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NATIONAL INSTITUTE OF MENTAL HEALTH

National Advisory Mental Health Council

Minutes of the 214th Meeting

January 11-12, 2007

Minutes of the 214th Meeting of the
National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 214th meeting in closed session to review grant applications at 11:00 a.m. on January 11, 2007, at the Neuroscience Center in Rockville, Maryland, and adjourned at approximately 5:00 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened for an open session on the following day, January 12, 2007, in Building 31C, National Institutes of Health, from 8:30 a.m. until adjournment at 12:30 p.m. In accordance with Public Law 92-463, the policy session was open to the public. Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH), chaired the meeting.

Council Members Present at the Grant Review and/or Open Policy Sessions
(See Appendix B: Council Roster)

Council Members:
Elizabeth Childs, M.D.
Jonathan D. Cohen, M.D., Ph.D.
Raquel E. Gur, M.D., Ph.D.
Martha E. Hellander, J.D.
Peter J. Hollenbeck, Ph.D.
Dilip V. Jeste, M.D.
Ned H. Kalin, M.D.
Jeffrey A. Kelly, Ph.D.
Norwood Knight-Richardson, M.D., MBA
Helena C. Kraemer, Ph.D.
Pat R. Levitt, Ph.D.
John S. March, M.D., Ph.D.
Enola K. Proctor, Ph.D.
Peter Salovey, Ph.D.
Suzanne E. Vogel-Scibilia, M.D.
Stephen T. Warren, Ph.D.

Chairperson:
Thomas R. Insel, M.D.

Executive Secretary
Jane A. Steinberg, Ph.D.

Ex-Officio Member Present at the Grant Review and Open Policy Sessions:
Robert Freedman, M.D., Department of Veterans Affairs (VA)

Liaison Representative Present at the Open Policy Session:
Anne Mathews-Younes, Ed.D., representing A. Kathryn Power, Substance Abuse and Mental Health Services Administration

Others Present:
Schahram Akbarian, University of Massachusetts School of Medicine
Bernard Arons, National Development and Research Institutes
Mark Bowman, Society for Neuroscience
Andrea Browning, Society for Research in Child Development
William Carpenter, Jr., University of Maryland School of Medicine
Jaclyn Diamond, Society for Neuroscience
Alan Friedman, Transcriber
Stephen Foote (NIMH contractor)
Chang-Gyu Hahn, University of Pennsylvania
Karina Havrilla, American Sociological Association
Elizabeth Hoffman, American Psychological Association
Sean Joe, University of Michigan
Alan Kraut, Association for Psychological Sciences
Timothy MacGeorge, Children and Adults with Attention-Deficit/Hyperactivity Disorder
Ann Michaels, National Foundation on Mental Health (Friends of NIMH)
Amy Pollick, Association for Psychological Sciences
Angela Ratkowski, Institute for the Advancement of Social Work Research
Stephanie Reed, American Association for Geriatric Psychiatry
Beth Roy, Social and Scientific Systems, Inc.
Bette Runck, Science Writer
Marian Scheinholtz, American Occupational therapy Association
Angela Sharpe, Consortium of Social Science Associations
David Shern, Mental Health America
Jean Shin, American Sociological Association
H. Blair Simpson, New York State Psychiatric Institute
Andrew Sperling, National Alliance on Mental Health
Barbara Wanchisen, Federation of Behavioral, Psychological & Cognitive Sciences
Thomas Wasser, KidsPeace
Vicky Whittemore, Tuberous Sclerosis Alliance

OPEN POLICY SESSION: CALL TO ORDER AND OPENING REMARKS

NIMH Director Dr. Thomas Insel called the open policy meeting to order by introducing four new Council members: Dr. Elizabeth Childs, Commissioner of the Department of Mental Health in Massachusetts, the first psychiatrist to head the department in two decades; Dr. Dilip Jeste, Professor of Psychiatry at the University of California, San Diego, and the Department of Veterans Affairs (VA) Medical Center in San Diego; Dr. John March, Professor of Psychiatry and Chief of Child and Adolescent Psychiatry at Duke University Medical Center; and Dr. Enola Proctor, Dean for Research and Professor of Social Work Research at Washington University in St. Louis.

Dr. Insel then marked the departure from the Council of Dr. Robert Freedman, who represented the VA in an ex officio capacity since September of 2000 and provided invaluable expertise and guidance. Dr. Ira Katz will represent the VA at the next Council meeting.
Dr. Insel also noted that Dr. Su Koester has joined the Institute's extramural program as Deputy Director in the Division of Neuroscience and Basic Behavioral Science, and Dr. Michael

Schoenbaum, a health and labor economist has joined the Division of Services and Intervention Research as a senior advisor.

APPROVAL OF THE MINUTES FOR THE PREVIOUS COUNCIL MEETING

Turing to the minutes of the September 2006 Council session, Dr. Insel asked if members had revisions or comments on the minutes. Hearing none, the minutes were adopted unanimously.

DIRECTOR'S REPORT

In his Director's Report, Dr. Insel updated the Council on several important issues and activities (see http://www.nimh.nih.gov/council/dirreportjan07.pdf).

