first aid; problems of debriefing; early intervention and treatment of acute stress disorder (ASD); the role of psychopharmacology in early intervention; and cultural considerations in early intervention. *For more information, please contact Farris Tuma at ftuma@nih.gov.*

Annual Family and HIV/AIDS Meeting
NIMH and the University of Puerto Rico cosponsored the Annual International Research Conference on the Role of Families in Preventing and Adapting to HIV/AIDS, in July, in San Juan, Puerto Rico. The conference theme was "Resilient Families Overcoming Poverty, Violence, Mental Illness and HIV/AIDS." The first day of this conference was a "Community Day," designed to engage service providers by conducting skills-building workshops to improve their delivery of evidence-based family prevention programs. The meeting included scientific presentations on the latest family-based research, which will lead to new research collaborations. *For more information, please contact Willo Pequegnat at wpequegn@mail.nih.gov.*

20th Anniversary of NIMH-Funded AIDS Research in Rwanda
NIMH staff participated in this July conference in Rwanda, joining the current Rwandan Minister of Health and his two predecessors, one of whom is now a member of Parliament; the Director for AIDS and STD Programs; and the Director of the AIDS Treatment Program. This program of AIDS research has resulted in the development of a model voluntary counseling and testing (VCT) program for couples and the preparation of a manual for scaling up this AIDS prevention program. This effort is especially important because heterosexual couples in whom partners have different HIV statuses account for the majority of new HIV cases. The Centers for Disease Control and Prevention (CDC), which administers the President's Emergency Plan for AIDS Relief (PEPFAR) funds, has budgeted $750,000 for next year to begin implementing this evidence-based VCT program for couples in other parts of Rwanda. *For more information, please contact Willo Pequegnat at wpequegn@mail.nih.gov.*

HIV Preclinical - Clinical Therapeutics Research
In May, the NIMH Center for Mental Health Research on AIDS (CMHRA) convened this two-day meeting in Bethesda, Maryland. The workshop had two broad objectives. The first objective was to review state-of-the-art NeuroAIDS therapeutics. The emphasis was on the best strategies for

preclinical drug discovery, translational research, and clinical trials for the development of CNS-targeted therapeutics for HIV-associated neurological and neuropsychiatric disorders. The second objective was to discuss and determine which resources and mechanisms NIH could provide to the scientific community to assist with such therapeutic interventions. The multidisciplinary group of participants presented and discussed the current challenges and limitations in NeuroAIDS therapeutics. The meeting also outlined the most promising approaches for the development of novel advances and provided recommendations regarding the future directions of research to eliminate/eradicate HIV brain reservoirs. In addition, the workshop addressed issues related to public-private partnerships and their role in drug discovery and development. *For more information, please contact Kathy Kopnisky at kkopnisk@mail.nih.gov.*

NAMI 2006: Changing Minds, Changing People, Keeping the Promise

NIMH's DATR and the Division of AIDS and Health Behavior Research (DAHBR) cosponsored this workshop, "The Science of Mental Illness: Changing Middle Schoolers' Attitudes About Mental Illness Through Education," at the National Alliance on Mental Illness (NAMI) annual convention, in June, in Washington, DC. The workshop was organized by Wayne Fenton and Emeline Otey to introduce NAMI members to the curriculum supplement for middle school science classes (grades 6–8). The supplement was developed by the NIH Office of Science Education in collaboration with NIMH and Biological Sciences Curriculum Study, and is available free of charge to science teachers and school administrators, in print or online at http://science.education.nih.gov/customers.nsf. Workshop participants heard about the six content modules comprising the curriculum supplement, the results of the field test to assess the supplement's impact on knowledge and attitudes about mental illness, and also had the opportunity to view the video, *Like Any Other Kid*, which is module 5 of the curriculum supplement. In addition, Drs. Fenton and Otey participated in the presentation "Addressing Stigma Through Education," and Dr. Fenton also answered questions during an "Ask the Doctor" session on schizoaffective disorder. *For more information, please contact Emeline Otey at eotey@mail.nih.gov.*

NIMH Workshop on the Classification of Eating Disorders

In July 2006, NIMH supported a workshop that focused on classification and diagnosis of eating disorders. The specific goals of this workshop were to address key, unresolved issues of contention in the current nosology of eating disorders; to identify existing data sets that may be useful for exploring what changes, if any, ought to be introduced in the upcoming fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V); and to discuss the most pressing research questions related to diagnosing and classifying eating disorders. The proceedings from this meeting will be published in a forthcoming special edition of the *International Journal of Eating Disorders*. *For more information, please contact Mark Chavez at mchavez1@mail.nih.gov.*

