**Department of Health and Human Services**

**PUBLIC HEALTH SERVICE**

**NATIONAL INSTITUTES OF HEALTH**

**NATIONAL INSTITUTE OF MENTAL HEALTH**

# National Advisory Mental Health Council

## Minutes of the 209th Meeting

## May 12-13, 2005

**Minutes of the 209th Meeting of the National Advisory Mental Health Council**

The National Advisory Mental Health Council (NAMHC) convened its 209th meeting in closed session for the purpose of reviewing grant applications at 10:30 a.m. on May 12, 2005, at the Neuroscience Center in Rockville, Maryland, and adjourned at approximately 3:30 p.m. *(see Appendix A: Review of Applications)*. The NAMHC reconvened in open session at the same location from 4:00 p.m. to 5:00 p.m. and continued the open session on the following day, May 13, 2005, in Building 31C, located on the main campus of the National Institutes of Health (NIH) in Bethesda, Maryland, from 8:35 a.m. until adjournment at 12:45 p.m. In accordance with Public Law 92-463, the open policy meeting was open to the public. Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH), chaired the policy meeting.

**Council Members Present at Closed and/or Open Sessions** *(see Appendix B: Council Roster)*:

Sergio A. Aguilar-Gaxiola, M.D., Ph.D.
Jonathan D. Cohen, M.D., Ph.D.
Susan M. Essock, Ph.D.
Faye A. Gary, Ed.D., R.N.
Megan R. Gunnar, Ph.D.
Raquel E. Gur, M.D., Ph.D.
Martha E. Hellander, J.D.
Peter J. Hollenbeck, Ph.D.
Ned H. Kalin, M.D.
Jeffrey A. Kelly, Ph.D.
Helena C. Kraemer, Ph.D.
Eric J. Nestler, M.D., Ph.D.
Charles F. Reynolds, III, M.D.
Suzanne E. Vogel-Scibilia, M.D.
Karen Dineen Wagner, M.D., Ph.D.
Stephen T. Warren, Ph.D.

**Chairperson**
Thomas R. Insel, M.D.

**Executive Secretary**
Jane A. Steinberg, Ph.D.

**Ex Officio Council Member Present at Closed and Open Sessions:**
Robert Freedman, M.D., Department of Veterans Affairs

**Liaison Representative**
Anne Mathews-Younes, Ed.D., Center for Mental Health Services, Substance Abuse and Mental Health Services Administration (SAMHSA)

**Others Present at Open Policy Session:**
Bernard Arons, National Development and Research Institutes, Inc.
Andrea Browning, Society for Research in Child Development
Perry Cohen, Parkinson's Disease Foundation
Cynthia Folcarelli, National Mental Health Association
Ranen Forzigen, J & J
E. Aracelis Francis, Council on Social Work Education
Ruth Hughes, Children and Adults with Attention-Deficit/Hyperactivity Disorder

Alan G. Kraut, American Psychological Society
Robert Levin, M.D., Food and Drug Administration
Stephen Marder, University of California, Los Angeles
George Mills, Food and Drug Administration
Pam Moore, LRP Publications
Elridge Proctor, Tourette Syndrome Association
Stephanie Reed, American Association for Geriatric Psychiatry
Darrel Regier, American Psychiatric Association
Mercedes Rubio, American Sociological Association
Eugene Russo, *The Blue Sheet/Washington Fax*
Angela L. Sharpe, Consortium of Social Science Associations
Ginger Simpson, Anxiety Disorders Association of America
Karen Studwell, American Psychological Association
Rajiv Tandon, National Schizophrenia Foundation
Barbara E. Troost, Child and Adolescent Bipolar Foundation
Richard W. Tsien, Stanford University School of Medicine
Tim Tunner, National Association of Social Workers
Joan Levy Zlotnik, Institute for the Advancement of Social Work Research

**OPEN POLICY SESSION: CALL TO ORDER AND OPENING REMARKS**

Thomas R. Insel, M.D., Director, NIMH, called the open session to order at 4:00 p.m.

**DEVELOPING PEDIATRIC RESEARCH**

Dr. Insel welcomed members of the public to the open policy session and invited Council members' comments concerning research on children. Dr. Kelly began by noting that the Institute was successful in stimulating research on AIDS by funding center grants that provided infrastructure support for researchers from different disciplines to engage in research on AIDS and that this same approach might be useful for stimulating research in the child area.

Dr. Gary noted that many current treatment guidelines for providing psychiatric care to children may not be easily understood or even rejected by parents. She suggested the need for further research on health literacy as it relates to basic issues about children's behaviors—especially the kinds of early risks that might be observed in the home and in the schools—in an effort to improve recognition of the signs and symptoms of mental illness in children and to move treatment forward so that it is more readily accepted by parents and ultimately made available to children.

Ms. Hellander noted the importance of expanding research on children, especially young children, and suggested that the successful strategies employed for stimulating research on women and minority participants be applied to mental health research on children. She also suggested that an examination of the outcomes of the last decade of K awards aimed at training researchers on the mental health needs of women and minority populations might provide some valuable insights for increasing the number of researchers in the child area. Dr. Vogel-Scibilia

commented that a major challenge is to provide education and training that is relevant to the changing nature of treatment approaches and service delivery systems.

Dr. Nestler advised careful consideration of the extent to which studies of normal function will inform pathology. Using Rett syndrome as an example, Dr. Nestler said that what truly advanced the field was not an understanding of the behavior associated with the disorder but rather the discovery of the genetic basis of the disease. He suggested that although research on normal social development is important, advances in autism may lie in better understanding of the neurobiology of the illness.

Dr. Insel emphasized the critical need for a developmental perspective on a variety of basic behavioral processes as they relate to psychopathology in children. He suggested that a greater specificity regarding the knowledge and skill base required for adequately trained child researchers may help to advance the field, acknowledging the value of a Conte Center-type mechanism to facilitate cross-disciplinary collaboration.

**COUNCIL WORKGROUP ON A NEW GENERATION OF NIMH NETWORK TRIALS: AN UPDATE ON ACTIVITIES**

Dr. Junius Gonzales, Acting Director, Division of Services and Intervention Research, NIMH, opened the presentation by providing a brief history of the networks as a prelude to the update on the Workgroup's activities. He noted that other Institutes (e.g., National Cancer Institute and National Heart, Lung, and Blood Institute) have a history of supporting practice-based research networks for trials. Similarly, NIMH participated with the Agency for Healthcare Research and Quality (AHRQ) in its multiphase approach to developing a national primary care practice-based research network. He also highlighted the prominence of the United Kingdom's new mental health research network, sponsored by the National Institute for Mental Health in England. That network does not fund research directly (i.e., research support will be provided by traditional funding agencies) but rather provides a platform to support research, which Dr. Gonzales opined would promote user-friendly research and more rapid adoption of findings into practice.