Budget

Dr. Insel reported that the NIMH was still operating under a continuing resolution although fiscal year (FY) 2007 had begun October 1. The budget recommended by the President and the House of Representatives is 0.6 percent lower than the FY 2006 funding level. The Senate has yet to take up the bill. (HJ Res20 [PL110-5] funding a full year continuing resolution was enacted on 2/15/07) The expected decrease, together with the expected 3.5 percent biomedical inflation rate, will reduce the Institute's purchasing power. NIMH has, in fact, experienced 4 years of sub-inflationary budget reductions. Dr. Insel pointed out that although some have questioned the impact of the NIH Roadmap on the overall budget, it accounts for only about 1 percent ($17 million) of the total NIMH FY 2007 research budget of almost $1.4 billion.

The number of competing research grants awarded each year since 1998 has remained relatively stable at between 500 and 600 awards. Applications, by contrast, have almost doubled during the same timeframe. Thus, the average success rate for a research project grant (RPG), such as an R01, R03, or R21, has gone from 28 percent in FY 1998 to 20 percent in FY 2006.

Over the past few years, the Institute has adopted several strategies for managing the mismatch between supply and demand from eliminating inflationary increases to emphasizing program priorities when making funding decisions. Dr. Insel said the goal is to ensure that the portfolio remains diverse and reaches for the most exciting and high-impact science.
The Institute's new mechanism, the K99/R00 Pathway to Independence Award, is one way to foster the development of new investigators. This mechanism funds up to 2 years of mentored K support for postdoctoral research scientists followed by up to 3 years of support as an independent investigator through an R01 award. NIMH plans to award ten K99 awards this year with an additional ten awards planned for next year.

To safeguard innovation, NIH will continue the highly successful Pioneer Award Program that provides support to individual scientists of exceptional creativity who propose pioneering approaches to major contemporary challenges in biomedical and behavioral research. NIMH is also hosting a series on innovation and creativity designed to encourage broad, interdisciplinary thinking in the development of scientific initiatives and programs and to press for leaps in science over incremental thinking. The speakers are innovators and leaders within their specific fields and include individuals involved in disciplines such as business, law,

technology, and art. In addition, through the NIMH-staffed Innovations Committee, NIMH awards one year of support to highly innovative applications that would otherwise not be funded in an effort to encourage innovation. This year of support is to be used to gather additional data for resubmission, and some of the awardees have been successful in obtaining subsequent funding through the peer review and award process.

Legislation

The NIH Reform Act (passed in December and signed by the President in January 2007) reauthorized the NIH for the first time since 1993. The Act reaffirms the importance of NIH and its vital role in advancing biomedical research to improve the health of the Nation. The Act outlines a new process to facilitate trans-NIH research by establishing a common fund, to be managed by the new Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the NIH Office of the Director. DPCPSI will be responsible for portfolio analysis, oversight of strategic initiatives, and management of trans-NIH interests and trans-NIH policies. The NIH Reform Act established an advisory Council of Councils for research proposals funded by the Common Fund. Also authorized by the Act is a new Scientific Management Review Board charged with the periodic review of the use of the NIH's organizational authorities and recommendations regarding the use of such authorities. Although the Act authorized an increase in the NIH budget for each of the next 3 years "as available," it does not appropriate that money.

Another law that was recently passed is the Combating Autism Act, which authorizes NIH to expand autism research but does not appropriate funds for the expanded research. NIMH has been the lead Institute on autism and has chaired the Interagency Autism Coordinating Committee, which is reestablished and modified by the Act to be subject to the Federal Advisory Committee Act.

New Science

Dr. Insel said that the NIH has been building public-private partnerships via the Foundation for the NIH (FNIH). FNIH is a congressionally established private, not-for-profit group that brings industry, government, and academia together to work with NIH for targeted initiatives. One such initiative is the Genome Association Information Network (GAIN), which supports six whole-genome association studies across all of biomedical research. Following the rigorous peer, technical, and ethical review of more than 30 applications, six were funded and four were studies of schizophrenia, bipolar disorder, major depressive disorder, and attention-deficit hyperactivity disorder. Much of the reason for this success is that several thousand samples of DNA from individuals with these disorders were already in the NIMH repository. This rapid $20 million effort is notable because both the genotyping and the phenotyping data will go into the public domain almost immediately after the genotyping is completed, and this expected by summer 2007.

Another FNIH initiative is the Biomarkers Consortium, which supports public-private efforts to identify biomarkers for a range of diseases. A neuroscience steering committee has been formed within this consortium to focus on central nervous system disorders. Two projects of interest to NIMH are being considered by the committee: one will develop novel positron emission tomography (PET) ligands for mental disorders; the other is a whole-genome association study of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study samples to try

to identify biomarkers that could predict treatment response to selective serotonin reuptake inhibitors (SSRI). As with the GAIN studies, all of the data collected will be in the public domain.

A third FNIH-funded effort is identifying opportunities to leverage the clinical trials networks and clinical trials in general. One public-private partnership is a study of adverse effects of antipsychotic medications, and another is aimed at developing compounds for cognitive deficits in schizophrenia.