Dimensional Approaches in Diagnostic Classification

NIMH, joined by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) and NIDA, supported the addition of a meeting on dimensional approaches to the series of meetings that the American Psychiatric Association is conducting in preparation for DSM-V. This meeting, "Dimensional Approaches in Diagnostic Classification: A Critical Appraisal," was held over two days in July on the NIH campus. Council member Helena Kraemer was a cochair of this meeting. The meeting participants were asked to address the research evidence for a dimensional approach, consider an illustrative example of a dimensional approach linked to a categorical definition, and the advantages and drawbacks of the example for six disorder categories: substance use, mood, major psychoses, anxiety, externalizing child, and personality disorders. As part of the preparation

for this meeting, more than 40 data sets were identified whose analysis might contribute to illuminating the possibilities and challenges of a dimensional approach. *For more information, please contact Jim Breiling at jbreilin@mail.nih.gov.*

Annual Computational Neuroscience (CNS) meeting

NIMH provided partial support for the15th annual CNS meeting held in July, in Edinburgh, Scotland. CNS is an interdisciplinary field forging a link between neuroscience, computer science, physics, and applied mathematics. It is also the primary theoretical method for investigating the function and mechanism of the nervous system. This meeting is the premier forum for presenting experimental and theoretical results exploring the biology of computation in the brain. More than 400 neuroscientists from 15 different countries attended. This year's meeting included sessions on neural coding and decoding, attention and memory, sensory and motor systems, plasticity and learning, and mechanisms of oscillations and synchrony. More than 20 workshops were held on the two days following the main meeting, with topics covering such diverse areas as cortical microcircuitry, stochastic dynamics of neurons and networks, interoperability of neural simulators, functional models of the hippocampal formation, and plasticity and stability of neural systems. *For more information, please contact Dennis L. Glanzman at glanzman@helix.nih.gov.*

Gene x Environment Interactions and Developmental Psychopathology: Research Challenges and Opportunities

In June 2006, researchers in psychiatric genetics, epidemiology, developmental psychopathology, and related disciplines met in Washington, DC, to examine the utility and potential applications of the gene x environment (GxE) paradigm in mental health research in child and adolescent populations. The meeting was organized by the NIMH DPTR and the Division of Neuroscience and Basic Behavioral Science (DNBBS) and the NIDA Division of Epidemiology, Services, and Prevention Research. The GxE paradigm is becoming increasingly more common in etiologic research on child psychopathology, but it is often misunderstood and inadequately applied. Issues addressed by meeting participants include: 1) the utility of the GxE paradigm for informing disease processes during childhood and adolescence, 2) the translational relevance of the research generated by the application of the GxE paradigm, and 3) the key issues and sources of complexity that need to be considered in applying the GxE paradigm broadly and to pediatric populations specifically. *For more information, please contact Eve Moscicki at em15y@nih.gov.*

American Psychological Society (APS) 2006 Annual Meeting

DAHBR sponsored the symposium "The Stigma of Mental Illness: Interdisciplinary Perspectives" at the 2006 annual meeting of APS in New York in May. The symposium, organized by Jennifer Crocker, University of Michigan, explored psychological and sociological insights in understanding the causes, consequences, and societal responses to mental illness stigma from the perspective of both the perceiver and the target. The intent was to entice researchers who study stigma or prejudice and discrimination to consider the implications of their research for the stigma of mental illness. *For more information, please contact Emeline Otey at eotey@mail.nih.gov.*

NIH State of the Science Conference on Tobacco Use: Prevention , Cessation, and Control

Tobacco use remains the Nation's leading preventable cause of premature death. Each year, more than 440,000 Americans die from disease caused by tobacco use, accounting for one in every five deaths. A better understanding of how effective strategies for prevention and treatment can be developed and implemented across diverse segments of the population is crucial to accelerate progress in reducing tobacco use. For this reason, NIH's Office of Medical Applications of

Research sponsored a three-day, state-of-the-science conference in June in Bethesda, Maryland. Since smoking rates are significantly higher in people with mental disorders than in the general population, NIMH cosponsored and participated in the conference's planning and execution. *For more information, please visit http://consensus.nih.gov/ or contact Mayada Akil at makil@mail.nih.gov.*