Turning to the NIMH contracted trials—Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)—Dr. Gonzales noted that as the studies near the completion of the 5-year contracted performance period, the Workgroup has been deliberating on how best to capitalize on the lessons learned from these studies in promoting effectiveness research through research networks that can inform decision-makers at multiple levels in real-world settings. Dr. Gonzales outlined several challenges to conducting clinical research, including a shortage of qualified investigators and study participants, incompatible information systems, and high costs. He then identified some of the benefits that NIMH networks might provide: the ability to continue an infrastructure of academic and community-based investigators that can rapidly and efficiently design high-quality studies; the ability to promote testing of public health and clinical questions in diverse populations that can be recruited quickly into new studies; rapid translation of results to practice and policy; improved research quality and efficiency conducted by collaborative groups experienced in design, recruitment data, outcome measurement, and analytical issues; training

opportunities for new researchers; engagement and retention of community health professionals and members of the community; and collaboration across Institutes and disease conditions.

Dr. Gonzales concluded by noting that efforts will be made to learn from the experience of other Institutes and agencies such as the National Institute on Drug Abuse's clinical trials and criminal justice networks and AHRQ's primary care research networks.

Dr. Sergio Aguilar-Gaxiola provided an update on the Council Workgroup on a New Generation of NIMH Network Trials. The Workgroup has been charged with providing input on how to optimize and sustain the platforms for future research provided by CATIE and STAR*D as a mechanism for answering "next step" questions of the highest clinical and public health significance. Clearly, there are a number of important challenges in this endeavor, including how to develop processes and procedures that will maximize the scientific value and immediate use of the existing platforms. The goal is to move these scientific priorities into projects within the networks in a timely but phased approach by encouraging diverse representation and participation in research networks and by incorporating innovation to reflect public health significance. In addition, it will be important to investigate the readiness of the field to participate in and benefit from the platforms, to explore possible partnerships with private industry, and to determine studies in NIMH's portfolio and at the Institute's Intramural Program that might benefit from the platforms. The Workgroup is supportive of a rapid concept submission and review process, with a structure in place to establish research priorities and to define key study questions for more rapid uptake of results into practice.

**Discussion**

Workgroup member Dr. Essock stated that one challenge is to rapidly mount studies of great public health significance on the platforms. Dr. Freedman stressed the importance of complete patient remission as a goal of future studies as well as identifying areas where new therapeutics are needed. Dr. Insel noted that CATIE has submitted a report of its findings for publication and that STAR*D is close behind, and that a challenge will be to quickly establish a process for identifying studies to participate in the network. Dr. Nestler endorsed the notion of working with industry, and Dr. Insel responded that an effective partnership with industry can be established and that there has been a genuine interest on the part of industry to work collaboratively with NIMH in a way that best serves the public. Dr. Insel concurred with Ms. Hellander's suggestion to explore broadening the network approach beyond the areas of study of the current trials to other mental illnesses.

**NIMH POLICY ON RECRUITMENT AND RETENTION IN CLINICAL RESEARCH**

Dr. Della Hann, Director, Office of Science Policy and Program Planning *(subsequently renamed Office of Science Policy, Planning and Communications)*, NIMH, discussed a new NIMH policy regarding the recruitment of participants in NIMH-supported clinical research. A major impetus for this policy was the report of the Council Workgroup on Clinical Trials (see http://www.nimh.nih.gov/council/interventions_research.cfm). While that report provided important recommendations about the areas of clinical science requiring further research, it also

highlighted the problems encountered in many investigator-initiated grants in meeting overall and minority recruitment goals.

An internal NIMH staff group was formed to address the problems of recruitment and found that the difficulties expand beyond clinical trials to clinical research in general. It became immediately clear that any new policy to address this issue must be clearly and effectively communicated to the scientific field and include a statement about the purpose of the policy, the role of the Institute in monitoring the policy, and the resources available to investigators and staff in addressing recruitment problems.

Dr. Hann reported that other Institutes have policies to address recruitment issues. For example, the National Heart, Lung, and Blood Institute has a policy that addresses the terms and conditions for the accrual of research subjects in clinical trials and epidemiologic studies that expect to recruit 150 or more human subjects (see http://www.nhlbi.nih.gov/funding/policies/terms.htm**).** Similarly, NIMH's new policy (see http://www.nimh.nih.gov/researchfunding/nimhrecruitmentpolicy.cfm) applies to clinical research studies expecting to enroll 150 or more human participants and specifies the need for communication with researchers prior to award to identify and establish recruitment milestones.
Dr. Hann explained that the new policy aims to ensure that realistic recruitment targets are established at the outset of research. Recruitment milestones will be incorporated into the notice of grant award, and adherence to recruitment milestones will be reported to NIMH three times annually. If recruitment falls significantly below the projected milestones at any point, NIMH will consider taking a number of actions, depending on the severity and duration of the recruitment shortfalls. Initially, NIMH would ask the principal investigator to explain and to consider remedial steps. If problems persist over time, consideration will be given to restricting or phasing out the award. A "points-to-consider" document will be posted on the web site (*now available at* http://www.nimh.nih.gov/researchfunding/Clinical%20Recruitment%20Points%20to%20Consider%206-1-05.pdf ), as will a sample milestone chart (see http://www.nimh.nih.gov/researchfunding/Sample%20Recruitment%20Milestone%20Report%205-27-05.pdf ). NIMH staff will be trained on the policy, and meetings will be held to disseminate the information to the community.

**Discussion**

Ms. Hellander expressed concern about the absence of specific policy language for child inclusion requirements, and Drs. Insel and Hann replied that the rules apply to any research population of 150 or more subjects and will allow for the tracking of specific subgroups within a research project. In addition, the policy will be revised to state specifically that children are included. Speaking from a reviewer's perspective, Dr. Gur noted that the policy will set a new standard for recruitment and that reviewers will need to consider investigators' prior publications with a special eye toward reported sample sizes, the proposed inclusion and exclusion criteria, and the adequacy of resources at the study site(s) in evaluating grant applications. Dr. Hollenback asked how recruitment data will be reported to NIMH, and Dr. Hann responded that such reporting will be part of progress reports for funded studies and will serve as an opportunity for discussion with grantees. Dr. Hann responded to Dr. Nestler that 800 of 3,500 currently

funded NIMH grants are clinical studies planning to enroll 150 or more participants. She pointed out that studies with differential recruitment across multisite centers would be handled on an individual basis. Dr. Gunnar observed that the responsibility for adequate recruitment rests with the universities as well as researchers and that it will be imperative for universities to make sufficient resources available for adequate recruitment. Dr. Hann agreed and indicated that university officials would receive the notices of grant awards with details about recruitment goals, as well as notices of any serious deficiencies in recruitment. The goal is to engage both the university and the investigator in addressing issues of recruitment. Dr. Aguilar-Gaxiola asked if NIMH review groups would be briefed on the new policy, and
Dr. Hann responded that the review groups at the Center for Scientific Review would become more familiar with the policy as more Institutes adopt similar recruitment policies.