Update on NAMHC Workgroup on a New Generation of NIMH Network Trials

Dr. Philip Wang, Director of the NIMH Division of Services and Intervention Research, reviewed the rationale for convening the Council Workgroup on A New Generation of NIMH Network Trials. The Workgroup was asked to propose and discuss potential research questions using the networks focusing on the public health significance, feasibility, size, resources, and time frames required for the proposed projects. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), STAR*D, and the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trials demonstrated that the NIMH practical clinical trials can provide unbiased evidence about clinical practices. However, this first round of studies also showed that improvements in the treatments for schizophrenia, bipolar disorder, and depression are urgently needed to optimize treatment strategies, personalize regimens, minimize adverse effects, increase adherence, and ultimately improve prognoses and decrease the burden of mental illness. To accomplish these goals, a new round of practical clinical trials may be necessary.

The Workgroup first met in 2005 and recommended that NIMH provide infrastructure-only funding to support the continuation of the networks so that this resource might be employed as a platform to conduct continued research. In fall 2006, the NAMHC encouraged NIMH to increase traffic on the supported networks. Dr. Wang said that the Institute issued a Request for Information (RFI) from the field and has reconvened the Workgroup. The goal of this effort is to set priorities and potentially issue Requests for Proposals (RFP) to increase use of these established networks.

Dr. Wang then introduced the Workgroup's chair, Dr. William T. Carpenter, Jr., Director of the Maryland Psychiatric Research Center and Professor of Psychiatry and Pharmacology at the University of Maryland School of Medicine. Dr. Carpenter said that the Workgroup meeting began with a presentation from each network and was followed by a discussion to develop ideas of how the networks might be effectively used in future research.

The Workgroup discussed multiple areas of study, those applicable both to the established networks in general and to specific networks. Some of the research themes that emerged were a focus on early intervention, longer follow-up periods, optimizing and augmenting existing treatments with either psychosocial intervention or medications, addressing comorbid conditions and adherence, and examining what treatments seem to benefit whom and when in the course of illness.

Dr. Carpenter emphasized the important resource that the trial networks represent and said that

the field should be urged to make use of these networks. Dr. Insel made it clear that the networks are open to the public, not only those investigators involved in the trials to date.

Dr. Kraemer said that the Workgroup also discussed the use of unorthodox designs--those that are best suited to answering clinically important questions. The networks appear to provide an ideal platform for implementing some of those designs, she said. Dr. Insel added that to make the best use of the networks, NIMH might need to be proactive and not rely on the usual investigator-initiated project grants that do not always fair well in peer review. Cooperative agreements and contracts may make it possible to guide the process more expeditiously. Dr. March said that he believes clinicians might be well suited to aid in formulating the questions to be studied. He was encouraged to hear that all the practical clinical trials include a genomics component.

Dr. Insel said that the networks provide an opportunity to leverage the clinical research now going on in academic health centers. This research has been reinvigorated via a Roadmap initiative which funds clinical and translational science via a national consortium of academic health centers. (http://www.ncrr.nih.gov/clinicaldiscipline.asp). Such research has become one of the largest parts of the Roadmap.

Dr. Childs asked whether the NIMH networks link with the broader health community, a connection that is important because of the high comorbidity of mental illnesses with other physical illnesses. Dr. Carpenter said that about half of the depression network sites are in primary care settings.

Dr. Vogel-Scibilia said that the effectiveness of translating the results of the practical clinical trials to date into grassroots providers is unprecedented. She said that it appears that the standard of care has been improved as a result of the networks. She also endorsed the idea of eliciting research questions from clinicians in the community.

Peer Review at the NIH Center for Scientific Review

Dr. Insel introduced Dr. Antonio Scarpa, Director of the NIH Center for Scientific Review (CSR), to discuss review-related issues. Dr. Scarpa, who joined CSR in summer 2005, had been a long-time grantee while at Case Western Reserve in Cleveland.

Dr. Scarpa said that the peer review system is the "heart and soul of NIH" and has made the United States preeminent in biomedical research. This process has created the best academic medical centers, been admired and imitated all over the world, and protected NIH from undue outside influence.

In 2005 and 2006, CSR received about 80,000 applications a year, double the number received in 1998. In 2006, 51,798 applications were reviewed at CSR by study sections and special emphasis panels. NIMH applications represent between 6 and 7 percent of the NIH total.

The peer review system has undergone very little change in its 60-year history, Dr. Scarpa said. While the system is very good, some criticism has been voiced suggesting there is room for improvement. These criticisms include the slow process; too few senior, experienced reviewers

on review panels; a fear that the process favors predictable research instead of significant, innovative, or transformative research; the impression that clinical research may not score as well as other types of research; and the heavy time and effort burden on applicants and reviewers.

Dr. Scarpa sees both mechanical and cultural issues that might be addressed when thinking about reengineering the NIH peer review system. The mechanical issue might involve redesigning and improving administrative and organizational systems and procedures. The cultural issues might involve facilitating the identification and advancement of more significant, innovative, and high-impact research as well as attempting to reduce the size of applications.

CSR has made some significant changes in an effort to improve the peer review process. These include replacing a majority of paper applications with electronic versions and using artificial intelligence, text fingerprinting, and algorithms to assign grants automatically to integrated review groups (IRGs) or study sections.

Dr. Scarpa said his vision for updating the peer review system involves several steps. The first is to shorten the review cycle to allow for more rapid resubmission. This can be achieved by shortening the timeframe for posting summary statements following review meetings.