Meeting-based Publications

Extinction: The Neural Mechanisms of Behavior Change

The proceedings of this February 2005 NIMH-sponsored conference were published in a special issue of *Biological Psychiatry* in August 2006. This conference brought together basic and clinical researchers studying extinction and anxiety disorders with the goal of fostering research at multiple levels (molecular, cellular, systems, behavioral, and clinical) to understand the mechanisms that prevent the development of fear disorders and facilitate extinction learning. The papers in this special journal issue provide examples of recent findings from each of these domains and highlight the many opportunities for basic research on extinction to be translated into clinical treatments for anxiety disorders.

Biol Psychiatry. 2006 Aug 15;60(4):317-422.

NIMH-MATRICS Consensus Statement on Negative Symptoms in Schizophrenia

Negative symptoms, referring to absence of or reductions in normal emotional and behavioral states, are common in schizophrenia and adversely impact functioning and quality of life. But the development of effective treatments for negative symptoms remains challenging. Due to the success in calling attention to cognitive deficits in schizophrenia through the MATRICS project, NIMH researchers Steve Marder, Wayne Fenton, William T. Carpenter, Jr., and Brian Kirkpatrick organized a conference in January 2005 to review the existing data on negative symptoms and to identify a method to measure the efficacy of treatments for negative symptoms. A summary of areas of agreement, unresolved issues, and future directions discussed at this conference was published in the April 2006 issue of *Schizophrenia Bulletin*.

Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006 Apr;32(2):214-9.

Budget

The FY 2007 President's Budget Request for the NIH was submitted to the Congress on February 6, 2006. The President's Budget proposed a total NIH program level of $28.6 billion, the same as the FY 2006 comparable level. The President's request for the NIMH was $1.4 billion, a decrease of $8.7 million or -0.6 percent below the FY 2006 comparable level (see Attachment 1).

On June 20, 2006, the House of Representatives accepted the President's Budget Request of $28.6 billion (see Attachment 2). The funding amounts provided in the House version were essentially identical to the President's Budget Request for all NIH components, except the House reduced the President's request for the National Institute of Allergy and Infectious Diseases (NIAID) by $25 million and increased NCRR by $25 million. The House provided an NIMH program level of $1.4 billion, the same as the President's Budget Request.

The Full Senate Committee on Appropriations reported its FY 2006 Appropriations Bill for Labor-HHS-Education, including the NIH, on July 20, 2006. The Senate bill provides a total program level of $28.8 billion for the NIH, an increase of $202 million or +0.7 percent over the comparable FY

2006 level (see Attachment 2). Funding for the NIMH in the Senate bill is $1.4 billion, an increase of $8.7 million over the President's Budget Request and $36,000 over the FY 2006 comparable level.

Major Awards for NIMH Grantees

Beatriz Luna, PhD, Associate Professor of Psychiatry and Psychology at the University of Pittsburgh, was awarded the Presidential Early Career Award for Scientists and Engineers (PECASE) in a White House ceremony in July 2006. Dr. Luna's grant, "Cognitive and Brain System Maturation through Adolescence," is focused on understanding the development and maturation of cognition, neuronal connectivity, and cortical function during adolescence, using fMRI, diffusion tensor imaging (DTI), and measures of cognitive performance. The PECASE is the highest honor bestowed by the U.S. government on outstanding scientists and engineers beginning their independent careers.

NIMH Staff Awards

Eve Mościcki, ScD, MPH, Acting Chief of the Psychosocial Stress and Related Disorders Branch, DPTR, was elected as a Fellow of the American Psychopathological Association (APPA).

David Sommers, PhD, Scientific Review Administrator, DEA, was awarded American Board of Professional Psychology specialty board certification in Clinical Psychology, in July 2006.