Dr. Kraemer urged NIMH to avoid reliance on overly restrictive inclusion/exclusion criteria, which could seriously limit patient recruitment. Dr. Insel stated that best practices will inform this effort. Dr. Kelly concurred with the need to share best practices and urged both tracking of children when they are part of broader studies to be sure that stated recruitment goals are met and requiring sufficient numbers of subpopulations for meaningful analysis of effects. Dr. Cohen urged a more proactive approach to inform the field about enhanced enforcement of the recruitment requirements. Dr. Gary commented that the proposed policy will require careful scrutiny of progress reports to ensure compliance with the new policy and that if the public is to be well served by proposed research, there must be clear expectations of the goals of any studies with the resources in place to assist researchers in achieving these goals. She supported Ms. Hellander's request that children be tracked in the same way that any population would be tracked. Dr. Essock stated that early negotiations with investigators in setting realistic recruitment goals, given likely budget reductions, would be essential. She urged NIMH to be proactive by having a dialogue with both the investigator and the university should serious deficiencies in recruitment be detected, noting that the university can play a critical role in addressing deficiencies. Dr. Kraemer suggested adding to the milestone chart a field that indicates the percentage of people who remain in the study, as the retention of study participants can also be a serious research issue.

**SESSION RECESS**

Dr. Insel recessed the initial session of the 209th meeting at 5:20 p.m. The Council reconvened to continue the session the following morning.

**CALL TO ORDER/OPENING REMARKS**

Dr. Insel called the open policy session to order at 8:35 a.m. He welcomed new Council member Suzanne Vogel-Scibilia, M.D., to the session and asked the other Council members to introduce themselves.

**Approval of the Minutes for the Previous Council Meeting**

The minutes of the February 3-4, 2005, Council meeting were adopted unanimously as presented.

## DIRECTOR'S REPORT

In his Director's Report, Dr. Insel updated the Council on several important recent issues and activities (see http://www.nimh.nih.gov/council/dirreportMay05.pdf).

### NIMH Reorganization

Dr. Insel reported that the Institute's reorganized extramural divisional structure is reflected in the new priority statements for each division that are now posted on the NIMH Web site (see http://www.nimh.nih.gov/researchfunding/reorganization.cfm). Staff recruitment is ongoing, and interdivisional teams have been developed for animal models, biomarkers, cognition, drug development, and functioning. The Office of Neuroinformatics has merged with the Division of Neuroscience and Basic Behavioral Science; the Office for Prevention Research has moved under the purview of the new Associate Director for Prevention Research; the Office of Rural Mental Health Research has been consolidated with the Office of Special Populations; the Office of Equal Opportunity has been consolidated into an NIH-wide program; and the Offices of Communications and of Science Policy and Program Planning are being merged to create the new Office of Science Policy, Planning and Communications.

### NIH-Wide Issues

Dr. Insel announced that NIH Director Dr. Elias Zerhouni will present NIH Director's awards to NIMH staff members Dr. Linda Brady for her work on the molecular libraries initiative; Drs. Wayne Fenton, Ellen Stover, and Linda Brady for their work on the MATRICS Project; and Drs. Molly Oliveri, Ann Wagner, and Audrey Thurm for their work on the STAART Program to support autism research. Dr. Karen Berman will receive an award for her work on Williams syndrome, and Dr. Ellen Leibenluft will receive an award for mentoring related to childhood bipolar illness. Several NIMH staff will be recognized for their contributions to the NIH Blueprint initiative, including Dr. Michael Huerta and Ms. Marlene Guzman.

The NIH Roadmap initiative (see http://nihroadmap.nih.gov/index.asp) continues to represent an important component of NIMH's budget commitment, at 1.5 to 1.8 percent of the research budget, with the total Roadmap budget including commitments across NIH in the $375 million range for fiscal year (FY) 2006. Progress is evident in several components of the Roadmap, including the Molecular Libraries Initiative, the Interdisciplinary Research Initiative, and the Re-engineering the Clinical Research Enterprise Initiative.

Turning to the Neuroscience Blueprint (see http://neuroscienceblueprint.nih.gov/index.html), which involves 15 NIH Institutes, Dr. Insel reported that several initiatives will begin in 2005, including an inventory of all database efforts within the United States and around the world. He commented that Council would hear more about this initiative when Dr. Michael Huerta presented later on during the meeting.

The new Office of Portfolio Assessment and Strategic Initiatives in the NIH Director's Office will help to improve management of the research portfolio across all of NIH by providing a

knowledge management system and, potentially, a study of global burden of disease. The Office also will facilitate development of trans-NIH initiatives.

**Recent NIMH Research Findings and Events**

Dr. Insel noted that his Director's Report (see http://www.nimh.nih.gov/council/dirreportmay05.pdf) describes many remarkable recent discoveries and publications, and he went on to describe emerging work showing the importance of neuroscience to inform the treatment and prevention of mental illnesses. He stated that cures for mental illnesses depend on understanding the architecture of disorders at the level of brain systems but that in no case yet has brain pathology been identified. Instead of finding involvement of cellular lesions, studies indicate that disorders of connectivity may be implicated. He asserted that systems neurology likely will produce biomarkers for the detection and ultimately prevention of many disorders.

Dr. Insel reminded the Council of the presentation by Dr. Wayne Drevets at a prior Council meeting concerning an area in the ventral forebrain (Area 25) that shows a 40 percent reduction in volume in people with major depressive disorder (see Drevets, W.C., Price, J.L., Simpson, J.R., Jr., Todd, R., Reich, T., Cannier, M., and Raichle, M.E. "Subgenual Prefrontal Cortex Abnormalities in Mood Disorders." *Nature* 386:824-827, 1997). Subsequent studies showed that this area is among the densest in the forebrain for serotonergic terminals in both humans and non-human primates, and there is abundant evidence that selective serotonin reuptake inhibitors (SSRIs) that work on this cellular target are effective treatments for depression. In a proof-of-principle MRI study, Dr. Helen Mayberg and colleagues examined functional interactions between specific limbic and neocortical regions associated with shifts in negative mood (see Mayberg, H.S., Liotti, M., Brannan, S.K., McGinnis, B.S., Mahurin, R. K., Jerabek, P. A., Silva, J. A., Tekell, J. L., Martin, C.C., Lancaster, J. L., and Fox, P.T. "Reciprocal Limbic-Cortical Function and Negative Mood: Converging PET Findings in Depression and Normal Sadness." *American Journal of Psychiatry* 156:675-682, 1999). They found that patients with depression who improve on either SSRIs or placebo demonstrate limbic metabolic decreases and neocortical increases; the reverse pattern was found in normal volunteers who experience sadness. In another study using deep brain stimulation in healthy volunteers and treatment-resistant patients, Mayberg and colleagues examined whether the application of chronic deep brain stimulation could modulate the elevated activity in Brodmann area 25 in six patients with refractory depression—four patients described a visceral sense of relief when area 25 was reached; these four patients continued to respond well after a year, and scans showed reductions in activity in the BA25 area (see Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., and Kennedy, S.H. "Deep Brain Stimulation for Treatment-Resistant Depression." *Neuron* 45(5):651-60, 2005). Dr. Insel cautioned that although the data are correlational, they pinpoint part of a circuit that may be important for mood regulation.