A second suggested modification to the CSR review process is to improve study section alignment and performance. IRGs, each of which comprises seven or eight study sections, could be reviewed every 5 years to evaluate them against the state of the science and the field to reduce any overlap or inefficiencies.

Dr. Scarpa said a third possibility for improving the process is to recruit and retain high-quality reviewers. To address retention, CSR is moving to alternative review platforms to augment the face-to-face meetings, including using telephone- and video-enhanced discussions and asynchronous electronic discussions on the Internet for Web chats. These electronic discussions are said to be preferred by many clinicians, physicists, and computational biologists and they appear to facilitate the participation of international reviewers. Another near-term solution for enhancing recruitment and retention is to hold shorter meetings.

The NIH is also considering a move to shorter applications and to align the application content with the scoring criteria, which were revised 10 years ago. Decreasing reviewer burden drives the goal to shorten applications. The criteria based application would facilitate a review of the impact of the research and its innovativeness rather than on approach and preliminary results. Dr. Scarpa said that the scientific community has indicated strong support for these changes.

Inclusion of Women and Minorities in NIMH Research

Dr. Insel noted that the NIH Revitalization Act of 1993 requires each Advisory Council to review its Institute's compliance with NIH guidelines on the inclusion of women and minorities in clinical research. Dr. Insel introduced Dr. Catherine Roca, Chief of the NIMH Women's Health Program, to present this year's report. Dr. Roca began by reminding Council members that NIH clinical research includes all patient-oriented research, including mechanisms of disease, therapeutic interventions, clinical trials, development of new technologies,

epidemiological and behavioral studies, and outcomes and services research.

Referring to the report's tables, Dr. Roca pointed out that in 2005, NIMH extramural research did well in its recruitment of women and African Americans into clinical studies, was on target in recruiting American Indians, Alaska Natives, and Hawaiian/Pacific Islanders, and somewhat exceeded census data for recruitment of Asian participants. Participants who identify themselves as Hispanic were underrepresented; although they make up 12.5 percent of the population, only 7.49 percent of study participants were Hispanic. The 2006 data showed a large decline in African-American recruitment, from 20 percent down to 12.6 percent. The reason for this decrease was the influence of one extremely large Web-based study, the Virtual Lab, that had low percentages of participation by African-American and Hispanic participants, although their absolute numbers were in the hundreds of thousands.

Dr. Roca then reviewed data from phase-III clinical trials. The NIH definition includes any broadly based study comparing an experimental intervention with standard or control interventions or comparing two or more existing treatments. It covers traditional studies of pharmacological agents, behavioral and preventive interventions, prophylaxis, diagnosis, or other therapies. Community trials and other population-based intervention trials are included. Dr. Roca pointed out that now that the large practical clinical trials have ended, the data reflect a shift to foreign studies, mostly studies of AIDS in Asia and Africa. Although the aggregate data for 2005 show nearly 62 percent of participants are Asian, for example, the domestic-only data indicate that participation of Asians is only 1.29 percent. More effort will be expended to recruit more Asian subjects into domestic phase-III trials, she said.

The NIMH Intramural Research Program (IRP) faces similar challenges in recruiting Hispanic and Asian subjects. As with the extramural trials, one study involving Army recruits begun many years ago skew the data. Excluding that study, the 2005 data were similar to the extramural data.

Following Dr. Roca's presentation, Council members voted their concurrence that the data are in compliance with the NIH inclusion rules.

Update on Diversity Efforts at NIMH

NIMH Deputy Director, Dr. Richard Nakamura, presented an annual update on racial and ethnic diversity among grantees and Institute staff. He explained that NIMH data on race and ethnicity are based on self-identification and that an individual may assign himself or herself to more than one category or choose not to report at all. Across all Institutes, there has been a slight decline in grants held by underrepresented minority scientists. However, NIMH, NIDA and NIAAA rank at the top in terms of the proportion of awarded R01 grants held by underrepresented minority scientists. Although that proportion had been rising steadily, it has recently decreased, and this is a cause for concern, Dr. Nakamura said. Analyses are underway to help address the decline in awards to minority scientists.

In terms of NIMH staffing, minority managers among the NIMH extramural staff increased from 8.7 in 2002 to 12.7 percent in 2006; the proportion of minorities in the nonmanagerial staff has

remained about the same during this period, somewhat less than a third. On the IRP managerial level, the proportion was relatively stable, 3.9 percent in 2002 to 4.2 percent in 2006. Minority non-managers made up 21.2 percent of the IRP staff in 2002 and 22.8 percent in 2006. In his new capacity as acting Scientific Director of IRP, Dr. Nakamura hopes to improve the minority representation.

Turning to the Minority Research Infrastructure Support Program (M-RISP), the Office for Special Populations examined the success of developing faculty members in obtaining grant support. For M-RISP grants supported for 9 years or more, 61 developing faculty members obtained grant support; this translates into a 30 percent success rate. In an effort to increase a focus on Hispanic mental health issues, Dr. Nakamura reported an initiative to mentor individuals who are seeking NIH grants to study these issues. During the first four years (2002-2006), 53 junior investigators were paired with more senior investigator (mentors). From this initiative, 32 grant applications have been submitted, and 13 grants have been funded; this translates into a 41 percent success rate.