The NIH Director annually recognizes individuals and groups whose special efforts and contributions beyond regular duty requirements have resulted in significant benefits to the programs or the people of the NIH and the fulfillment of the NIH mission. The following NIMH staff were honored at a ceremony on the NIH campus in July 2006:

- **Della Hann, PhD,** Director, Office of Science Policy, Planning, and Comunications (OSPPC); NIH Director's Award for exemplary leadership, dedication, and service in the areas of science policy and communications.
- **Michael F. Huerta, PhD,** Director, Office of Interdisciplinary Research and Scientific Technology, DNBBS; NIH Roadmap for Medical Research Award, with Gregory K. Farber, PhD, NCRR, for "outstanding leadership of the NIH Roadmap Interdisciplinary Consortia Initiative."
- **Susan Koester, PhD**, Associate Director for Science, Division of Intramural Research Programs (DIRP); NIH Director's Award for extraordinary service following the departure of the Scientific Director
- **CDR Francois Lalonde, PhD,** Geriatric Psychiatry Branch, DIRP; PHS NIH Commissioned Corps Award for continuous leadership in carrying out the mission of the PHS through the development, support, and advancement of neuroimaging technologies in studies of Alzheimer's disease.
- **Editha Nottelmann, PhD,** Chief, Affective and Regulatory Disorders Branch, DPTR; NIH Director's Mentoring Award for mentoring that extends widely to junior and senior investigators in the research field of childhood depression.

- **Donald Rosenstein, MD**, Acting Clinical Director, DIRP; NIH Director's Award for his heroism, compassion, and outstanding clinical skills in a time of crisis at the NIH
- **David Shore, MD**, Acting Director, DSIR; NIH Director's Award for exemplary leadership, dedication, service, and teamwork in managing the Services and Interventions Research Division.
- **Ad Hoc Crisis Response Team**, NIH Director's Award for their heroism, compassion, and outstanding clinical skills in an emergency at the NIH Clinical Research Center. The team included Jose Apud, MD; Sandra Bowles; Virginia Daine; David K. Henderson, MD; Laura Lee; Jean Murphy, RN; Denise Niner; and Maryland Pao, MD.
- **NIH MRI Study of Normal Brain Development Group**, NIH Director's Award for creating a database of normal brain development as a resource for developmental neuroscience communities. The team included Lisa Freund, PhD; Katrina Gwinn-Hardy, MD; Carlo Pierpaoli, MD; Don Preuss; Alexander I. Rosenthal; Judith Rumsey, PhD; Giovanna M. Spinella, MD; and Laurence R. Stanford, PhD.

In July, NIH held a special event to honor individuals and groups for their contributions to Blueprint initiatives. The following NIMH staff were presented with Blueprint for Neuroscience Research Directors Awards for Significant Achievement:

- **Andrea Beckel-Mitchener, PhD,** Chief, Functional Neurogenomics Program, DNBBS, for outstanding leadership of the Blueprint Neuromouse Project Team and for facilitating the use and availability of key model organisms across and beyond the NIH
- **Nancy Desmond, PhD,** Director, Office of Research Training and Career Development, DNBBS, for outstanding leadership of the Blueprint Course Development in the Neurobiology of Disease Project Team and for efforts to facilitate trans-NIH research training initiatives generally
- **Marlene Guzman,** Senior Advisor to the Director (Contractor), NIMH OD, for exemplary leadership and outstanding contributions to the overall management of the NIH Blueprint for Neuroscience Research
- **Michael Huerta, PhD,** Director, Office of Interdisciplinary Research and Scientific Technology, DNBBS, for exemplary leadership and outstanding contributions to the overall management of the NIH Blueprint for Neuroscience Research
- **Center Cores Project Team,** including Laurie Nadler, PhD, for exemplary dedication and teamwork in developing a Blueprint Center Core Grants Program
- **Course Development in the Neurobiology of Disease Project Team**, including Nancy Desmond (Team Leader), PhD; Rehana Chowdhury; A. Roger Little, PhD; and Yong Yao, PhD, in recognition for outstanding team efforts in developing and managing the Blueprint Course Development in the Neurobiology of Disease Initiative
- **Blueprint Pediatric MRI Study Project Team,** including Judith Rumsey, PhD, in recognition of outstanding effort and exemplary teamwork in developing the NIH Neuroscience Blueprint Diffusion Tensor Imaging Expansion Project for the Pediatric MRI Study of Normal Brain Development

- **Blueprint Informatics Team,** including Michael Huerta (Team Leader), PhD; Kathryn Bognovitz; and German Cavalier, PhD, for advancing informatics research and making neuroscience a prominent aspect of the NIH informatics research agenda
- **Neuromouse Project Team**, including Andrea Beckel-Mitchener (Team Leader), PhD; Michael Huerta, PhD; A. Roger Little, PhD; and Yong Yao, PhD, for exemplary dedication and teamwork in developing mouse resources for the neuroscience research community
- **Blueprint Website Development,** including Mayada Akil, PhD, for exemplary dedication, creativity, and teamwork in expanding and redesigning the Blueprint Website
- **Research Training Project Team,** including Nancy Desmond, PhD, and Dennis Glanzman, PhD, in recognition of their dedication, contributions, and support to meet the goals of the FY 2006 Neuroscience Blueprint Research Training Initiative