Turning to how individuals become vulnerable to depression from a molecular vantage point, Dr. Insel described work on the serotonin transporter (SERT) gene and vulnerability to depression. The promoter sequence of the gene appears to be functional; with the short allele, fewer transporters are made and less protein is available because the promoter seems to confer the efficiency of transcription for this gene. Work by Drs. Caspi and Moffitt suggests that the short allele, contrasted with the long allele, doubles the risk of vulnerability to depression in the

context of multiple life-stress events (see Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill J., Martin, J., Braithwaite, A., and Poulton, R. "Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene." *Science* 301(5631): 386-389, 2003). This finding provides a paradigm for studying gene/environment interactions. Neuroimaging in people with the short versus the long allele shows differences in response by the amygdala and that the short allele also might affect some aspects of the regulation of emotional response. A new paper from NIMH's Intramural Program in *Nature Neuroscience* (Pezawas, L., Meyer-Lindenberg, A., Drabant, E.M., Verchinski, B.A., Munoz, K.E., Kolachana, B.S., Egan, M.F., Mattay, V.S., Hariri, A.R., and Weinberger, D.R. "5-HTTLPR Polymorphism Impacts Human Cingulate-Amygdala Interactions: A Genetic Susceptibility Mechanism for Depression." *Nature Neuroscience* 8:828-834, 2005) describes an unbiased, computer-generated morphological analysis of a structural MRI study of 109 healthy subjects. The investigators found reduced gray matter volume in limbic regions critical for processing negative emotion in persons with the short allele, particularly perigenual cingulate and amygdala. The data showed a robust correlation between activity in the presence of threatening stimuli between Area 25 and the amygdala—a coupling of functional activity in the healthy brain. Among persons with the short allele, however, Area 25 and the amygdala become functionally uncoupled, and the investigators have preliminarily determined that the uncoupling factor predicts about 30 percent of variants in "anxious temperament."

More work remains to be done in unraveling how these systems work in people with anxiety disorders, but Dr. Insel expects the model to be useful in moving from an examination of the genetic variation with a known functional polymorphism that occurs during development to an understanding of what this means in an area that has a high serotonergic innervation—Area 25. If it occurs across development, Dr. Insel said, we know that serotonin is essentially a trophic factor early in development and is important for cortical innervation early on. If that means that there is biased information processing between this region and an area that modulates affect or if there is something about that circuit that becomes disordered as a result of volume change and the inability for that area to provide the correct trophic factors, this might translate into a vulnerability to mood disorder. Dr. Insel acknowledged problems with the model but asserted that it provides strategy for moving from gene to cell to system in describing the neurobiology for behavior.

Dr. Insel stressed the importance of conveying to the public the excitement that research offers to further understand and develop new treatments for mental illnesses. In an effort to inform the broader community, NIMH staff members will participate in a research track at the upcoming annual meeting of the American Psychiatric Association and at a translational research track at the New Clinical Drug Evaluation Unit meeting in June. In addition, NIMH has the opportunity to interact with the public around these discoveries at meetings of the Professional Coalition for Research Progress and NIMH's outreach partners meetings. Relatedly, Department of Health and Human Services Secretary Michael Leavitt has recognized, for his annual award for service, the *Real Men. Real Depression.* campaign, which is being implemented in Brazil and parts of Africa and globally for the U.S. military.

**NIMH Budget**

Dr. Insel stated that the President's FY 2006 budget request for NIMH (about $1.4 billion) calls for a 0.7 percent increase for non-AIDS research but a decrease of 1.2 percent for AIDS research (the latter resulting from an NIH-wide AIDS research funding allocation made by the NIH Office of AIDS Research), with a resulting overall NIMH increase of 0.4 percent. This contracts with an FY 2005 increase of 2.2 percent and prior-year increases ranging from 8 to 14 percent. Despite the recent declining rate of increases, NIMH will have a larger research budget for FY 2006 than ever, which is anticipated to result in an increase of about 10 percent in the number of and funding for new and competing grants in the research project grant category, a reduction of 12.6 percent for these grants in the AIDS area and an overall increase of about 7.3 percent for research project grants. This increase is made possible largely due to the timely completion of many continuation grants. Dr. Insel commented that the average cost of grants continues to increase as the number of submitted applications also increases. He cautioned that the budgets for all funded competing applications will be closely evaluated with the goal of redirecting funds to support a wide array of innovative studies—with an emphasis on supporting new investigators.

**Discussion**

Responding to a question from Dr. Warren regarding NIMH's success rate, Dr. Insel stated that the overall success rate for competing research project grants is about 20 percent; competing continuation grants' success rate is about 40 percent. Dr. Kalin urged disseminating the positive information concerning the FY 2006 budget to counter the pessimism in the field related to funding.

Dr. Nakamura observed that as more is understood about the circuitry underlying depression, the potential for developing genetic, medication, and behavioral approaches that target the circuitry is becoming significantly enhanced. Dr. Insel stated that similar research is underway on schizophrenia. The process promises to provide biomarkers for the disorders and tools with which to look at brain systems in order to help with diagnosis, treatment, detection, and prevention of disorders. Dr. Cohen emphasized the importance of basic genetic and behavioral technology to gain an understanding of how to activate the circuits. Correct behavioral paradigms must be coupled with imaging technology and the genetics that define populations. Dr. Insel stated that a cross-disciplinary approach is appropriate with studies in humans and non-human primates and that mouse (or other species) studies may be useful to answer questions about the development and role of the serotonin transporter early in the elaboration of the cortex. Dr. Gunnar suggested accelerating the growth of the knowledge base by convening researchers with relevant published and unpublished data, as well as developmental researchers.

Dr. Tsien questioned at what levels Area 25 is clearly demarked, and Dr. Insel responded that if the definition is to be made by cytoarchitecture, there is confidence that Area 25 can be found across primates. The homologue for mice and rats is less clear—the infralimbic cortex or possibly the infralimbic area. He observed that no specific genetic marker identifies this region with high fidelity and that more mapping work must be conducted.

Dr. Hollenbeck acknowledged the excitement in developing new targets for disorders such as depression but emphasized the importance of accurate quantitative descriptions of endophenotypes. Dr. Insel added that a goal is to personalize treatments, as is done routinely for various types of cancer, for which it will be necessary to have the phenome as well as the genome. Dr. Hollenbeck cautioned that if a particular disorder were to break down into multiple different targets, the pharmaceutical industry might find them less attractive as therapeutic targets. Dr. Insel replied that pharmaceutical companies have indicated a genuine interest in newly identified targets for developing new treatments.