NIMH-Supported New Investigators

Dr. Insel introduced the next series of presentations by noting that the Institute is committed to supporting new investigators and to facilitating the independence of emerging scientists. These investigators are a critical resource to the research enterprise both in terms of the new knowledge they are contributing to the field and as a resource to the Institute in terms of how we can best serve researchers**.**

Maximizing Outcome in Obsessive-Compulsive Disorder (OCD)

Dr. Insel introduced Dr. H. Blair Simpson, Associate Professor of Clinical Psychiatry at Columbia University, Attending Psychiatrist at Columbia Presbyterian Hospital, and Director of the Anxiety Disorders Clinic at New York State Psychiatric Institute (www.Columbia-OCD.org). Dr. Simpson said that the goal of her research program examining obsessive-compulsive disorder (OCD) is two-fold: (1) to improve current treatments and (2) to understand the mechanisms underlying OCD to be able to develop novel treatment strategies for the future. Both lines of research have received NIMH funding.

Dr. Simpson emphasized the impairment in social and occupational functioning caused by OCD symptoms. The World Health Organization lists OCD as one of the leading disabling disorders because of its high lifetime prevalence, early age of onset, typically chronic course, and the high proportion of severe and moderate cases.

Dr. Simpson traced the evolution of her research from her participation as a fellow in an NIMH-funded multicenter trial that compared the effects of exposure therapy, the serotonin-reuptake inhibitor (SRI) clomipramine, and their combination in a randomized, placebo-controlled clinical trial. The trial showed that after 12 weeks of treatment, all active treatments resulted in a reduction of symptom severity, whereas treatment with placebo did not. On average, those who received clomipramine alone still had symptoms considered clinically significant; however, those receiving a combination treatment or exposure treatment alone had achieved reduction of symptoms below that level. She pointed out that the exposure therapy used in this study was a form of cognitive-behavioral therapy using exposure and ritual prevention and was delivered intensively by skilled therapists. Because such skilled therapists are rare and the treatment is

very time-consuming, most OCD patients receive SRI medications such as clomipramine alone as first-line treatments.

These promising findings helped launch the next NIMH-funded multicenter trial to explore whether twice weekly exposure therapy could augment SRI treatment. Dr. Simpson is co-PI of this study, and the data are under review for publication. In this study, OCD patients were recruited who had received an adequate SRI trial but who still had symptoms causing impairment. While continuing on their medication, these patients were randomized to either twice weekly exposure therapy or another type of cognitive-behavioral treatment, called stress-management therapy, which teaches anxiety-management skills but has no exposure or response-prevention components. As hypothesized, the investigators found that OCD symptoms can be significantly reduced by the addition of exposure therapy to medication but not by stress-management therapy as administered in this study. About three in four patients responded with the addition of exposure therapy— a greater proportion than has been shown in other studies to respond when antipsychotic medications are added. However, only some patients achieved complete or nearly complete remission after 8 weeks of either treatment.
These findings led to a new NIMH-funded multicenter trial, which Dr. Simpson is doing in collaboration with Dr. Edna Foa from the University of Pennsylvania. Again, the subjects are patients with OCD who are taking an SRI but who remain symptomatic. One aim of the study is to directly compare the effects of adding 8 weeks of antipsychotic medications to exposure/response-prevention therapy. A second aim is to examine the effects of 6 additional months of treatment in those who show at least minimal response in the first 8 weeks to see how many patients were able to achieve full remission of symptoms. The study's ultimate goal is to provide clinicians with evidence-based guidelines for treating current patients with OCD.

For the patients of tomorrow, Dr. Simpson's second line of research focuses on examining the underlying mechanisms in OCD. Much of what is now known comes from imaging studies, which have primarily focused on the structure of the brain or such nonspecific measures such as blood flow and metabolism. Those studies have led to the suggestion that OCD results from a malfunctioning brain circuit involving the orbitofrontal cortex and the basal ganglia. Dr. Simpson, collaborating with experts in neurochemical imaging of the brain, is examining the serotonin system. The first study, which focused on serotonin transporters, showed no difference between patients with OCD and controls in the brain regions examined. In subsequent pilot studies of the 5-HT2A postsynaptic receptor, the investigators found abnormalities in the orbitofrontal cortex in OCD patients. Dr. Simpson said the findings are intriguing because the 5-HT2A receptor has been implicated in OCD in pharmacological studies and theoretical models, and recent data in mice suggest that cortical 5-HT2A signaling may modulate anxiety-like behavior in mice.

Recently Dr. Simpson received NIMH funding to confirm and extend the findings. The goal is to compare the brain distribution of 5-HT2A receptors in patients with OCD with healthy matched controls and to determine whether the 5-HT2A findings predict individual SRI response.

Dr. Simpson said she sees her research as a series of steps aimed at developing cellular and circuit models of brain mechanisms of OCD that eventually can lead to significant therapeutic advances.