Staff Changes

Arriving:

Philip S. Wang, MD, PhD, joined NIMH as the Director of DSIR in September. Dr. Wang is a graduate of Harvard College, Harvard Medical School, and Harvard School of Public Health. He comes to NIMH from his current positions as Associate Professor of Health Care Policy and Psychiatry at Harvard Medical School and Associate Physician at Brigham and Women's Hospital. One of the leading researchers in services and pharmacoepidemiology, Dr. Wang is a recipient of the American Psychiatric Association's Health Services Research Scholar Award, and is one of the most highly cited scientists in areas as diverse as depression in the workplace and noncompliance with antihypertensive medications.

Linda Brady, PhD, was selected as the Director of DNBBS and started her new position in July. Dr. Brady formerly served as Chief of the Molecular, Cellular, and Genomic Neuroscience Research Branch in DNBBS. Over the past 10 years, she has administered programs in neuropharmacology, drug discovery, and clinical therapeutics. She also served as a coordinator for the discovery and preclinical development of novel imaging agents and pharmacologic ligands as research tools for use in pathophysiological studies and in drug development. She has spearheaded many initiatives, including Development and Application of PET and SPECT Ligands for Brain Imaging Studies, National Cooperative Drug Discovery Groups for the Treatment of Mood Disorders and Nicotine Addiction, and has been actively involved in the MATRICS and TURNS (Treatment Units for Research on Neurocognition in Schizophrenia) programs. Lois Winsky, PhD, has assumed leadership responsibilities of the Chief of the Molecular, Cellular, and Genomic Neuroscience Research Branch until a permanent replacement has been selected.

Alcino J. Silva, PhD, has accepted the position of Scientific Director of the Intramural Research Program, where he will be responsible for overseeing all of NIMH's research efforts conducted on the Bethesda, Maryland campus; he will start in October. In his current position, Dr. Silva serves as professor in the departments of neurobiology, psychiatry, and psychology at the University of California, Los Angeles (UCLA). He also runs UCLA's Center for the Biology of Creativity, serves as Coordinator of Learning and Memory at the Brain Research Institute, and is President of the Molecular and Cellular Cognition Society. Dr. Silva received his doctoral degree from the University of Utah and completed postdoctoral training at the Massachusetts Institute of

Technology. A pioneer in the field of molecular and cellular cognition, his current research interests encompass molecular and cellular mechanisms of learning, memory storage and disorders, cognitive deficits and functional enhancements, and the biological basis of creativity.

Michael Stirratt, PhD, joined the Secondary Prevention and Translational Branch within the Center for Mental Health Research on AIDS, DAHBR, as a Program Officer in July 2006. He will oversee the Branch portfolio of HIV treatment adherence research. Dr. Stirratt recently graduated from the NIMH-funded T32 Postdoctoral Training Program in Behavioral Sciences Research in HIV Infection at the Columbia University HIV Center for Clinical and Behavioral Studies. Prior to that, he worked for seven years as a Project Director on NIMH and CDC-funded behavioral intervention studies targeting antiretroviral medication adherence and secondary HIV prevention. Dr. Stirratt received his doctoral degree from the Graduate Center of the City University of New York.

Cynthia I. Grossman, PhD, joined the DAHBR Center for Mental Health Research on AIDS as a Program Officer of the Secondary Prevention Program. Dr. Grossman received her degree in Clinical Psychology and recently completed postdoctoral training at Brown University, with an emphasis on HIV prevention research and clinical work as it pertains to children and adolescents affected by HIV.

Wanda Harris-Lewis has accepted a position as Program Assistant in the Office for Special Projects, having previously served as a Grants Program Assistant in DNBBS.

Aleksandra Vicentic, PhD, joined the Behavioral Science and Integrative Neuroscience Research Branch in DNBBS in September and will be responsible for the Circadian Rhythms, Sleep and Regulation of Behavior Program. Dr. Vicentic comes to NIMH from the Yerkes National Primate Research Center and Emory University.