**EVALUATION OF RESEARCH TRAINING AND CAREER PROGRAMS AT NIMH**

Dr. Della Hann explained that NIMH devotes about 12 percent of its budget—more than any other NIH Institute—on individual fellowship awards, institutional training programs, and career awards, compared with the NIH-wide Institute average of 7 percent. In 2004, NIMH supported 1,924 people for a total of about $119.7 million. This compares to 628 awards for competing research project grants at a budget of $185 million during this same timeframe.

Given the current era of slowed budget growth, tough decisions must be made about the Institute's investment in research training and career development versus that for independent research project grants. Recognizing the critical need to continue to prepare people for research careers, NIMH has been considering options to stabilize or even reduce its support for training, which has continued to increase given rising costs of stipends and tuition. However, an evaluation of the success of research training and career programs could provide critical information to guide such decisions, and this led to discussions with staff at NIDA and NINDS about an evaluation of training, which progressed to a feasibility study to determine the practicality and value of evaluating research training.

In consultation with key personnel in the three Institutes and with support provided by the Office of Evaluation in the Office of the Director, NIH, a feasibility study was contracted out to address key research questions: What are the outcomes of interest to assess research training success? What data sources exist to evaluate these outcomes? Is there a need for primary data collection and, if so, what is the best way to collect this data. Through a series of interviews with staff, outcomes of interest were identified in three domains: the trainee's role (e.g., are they actively conducting research), the setting in which work was being conducted, and the source of research funding.

In addition to the feasibility study, a limited in-house evaluation was conducted at NIMH to determine whether persons trained via the T34, T32, F31, F32, and mentored K program have applied/received NIH grants using data in existing NIMH databases. The results showed that trainees who individually applied for their training award were more likely to continue in research—that is, recipients of mentored K awards, F31 and F32 individual fellowship awards were more likely to apply for and receive an NIH grant than those supported by an institutional T32 award. The evaluation also found a similar trend regarding the probability that NIMH trainees would apply/receive an NIMH grant, although the numbers were reduced (compared to the numbers for any NIH grant).

Dr. Hann stressed that the database is limited since it does not capture information on the success of trainees who served as co-principal investigators or who have entered teaching or mentoring careers. It also does not capture data on funding sources outside of NIH.

Dr. Hann concluded by reporting that the contracted feasibility study determined that training outcomes can be assessed in a cost-effective way by sampling, Internet searches, and other means. The contractor (Westat) has proposed a design, should NIMH decide to proceed with a larger-scale evaluation of its research training portfolio. An NIH-funded evaluation would take about 18 months to complete.

**Discussion**

Council members discussed whether or not to proceed with a large-scale training evaluation. Dr. Nestler pointed out the continuing severe shortage of mental health researchers, particularly in targeted areas of research such as child psychiatry. He suggested examining the comparative success rates of specific programs and determining the critical ingredients of those that are more successful. He concluded by noting that it may be more useful to target K awards for the development of clinical scientists.

Dr. Aguilar-Gaxiola recommended undertaking the full evaluation, cautioning the need for care in comparing the goals and outcomes of the various training mechanisms and their cohorts, and urged the use of multiple indicators of success. Drs. Nestler and Aguilar-Gaxiola concurred that the evaluation should be data driven and that attention should be focused on means to add diversity to the NIMH grantee pool.

Dr. Essock urged Council members to provide comments on the proposed outcome measures for the full scale evaluation that are detailed in the report provided to Council. She noted the need for data to inform decisions about mechanisms to maximize increased representation of racial and ethnic minorities as researchers. Dr. Kraemer recommended compiling a transition matrix to analyze existing data on the success of obtaining grant support to provide more specific information for the value of the various training mechanisms, to identify the training stage where a drop-off in success occurs, and to offer a basis for future decision-making. Dr. Hann reported that recipients of T32 and T34 support typically apply for a subsequent fellowship award or for one of the "R" mechanisms of support (rather than for a career development (or K) award), whereas recipients of K awards most likely would apply for one of the "R" mechanisms. Dr. Kalin supported Dr. Nestler's notion of targeting training in areas of greatest need and suggested an analysis of the factors that make investigators successful.

Dr. Insel stated that the training team, division directors, and Institute leadership would convene to project the desired composition of the R01 portfolio in 2015 and how to achieve that goal. Dr. Kelly suggested that specific training programs may have data on their graduates' achievements and noted the importance of characterizing successful programs. Dr. Cohen applauded the evidence-based approached to evaluating the training program and urged consideration of the experience of NIMH trainees versus those supported at other Institutes, as well as investigators who have never received a training award. Dr. Wagner commented that in this era of restricted funding, it will be important for the assessment process to move forward quickly. She urged

prioritizing the outcomes of highest relevance to NIMH's mission. Dr. Gary suggested attention to age factors, particularly to attrition between ages 30 and 40, and to an identification of factors that might inhibit/support trainees in pursuing research careers in an effort to reshape future research programs.

**NIH NEUROSCIENCE BLUEPRINT**

Dr. Michael Huerta, Associate Director for Scientific Technology Research, NIMH, explained that because mental disorders are nervous system disorders, the basic science relevant to NIMH overlaps with that of other NIH Institutes and Centers with an interest in neuroscience.

Dr. Huerta reported that by one measure, NIH's investment in neuroscience will be about $5 billion in FY 2005 and pointed to such investment payoffs as molecular neuroanatomy, which enables mapping gene expression in the brain across the life span of model organisms; stem cell research, which permits directing the development and growth of particular types of brain cells; and neuroimaging, which is a powerful way to link genes, cells, circuits, and behavioral, and health and disorder.

Dr. Huerta stated that the Neuroscience Blueprint (see http://neuroscienceblueprint.nih.gov/) aims to accelerate the pace of discovery and translation of neuroscience research and to increase the payoff of NIH's investment in this important research area. The nature and rate of discovery in neuroscience are limited by the available scientific tools and resources; dissemination and sharing of tools, resources, and data; and the rate at which data evolve into knowledge and insight. To counter these limitations, the Blueprint will prospectively coordinate the activities of 15 participating Institutes and Centers to create enabling tools and resources available to all neuroscientists and will develop strategies to share them with the broad research community.

The Blueprint aims to coordinate research efforts across the participating NIH Institutes/Centers to reduce duplication of effort, produce efficiencies of scale, and create new avenues of discovery and translation. The Blueprint has established a systematic process to plan and coordinate prospectively efforts of common interest to its 15 participants, led jointly by NIMH and NINDS.