Molecular and Cellular Logic of Experience-Dependent Cortical Information Processing

Dr. Insel introduced Dr. Kuan Wang, an investigator in the NIMH Intramural Genes, Cognition and Psychosis Program, who discussed how his work on the molecular and cellular logic of experience-dependent cortical processing may lead to new treatments for mental disorders. The brain, he said, can be considered as an adaptive information-processing system, where input signals are first detected and properly represented, then integrated for output control. Once sensory information is detected, neural activities can trigger cascades of molecular and cellular changes in the brain circuits, which then affect subsequent cognitive events. These experience-dependent adaptive changes may adjust the brain systems according to the demands of the outside physical and social environments and ultimately benefit the survival of individuals.

Maladaptation in this process can contribute to the development of a variety of mental disorders, such as schizophrenia and depression. To understand the process, Dr. Wang and his colleagues set out to identify molecules that are regulated by an animal's experience by examining the spatial and temporal expression patterns of the candidate molecules in cortical circuits and determining their contributions to cortical functioning. This integrated multilevel approach requires observation of nerve cells in action in intact cortical circuits. Traditionally, studies of cortical representations have relied on electrophysiological recordings of neuronal spiking signals. But it is challenging to ascertain the physical identity of the recorded cells and then maintain long-term stability, Dr. Wang said. The introduction of functional magnetic resonance imaging (fMRI) has allowed repeated observation of brain activation patterns. Because this technique is dependent on blood oxygenation signals, however, resolution at a single-cell level is yet to be achieved.

A more recently developed technique, two-photon microscopy, uses two infrared photons to excite fluorescence simultaneously from a point of focus. When this technique is applied to live animals, individual neurons that are injected with fluorescent dyes can be imaged with single-cell resolution. Then the challenge becomes imaging activity-dependent molecular changes and tracking the changes over extended periods of time in live animals. To track the changes, Dr. Wang's group designed a genetic reporter of activity-regulated gene expression. Such genes are normally silent in nerve cells but can be rapidly induced in response to strong synaptic inputs. By replacing a part of the activity-regulated gene with jellyfish green fluorescent protein (GFP) and combining it with two-photon imaging, the investigators are able to track neuronal activation patterns in response to repeated sensory stimulation with single-cell resolution. This aids in the determination of the functional requirements of the targeted gene.

Dr. Wang and his colleagues focused on a neural activity-regulated gene named *Arc* because it is highly induced by activity and because it encodes an intracellular protein involved in synaptic transmission. After generating Arc-GFP mice, Dr. Wang and his colleagues first looked at the dynamics of Arc-GFP response to visual stimulation, which peaks at 2 hours and completely disappears 12 hours after initial stimulation. This dynamic cycle made it possible to examine experience-dependent molecular changes daily. Using a chronic two-photon imaging method in live animals, they also examined whether Arc-GFP activation patterns contain stimulus-specific information and concluded that the Arc-GFP expression pattern can reflect orientation-specific activation of neurons.

Upon examining the visual cortex in mice with the Arc protein completely knocked out, the investigators found that there were more neurons with low orientation specificity and neuronal

spike tuning response to orientated stripes was also broadened in Arc knockout mice.

Together, the imaging and the electrophysiological evidence suggest that Arc plays an important role in enhancing the overall orientation specificity in the visual cortex. Dr. Wang said that it seems to accomplish this task by functioning as a molecular filter to suppress neurons that respond to a broad spectrum of orientations, while maintaining those with a high degree of orientation selectivity.

The Arc-GFP imaging system allows the investigators to address many fundamental questions about brain functions at the molecular and cellular levels. Starting with their work on the perceptual microcircuits in the visual cortex, the investigators are exploring the molecular determinants of neuronal response specificity, how past environmental exposures affect the neuronal response patterns, how the emotional and motivational states of an animal affect its perceptual activation patterns, and how perceptual activation patterns are integrated for decision-making. Studies such as these can also help to understand the functions of genetic risk factors for mental illness at a cellular and a systems level, Dr. Wang said. Human genetic risk factors can be introduced into mice to generate mouse models. By combining with mice that are carrying activity reporters such as Arc-GFP, brain activity changes associated with genetic risk could be identified. Genetic risk factors for mental illness may create bottlenecks in the experience-dependent cortical processing. Dr. Wang said that the integrated approach he is using may offer unique opportunities to observe the development of mental disorders in real time and reveal the impact of genetic risk factors, psychotropic drugs, and environmental exposures on mental disorders.

Prevalence and Correlates of Black Suicidal Behavior

Dr. Insel introduced Dr. Sean Joe, who is a social worker and mentor with the African-American Mental Health Scholars Consortium and holds Assistant Professorships in the School of Social Work and the Department of Psychiatry at the University of Michigan and is Director of the Emerging Scholars Interdisciplinary Network. Dr. Joe discussed the findings of the National Survey of American Life (NSAL) related to suicidal behavior among African Americans. He pointed out the significant increases in suicide and suicidal thoughts and actions among young blacks since the mid-1980s. As highlighted by the Institute of Medicine (IOM) report (http://books.nap.edu/execsumm_pdf/10398.pdf), suicide among African Americans and ethnic minorities is understudied, and little is known about the risk factors for these populations or measures that can be taken to reduce their suicide risk. Before the recent upsurge of suicidal behavior among young blacks, ethnic minorities had significantly lower rates of suicide than whites. Now that gap has been narrowed because the suicide rates for blacks are rising.