Maria Bukowski joined NIMH in June as the Chief for Reports and Analysis Branch, OSPPC. Ms. Bukowski previously worked in the NIH Office of Extramural Research, Division of Statistics and Analysis, where she was responsible for a wide array of reporting for NIH, as well as working on data quality issues with the NIH databases.

John Harris was appointed as NIMH's Information Technology Officer in June. Mr. Harris has had a stellar career in both the private sector and in the Federal Government and most recently worked with the Centers for Medicare and Medicaid Services. In his new role with NIMH, Mr. Harris will manage the Institute's information technology resources.

David Zielinski, PhD, joined the Science Policy and Evaluation Branch, OSPPC, in August as a policy analyst. Dr. Zielinski earned his doctoral degree in developmental psychology, in 2004, from Cornell University, and just completed two years as a postdoctoral research scientist at the Center for Child and Family Policy at Duke University.

Christopher Baker, PhD, is a new Tenure Track Investigator, who started at the beginning of September as Chief of the Unit on Learning and Plasticity, in the Laboratory of Brain and Cognition, DIRP. His research focuses on using fMRI to study human brain processes. Dr. Baker, a UK citizen, received his PhD in Psychology from the University of St. Andrews in 1999. He held two postdoctoral fellowships, first at the Center for the Neural Basis of Cognition, Carnegie Mellon

Institute, from 1999 to 2003; and then at the McGovern Institute for Brain Research, MIT, until August 2006.

Zheng Li, PhD, is a new Tenure Track Investigator, who also started in September as Chief of the Unit on Synapse Development Plasticity, in the Genes, Cognition and Psychosis Program, DIRP. Her research focuses on cellular functions of schizophrenia-susceptibility genes. Dr. Li received her PhD in 2001 from the Department of Neurobiology and Behavior, State University of New York at Stony Brook and Cold Spring Harbor Laboratory. From 2001 until August 2006, Dr. Li was a postdoctoral fellow at the Picower Center for Learning and Memory at MIT.

Kuan Hong Wang, PhD, will be a new Tenure Track Investigator, starting in October 2006 as Chief of the Unit on Neural Circuits and Adaptive Behaviors, in the Genes, Cognition and Psychosis Program, DIRP. His research will focus on cell biology relevant to cognition and psychosis. In 1999, Dr. Wang received his PhD in Cell Biology from the University of California, San Francisco, with a world-renowned scientist in the field of neuroscience, Dr. Marc Tessier-Lavigne. From 1999 to present, he has been a postdoctoral research associate in the Laboratory of Dr. Susuma Tonegawa at the Picower Institute for Leaning and Memory at MIT.

Departing:

Captain Gordon R. Seidenberg, MPA, MPH, retired in June after 30 years of service in the Commissioned Corps. Captain Seidenberg served as Deputy Director as well as Deputy Executive Officer in the NIMH Office of Research Management for a number of years. In 1998, he accepted the position of Deputy Director of Management and Program Operations in the Division of Mental Disorders and Behavioral Research, and transitioned in this capacity to DAHBR and DATR in 2002. Captain Seidenberg brought impressive leadership abilities, in-depth understanding of management strategies, and professional integrity to a series of increasingly challenging and influential positions within NIMH.

Julie Phillips retired in July from her position as Social Science Analyst in the Reports and Analysis Branch, OSPPC. She had been with NIMH for 41 years, starting out in the intramural program working under the supervision of Carmi Schooler in the Lab of Socioenvironmental Studies. In 1970, she transitioned to the extramural program with a position in the Division of Special Mental Health Programs. Through her years of service, Ms. Phillips received three awards of achievement, including the Director's Award for Significant Achievement in 1990 and the Director's Merit Award for Significant Achievement in 2004. She is spending her retirement visiting family and friends and enjoying her many hobbies.

Cheryl Parker retired in June after serving NIMH for 26 years. During that time, she was the lead Administrative Officer (AO) for DNBBS, which has transformed throughout the years. Ms. Parker served the Division under many directors, including Lyle Bivens, Steven Koslow, and Steve Foote. In addition to her loyalty to the Institute, she had held many positions and was part of a number of committees within NIH. She was active in the Extramural Administrative Officers group, which was a valuable resource for extramural administrative officers to discuss administrative issues.

Pamela Klein has left NIMH after serving the Institute for nine years; her most recent role was Lead Administrator Officer, Administrative Services Branch, DIRP. She recently started as an Administrative Officer in the National Human Genome Research Institute.