The Blueprint effort has resulted in an inventory of major collaborative NIH neuroscience initiatives, meetings of and elicited recommendations from consultants to NIH, outreach to professional societies and patient advocacy groups, and the launching of the Blueprint in fall 2004. Each participating Institute/Center contributes the same percentage of its neuroscience budget to a common fund (NIMH counts about half of its overall budget as neuroscience). The FY 2005 contribution is 0.15 percent, which will rise to 0.6 percent in FY 2008, and the joint contribution to the effort across participating Institutes will amount to $100 million over 5 years. The Office of the Director, NIH, will contribute an additional $50 million through FY 2008, for a total of $150,000 million of collaborative funding for the Blueprint.

Approved Blueprint initiatives for FY 2005 include GENSAT—a project to map the expression (activity) of thousands of genes in the brain and spinal cord—a global inventory of neuroscience tools and resources, curriculum development for linking basic neuroscience to the neuroscience

of disease against multiple disorders, Microarray Consortium expansion, expansion of pediatric MRI study of normal development, and funding of the International Neuroinformatics Coordinating Facility. Potential FY 2006 activities include developing and validating driver mouse lines for important genes; training scientists in neuroimaging, computational neuroscience, and neurobiology of disease; developing core facilities for neuroscience research; creating neuroimaging tools and resources; and developing a neuroepidemiology instrument to assess cognitive and emotional health.

## THE POWER AND ADAPTABILITY OF SYNAPSES OF THE BRAIN

Dr. Richard Tsien, George D. Smith Professor of Molecular and Cellular Physiology, Stanford University School of Medicine, described the importance of studying fundamental aspects of synaptic transmission for setting the stage for advances in our understanding and treatment of brain disorders. He explained how the brain uses small synaptic terminals to send large amounts of information from one neuron to another. He noted the broader research implications of understanding the healthy brain. He explained that the there are an enormous number of neurons within the brain and that each neuron might have on the order of 5,000 synaptic connections, giving rise to around $10^{15}$ synapses processing information at a rate of 10 million gigahertz per second—much faster than any existing computer. These synapses are important for information storage and are modulated in both short- and long-term plasticity.

Dr. Tsien contrasted the classical view of vesicle recycling (discovered by Heuser and Reese)—in which all vesicles fuse, fully collapse and lose the identity of its parts, and get taken up slowly—with a non-classical fusion mechanism named "kiss and run" in which a vesicle kisses or fuses with the surface membrane but retains its identity and is allowed to refill with transmitter. "Kiss and run" permits reuse of vesicles for transmitter release without the long delay of classical recycling.

Proceeding to a discussion of imaging at the level of a single synaptic vesicle, Dr. Tsien explained that tracking these vesicles in living nerve terminals can be powerful in revealing the underlying mechanisms. The ultimate goal is to try to understand each fusion event, either optically, electronically, or both, and to study all of the events that are happening.

Dr. Tsien explained that it is now possible to label and image single synaptic vesicles within synaptic terminals using the FM dyes, and he went on to explain the mechanisms underlying FM labeling. With this technology, Dr. Tsien and his colleagues discovered that only about 15 percent of synapses undergo full vesicle fusion, while 85 percent undergo "kiss-and-run" signaling. In collaboration with Dr. Jason Pyle, Dr. Tsien showed that synaptic vesicles undergoing "kiss-and-run" cycling can refill rapidly with FM dyes, suggesting that these vesicles can refill with neurotransmitter very quickly.

Dr. Tsien suggested that the kiss-and-run mode of signaling might have evolved to lessen the demands on vesicular cell biology by imparting a kinetic advantage to increase synaptic throughput and to improve economy by keeping the reserve pool largely intact and more often in a state of readiness. He also suggested that fusion pore modulation may allow for an additional level of modulation of quantal transmission.

Dr. Tsien went on to emphasize how seemingly esoteric fundamental studies of basic signaling mechanisms can, over the years, lead to important therapeutic advances for nervous system disorders. He used his own work on the N-type Ca2+ channels as an example and described how his discovery of these channels, which for many years was quite controversial, was followed by the discovery of the conotoxins, which was followed by the discovery that the N-type channel is modulated by G proteins. The importance of these channels in norepinephrine release followed, and this led eventually to a highly effective therapeutic agent for intractable pain that received FDA approval this year. In addition to this 20-year history on N-type channel blockers, Dr. Tsien discussed a recent finding by one of his former students, Mark Keating, demonstrating that the dysfunction of one of the voltage-activated calcium channels, $Ca_v1.2$, leads to "Timothy syndrome," a multisystem disorder that includes autism. Apparently, a point mutation in $Ca_v1.2$ results in a considerably slower calcium entry in affected individuals. Dr. Tsien discussed how postsynaptic remodeling is likely to be important in the pathology and pointed out some recent findings on L-type channels and on autism and Rett syndrome from other laboratories including Dr. Huda Zoghbi's laboratory, suggesting that the remodeling of postsynaptic dendrites is likely to be important for our eventual understanding of neurodevelopmental disorders.

Dr. Tsien then discussed how neurons adapt to chronic changes in synaptic activity by maintaining natural firing frequencies within a functionally appropriate range. Adaptive responses to chronic changes in synaptic activity have come to be known as 'synaptic scaling,' and he explained how this process is thought to safeguard the full functionality of neurons as signaling elements in brain circuits by keeping neuronal firing rates away from extremes of frequency where information transfer would be compromised. He explained that Hebbian plasticity and adaptive, negative feedback plasticity—both critical for stable learning networks—are distinct, and he described their underlying mechanisms. If a number of synapses become stronger with intense stimulation, the post-synaptic neuron would fire more rapidly and eventually reach the point where it fires at its maximum rate—a condition not useful for transmitting information but that can be accommodated with uniform scaling.

Dr. Tsien went on to discuss how hippocampal cultures show an array of changes in response to chronic inactivity, not just amplitude scaling, and that these changes are linked to changes in AMPA receptor GluR1 subunits. Dr. Tsien discussed how the induction of these changes involve depolarizations through L-type calcium channels, not NMDARs, that changes occur both pre- and postsynaptically, and that changes in synaptic strength are not scaled uniformly, that is, already strong synapses change the most.

Dr. Tsien concluded by emphasizing that understanding these rules of synaptic plasticity will be fundamental to understanding the healthy brain and how the brain copes with stress, damage, and other genetically based phenomena in mental and neurological disorders.