The NSAL provided the data to examine the national prevalence, age of onset, and psychiatric correlates of black suicidal behavior. Conducted from February 2001 to June 2003, the NSAL is a national probability sample of 5,181 black respondents aged 18 years and older. The NSAL respondents reported a lifetime prevalence of 11.7 percent for suicide ideation and 4.1 percent for attempts among black Americans. A new finding that is of significance is that 7.5 percent of Caribbean black males in this sample reported a suicide attempt, whereas 2.7 percent of

Caribbean black females attempted suicide. This finding is striking because it is a reversal of the usual gender pattern with higher reports of suicide attempts expected for females

Dr. Joe also shared several noteworthy findings about the sociodemographic predictors of suicide in this population. Those born after 1975 (the youngest cohort) were at highest risk for suicide attempts. Respondents with less than a high school diploma were more likely to attempt suicide than those with a college diploma. Those who lived in the Midwest region were at a higher risk for suicide attempts than those who lived in the South.

Black Americans with any identifiable DSM-IV diagnosis were more likely to attempt suicide than those without such diagnoses. Respondents with mood disorders were, as expected, at higher risk. Surprisingly, however, those with an anxiety disorder were more likely than those with mood disorders to attempt suicide. This finding contrasts with the findings of the National Comorbidity Survey (NCS) (http://www.hcp.med.harvard.edu/ncs/), which found that a mood disorder is the strongest psychiatric determinant of suicide risk.

Unfortunately, about a quarter of those who attempted suicide did not use any mental health services. The majority who attempted suicide and sought mental health services tended to use health-related services (i.e., general medical service) rather than non-health-related services (i.e., complementary and alternative treatments). About a third of those who did use mental health services sought them from general medical practitioners rather than mental health specialists. Of those who did see specialists, 45 percent saw psychiatrists and 35.5 percent saw other mental health professionals.

Dr. Joe identified several next steps in terms of research. He called for research to explain the unexpected higher risk for attempted suicide among Caribbean black males. In addition, research might focus on understanding the factors that influence the transition from suicidal thoughts to a suicide attempt, an understanding of which is vital to health care professionals screening blacks at risk for suicide. Research is also needed to focus on the underlying biological, genetic, and familial risk factors that are associated with black suicide behaviors. Dr. Joe also called for multisite research studies to aid in the development of efficacious and effective treatments.

Neuregulin 1-erbB4 Signaling in Schizophrenia

Dr. Insel introduced Dr. Chang-Gyu Hahn, Associate Director for the Cellular and Molecular Neuropathology Program at the University of Pennsylvania, to discuss the study of molecular and cellular signaling pathways in postmortem brain tissues.

Over the past decade, a list of candidate genes have been identified that may be critical in the pathogenesis of schizophrenia. It is now quite clear that multiple genes are involved and that they interact with each other and with environmental factors. One of the candidate signaling pathways supported by robust data is neuregulin 1-erbB4. The functions of neuregulin 1 have been independently implicated in the pathophysiology of schizophrenia. Previous work had shown, for example, that the expression of neuregulin 1 is subtly but distinctly different in the brains of schizophrenia patients than in controls. Neuregulin 1 is a ligand that binds to the erbB4, erbB2, and erbB3 protein receptors. When neurogulin 1 binds to receptor erbB4, it turns

the receptor on and triggers a sequence of events. The effects of neuregulin 1 are important because of the molecular events that occur after the receptors have been activated.

To learn whether the signaling mechanisms changed in response to the stimulation of these receptors, the laboratories of Drs. Hahn and Hoau-Yan Wang (City University of New York) attempted to activate the receptors in postmortem brains and then monitor signaling activation. Drs. Hahn and Wang's laboratories established a method they called *postmortem brain stimulation paradigm.* This technique involves obtaining a small slice of postmortem brain and then incubating it with a ligand (neuregulin 1 in this case) in the hopes that this biochemical stimulation would trigger signaling.

The researchers found a striking difference in the extent of the stimulation induced by neuregulin 1 in the tissue from patients with schizophrenia when compared with tissue from controls. They confirmed that finding by examining three other parameters, which also resulted in downstream signaling. Thus, enhancement of this kind of signaling was shown in four different ways: tyrosine phosphorylation, activation of AKT, activation of ERK, and erbB4/erbB2 heterodimerization (erbB4 binding to erbB2).

In their explorations of the cause of erbB4 hyperactivation in the postmortem brains of schizophrenia, Dr. Hahn and his colleagues called on past research demonstrating that activity of erbB4 is increased when it binds with PSD-95. They hypothesized that erbB4 hyperactivation would be enhanced by erbB4 association with PSD-95. Using a technique called *immunoprecipitation* to assess how the molecules associate with each other, they found a striking enhancement that was actually quantitatively more striking than erbB4 activation. They next found that the enhanced association was not caused by increased availability of PSD-95.

PSD-95 is also associated with several other receptors. It plays a key role in the activation of N-methyl-d-aspartate (NMDA) receptors. It also is associated with other postsynaptic density proteins. The enhanced erbB4 activation and PSD-95 association suggested that a similar association might occur between PSD-95 and NMDA receptors, which are the focus of one of the leading hypotheses for the pathophysiology of schizophrenia. The researchers stimulated the brain tissues with NMDA in the presence or absence of neuregulin 1. They found that NMDA receptor function, which was measured by tyrosine phosphorylation, was significantly decreased in postmortem brains of patients with schizophrenia. Dr. Hahn said that this was the first known direct demonstration that NMDA receptor hypofunction could actually be observed in patients' brain tissue.