**Discussion**

Dr. Tsien responded to a question from Dr. Nestler about the blockade of the L-type calcium channel, that a non-polarized form of CAMP kinase Type II is involved but that the mechanism by which turning down L-type channels increases the expression of beta-CAMP kinase has not

been worked out. He explained that autism involves an over-expression of calcium entry, presumably in post-synaptic sites, and that it is possible to look at all post-synaptic signaling events that might follow L-type channels, including things that regulate gene expression. Dr. Gunnar questioned at what point in the development of basic research it is most useful to integrate the work described by Dr. Tsien into specific subject areas of investigation. Dr. Tsien responded that he pursues integration of knowledge by teaching and learning across disciplines, mentoring, and attending meetings and conferences, which provide the opportunity to interact across disciplines. Dr. Gunnar suggested consideration of strategies to increase the applicability of basic science finds into other areas of research. Dr. Tsien urged seeking out the very best basic science around and then offering incentives for demonstrations of relevance. To a question from Dr. Cohen about the interaction of Dr. Tsien's group with computational neuroscientists, Dr. Tsien stated that he has benefited greatly from that expertise, which led to exciting new observations such as the importance of the interval between the bursts and pattern of bursts. Ms. Hellander questioned what implications this work might have for treatment or therapeutics, and Dr. Tsien responded that if a form of autism is caused by calcium channels not turning off enough, it is possible that treating the brain with an FDA-approved calcium channel blocker at an early enough stage may serve well. He envisions collaborating with another group that may have more information about the location of the circuits in autism in looking at the role of L-type channels in the adaptive plasticity of the nervous system to modifications that happen during daily life, and then target to the brain blockers of those channels. He suggested also a pharmaceutical that spares the pre-synaptic calcium channels that release the transmitter and modify the overactive L-type channels involved. He acknowledged the early stage of the research and the complexities involved in extending findings to therapeutics.

**REPORT OF THE NIMH MATRICS PROJECT**

Dr. Wayne Fenton, Director, Division of Adult Translational Research and Treatment Development, NIMH**,** noted the complexity of the traditional path to develop pharmacological treatments for improved clinical care—molecular targets are identified through basic research programs; biochemical assays then are used to screen for lead compounds; animal models are developed for safety and toxicology studies; and human clinical trials are conducted. However, the traditional pathway of discovery for the currently available pharmacological treatments in psychiatry has not followed this same course; rather, it has been marked by serendipity with discoveries tested in rigorous clinical trials to establish treatment effectiveness, and then basic science has been applied after the fact to identify the molecular targets impacted by developed treatments. This formula has produced only a limited number of molecular targets for mental illnesses.

Dr. Fenton enumerated that in order to move treatment development in psychiatry forward and facilitate the discovery and translation of novel targets into treatments, collaboration among government, industry, and academia will be essential.

Turning to clinical targets for schizophrenia, Dr. Fenton noted that the cognitive deficits associated with the disorder, although important clinical targets for the past 15 years, continue to be experienced frequently by patients receiving treatment. Dr. Fenton reported that the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)

program was developed in response to the need to develop new drugs to address cognitive deficits and to facilitate their regulatory approval.

Dr. Stephen Marder, Chief, Executive Committee, MATRICS, and Professor, Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, described aspects of MATRICS that pertain to communication between NIMH and FDA. At the start of MATRICS, in addition to a consensus cognitive battery for trials of cognitive-enhancing agents for schizophrenia, FDA asked for development of measures of functional capacity and interview-based assessment of cognition. Initial MATRICS principles included seeking the broadest possible consensus; inclusion of persons with divergent views from academia, NIMH, industry, FDA, and consumer representatives; transparency of process, including publication of findings and processes; a priori development of a path to consensus; and management of conflicts of interest.

Dr. Marder described the multiple consensus processes, noting that consensus was most difficult for the neuropsychological battery. Consensus on cognitive domains was achieved for speed of processing, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition. Essential criteria to test these domains were developed; the domains were tested, and a RAND panel evaluated the tests. A beta form of the battery was administered and repeated, which led to a final proposal for a battery, which is now being co-normed with community samples at five sites.

MATRICS recommendations include using the Consensus Cognitive Battery for Clinical Trials for Schizophrenia in its entirety as the standard battery for all clinical trials of cognitive enhancers. An overall cognitive composite score consisting of equal weighting of the seven domain scores would be the primary cognitive endpoint for agents targeted at enhancing cognition broadly. Alternatively, a small subset of domains may be combined as the primary cognitive endpoint for agents believed to enhance cognition selectively (e.g., learning and memory).

Approaches to co-primary outcome measures include functional measures that simulate daily activities or social problem-solving situations and that demonstrate that a person is capable of performing the functional task (but not whether he/she does so in the community). Interview-based assessments of cognition can estimate the level of cognitive abilities or the degree to which cognitive deficits affect community function. These assessments can be self-ratings or estimates from a caregiver. Refinement of measures is anticipated.

Consensus regarding trial design was published recently in *Schizophrenia Bulletin.* Recommendations for clinical trial methods include the inclusion of subjects who are clinically stable; exclusion of subjects only if impairment compromises test validity or if they perform at ceiling; for co-medication, comparison of the addition of drug or placebo to current antipsychotic medications; for broad spectrum antipsychotic, comparison of experimental drug to an antipsychotic that does not impair cognition; and monitoring outcomes with the MATRICS battery and a co-primary measure of functional capacity or interview-based cognitive assessment.

MATRICS currently is working on packaging and disseminating the battery, anticipated within the coming year. The tests are available and are already being used in the field in drug trials and in the network.

Discussant Dr. Robert Levin, Medical Officer (Psychiatry), Division of Neuropharmacological Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA)**,** stated that FDA staff members have concluded that the MATRICS process is an ideal model for the conduct of clinical trials in terms of determining the target population, the exact targets, outcome measures, design types, and statistical design. He noted that the process has been completely data driven and evidence based—an excellent strategy for designing trials.

**Discussion**

Dr. Fenton requested Council advice and approval for the recommendations to be sent formally to FDA. Dr. Cohen applauded the MATRICS efforts in bringing cognitive assessments into view at the FDA. He urged incorporating into the recommendations a forward-looking mechanism to bring cognitive measures as they are developed into the assessment process—should their usefulness be proven—in order not to lock the science into dated measures and miss the opportunity to translate from the basic behavioral laboratory to the clinical setting. Dr. Marder responded that a consensus paper is in process that looks at the next direction for development. Drs. Fenton and Insel concurred with Dr. Cohen's concern, and Dr. Insel noted that the literature must to be mined to ensure that the best science is being utilized to determine targets. Ms. Hellander urged development of cognitive enhancers for children. Dr. Gur commented on the value that functional imaging might provide in validating new measures.

Council members generally supported the recommendations as proposed, with the changes noted above, and Dr. Insel stated that NIMH will transmit the MATRICS recommendations, together with Dr. Cohen's concern about the development of new tools, to FDA.

**EXPLORATORY IND DRAFT GUIDANCE AND DISCUSSION ON PARTNERSHIP BETWEEN NIMH AND FDA DIRECTED AT THE DISCOVERY AND EVALUATION OF NOVEL IMAGING AGENTS IN CLINICAL RESEARCH AND IN DRUG DISCOVERY**

Dr. George Mills, Director, Division of Medical Imaging and Radiopharmaceutical Drug Products, FDA, discussed the issue of developing Investigational New Drug (IND) draft guidance around the need for imaging probes. He described the FDA's critical path initiative to describe and delineate the processes to identify imaging biomarkers and the qualification process for imaging surrogates. Part of the initiative is to conduct a gap analysis on data and specifications and standards for imaging biomarkers and regulatory and technology challenges regarding imaging biomarkers as surrogates. He also stressed that stakeholder collaborations serve as a mechanism to enable further studies.

The FDA currently is seeking comments on the draft guidance, published in the *Federal Register* in April. The guidance is aimed at enabling rapid progress from Phase 0 (or preclinical) to Phase 1 development, reducing initial entry pharmacology/toxicology requirements and allowing for a

diagnostic dose with no therapeutic intent that will permit proof-of-concept development trials for new imaging agents and imaging biomarkers.

Dr. Mills explained that exploratory IND facilitates early first-in-human diagnostic imaging biodistribution studies; early first-in-human drug/biologics development seeks to confirm promising preclinical findings for new molecular entities in early trials for targeting organ localization and routes of clearance. Combining techniques permits combining and radiolabeling of promising new molecular candidates and obtaining first-in-human biodistribution images for these new molecular entities. He commented that this is a direct application of the techniques of interest to NIMH. Exploratory IND facilitates first-in-human biodistribution imaging trials, whether in whole body or brain, and provides confirmation of preclinical assessments for tumor targeting, PK, biodistribution, normal organ targeting, and rates of clearance. Trial findings can inform efficacy and safety selection, which produces an excellent proof of concept to determine whether new molecular imaging techniques have promise. Dr. Mills stated that biodistribution imaging can be done quickly, demonstrating receptor and receptor occupancy related to the various types of existing imaging modalities.

Portfolio analysis can be conducted to radiolabel competing candidates and do comparative whole body biodistribution studies. The same can be done with PET and MRI to demonstrate confirmation of preclinical findings from Phase 0 to Phase 1 and therefore sort out quickly the promising entities. This results in reduced pharmtox costs in funds and time for the not-so-promising new molecular entities and a complete pharmtox with the completion of the initial Phase 1 study. Dr. Mills asserted that the challenge will be to relate those imaging signals to long-term drug development for expected imaging.

Dr. Mills concluded his comments by noting the importance of enhanced communications to understand better, for example, NIMH's inventory of initiatives and to facilitate collaborative work where real progress can be achieved.

**Discussion**

Dr. Insel stated that the process outlined by Dr. Mills is an important step in accelerating the development of radiopharmaceuticals. Dr. Robert Innis, Chief, Molecular Imaging Branch, Division of Intramural Research Programs, NIMH, who directs a program on PET radioligand development, concurred on the importance of the ongoing collaborative work with FDA on translational tools to measure specific proteins in the brain. He noted that pharmaceutical companies have recognized the importance of these tools for their therapeutic drug development. Many tools are about to emerge, but they face the barriers of going into first-in-human use; and thus collaboration with the FDA is crucial to address these barriers and move research forward.

**CONCEPT CLEARANCE**

- Dr. David Stoff, Program Chief, Neuropsychiatry of HIV/AIDS, AIDS Research Training, Center for Mental Research on AIDS, Division of AIDS and Health Behavior Research, NIMH, introduced a concept for clearance related to development of a regional T32 training program for AIDS (see http://www.nimh.nih.gov/council/cncptstoffmay05.pdf). The proposed

Minority Institutional Research Training Program in HIV/AIDS would support development of research training programs for individuals in doctoral and post-doctoral programs at minority schools, and would create a research environment that would facilitate partnership development and provide focused training experiences. The program is expected to significantly enhance the number of minority scientists trained to conduct mental health research in HIV/AIDS. The initiative plans two initial grants for regional programs totaling approximately $750,000.

**Approval of the Concept**

The Council voted unanimously to approve the concept.

- Dr. Farris Tuma, Chief, Traumatic Stress Research Program, Division of Adult Translational Research and Treatment Development, NIMH**,** introduced a concept for clearance related to innovations in treatment and services for combat-related mental disorders (see http://www.nimh.nih.gov/council/cncpttumamay05.pdf ). Dr. Tuma stated that as of March 2005, approximately 360,000 troops returning from Iraq and Afghanistan have become eligible for health care benefits through the Department of Veterans Affairs (VA), about 20 percent of whom have sought care at a VA facility. Among that group, more than 28 percent have sought mental health treatment. This initiative, in collaboration with the VA and U.S. Army, will try to improve the identification, treatment, and management of combat and war-related conditions among returning troops. He proposed an announcement to stimulate new intervention-development applications and projects in collaboration with the Department of Defense, VA, and other researchers and clinicians. Dr. Tuma stated that NIMH also would continue to collaborate with Substance Abuse and Mental Health Services Administration, which is working to prepare community mental health facilities for returning National Guard and Reserve troops who may not access VA facilities.

**PUBLIC COMMENT**

Family member Barbara Troost described her family's experience with bipolar disorder. She urged NIMH to make early diagnosis a priority, especially by educating and disseminating information to pediatricians, and to move funds from the adult program to child research, since it is known that the roots of schizophrenia, bipolar disorder, and mood disorder all begin in the early years.

Perry Cohen, Parkinson's Disease Foundation, stated that about half of Parkinson's patients have a psychological or cognitive deficit resulting from the disease or the medication. He urged that mental health consumers take part in decision making around development of new therapies, and he referenced the Parkinson Pipeline Project's Research Participant's Bill of Rights (see http://pdpipeline.org/rights.htm). He noted that the FDA has begun to pilot a patient consultant program for Parkinson's that will have patients at the table to offer advice in the pre-approval stages of the clinical development process.

Cynthia Folcarelli, National Mental Health Association, stated that her organization works in partnership with 340 states and local mental health association affiliates on public education and

advocacy. An important priority is the translation of cutting-edge research findings into practice and public policy. She lauded NIMH's focus on the mental health needs of returning U.S. veterans and urged continuing attention to increasing the numbers of researchers from multiple underrepresented groups. She called members' attention to a projected $10 billion cut in Medicaid, which pays for half of all public funding of mental health services. She also called for educational measures to counter a robust anti-psychiatry movement in the country.

Dr. Darrel Regier, American Psychiatric Association (APA), echoed concern about the anti-psychiatry movement, noting that the public image of mental health and mental disorders will have important implications for funding for mental health services. He expressed appreciation to NIMH for its research track at the upcoming APA meeting that will help to translate world-class scientific research to clinicians. He recommended linking the training research evaluation to the work of the American Association of Medical Colleges, which tracks academic progression of medical students. He stated that the APA intends to use the Council's discussions on biomarkers for Area 25 and the MATRICS project in the NIH-supported conference on the research base for DSM-V.

**ADJOURNMENT**

Dr. Insel adjourned the 209th meeting of the NAMHC at 1:10 p.m. on May 13, 2005.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

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Thomas R. Insel, M.D., Chairperson