Summarizing his group's findings, Dr. Hahn said that in the brain tissue of patients with schizophrenia, tyrosine phosphorylation was enhanced, a process that was probably caused by or occurred in parallel with the enhanced association with PSD-95. PSD-95 was also shown to be important for other signaling mechanisms, such as NMDA receptors. The research suggests that enhanced erbB4 signaling might be one of the causes or associated findings for NMDA receptor hypofunction. The observation that the extensive interactions among proteins in this "microdomain" is particularly attractive, Dr. Hahn said, because it may lead to an understanding of how each dysregular receptor system interacts with others to produce global changes in postsynaptic density, which in turn may be accompanied by changes in other receptor signaling mechanisms that occur in schizophrenia.

Chromatin Remodeling at GABAergic Gene Promoters in Developing and Diseased Human Prefrontal Cortex

Dr. Insel introduced the next speaker as a seasoned researcher who recently began exploring a new area of research. Dr. Schahram Akbarian is an Associate Professor in the Department of Psychiatry at the University of Massachusetts Medical School. He is a pioneer in thinking about epigenetics and how modifications of the genome might affect dopaminergic regulation.

Dr. Akbarian's research is largely concerned with GAD1, a gene that encodes a key enzyme for GABA (gamma-aminobutyric acid) neuron synthesis. He said that he had introduced the gene to the field 12 years ago because it was one of the first RNA molecules shown to be at a decreased level in postmortem brain tissue of schizophrenia subjects. Other, more senior Investigators have since replicated and extended this finding. In addition, NIMH intramural scientists have identified this gene as a modifier because some of its allelic variants appear to be associated with an increased risk for childhood-onset schizophrenia and other brain abnormalities.

Dr. Akbarian said that he believes that a molecular process involving the protein histone H3 points toward the responsible defect for this gene in the production pipeline. These molecules are the "protein backbone" of chromosomal material, he said. They can be chemically modified at certain amino acid positions. That modification serves as a flag at a particular chromosomal location; methylation of the molecule indicates that the chromatin fiber of the chromosome is active in the production pipeline meaning that there is very active turnover or transcription of RNA from the DNA strand.

Dr. Akbarian and his colleagues were among the first to explore the developmental regulation of this chemical chromosome modification in the human prefrontal cortex. The first question they asked was what happens with the methylation marks during the life of a human brain, examining brains prenatal age through the second decade of life. They found that whichever chromosomal location they examined, whether the telomeres, GAD1, the hemoglobin locus, or other GABAergic marker genes, the methylation levels were very low throughout the line. However, the brains of young adults showed a dramatic increase in levels of methylation at the sites where GABAergic marker genes such as GAD1 or SST and NPY are expressed. On regions of the genome that are inactive, such as the telomere or the hemoglobin locus, which is important for blood but not for brain, these methylation marks stayed at similar levels as in the fetal brain.

The next step was to identify the underlying molecular players because methylation has to be mediated by the enzyme methyltransferase. The investigators focused on the mixed-lineage leukemia 1 gene, which, in addition to contributing to a type of leukemia, is also a histone methyltransferase. They found that this molecule was expressed at robust levels throughout the cortex; it was present in the large majority of GABAergic neurons, the nerve cells that express GAD1. This finding was verified in a mouse model.

The results were among the first pieces of evidence that the chromosomal material in a human brain continues to be remodeled for at least two decades of life. The researchers then asked themselves whether that remodeling is relevant for human brain disease. Dr. Akbarian reiterated that certain GAD1 allelic variants appear to play a role in increasing the risk for childhood-onset schizophrenia and perhaps bipolar disorder. In further studies, he and his colleagues used a case-control design to examine the postmortem brains of subjects diagnosed with schizophrenia or

autism who had two copies of the risk alleles. They found that those individuals were at three- to seven-fold increased risk for having a chromatin alteration at the GAD1 locus; that is, they had a loss of the "go" signal, the histone lysine 4 flag for active RNA production, and instead they had an overblown "stop" signal, meaning a chemical modification or another amino acid which normally serves as a stop signal for chromosome and RNA production.

The investigators subsequently showed that mice treated with daily injections of the antipsychotic drug, clozapine, had increased levels of the histone methylation tag at the GAD1 locus.

In summary, Dr. Akbarian said that the GAD1 gene may be one of the first examples of how both genetic and epigenetic determinants of gene expression in GABAergic dysfunction operate in conjunction in major brain disorders such as schizophrenia, autism, and bipolar disorder. He noted that recent research by others had linked the gene to early-onset schizophrenia and may to some degree regulate frontal lobe activity. The work of his group suggests that the chromatin at this particular gene locus is continuously modified during the first two decades of human frontal lobe development. Chromatin methylation may be further upregulated at this locus by repeated exposure to antipsychotic drugs. This chromatin structure could be affected in some, but not all, individuals diagnosed with schizophrenia or related disease, including some cases of bipolar illness or autism.

Discussion

Dr. Proctor asked how various funding mechanisms had accelerated the scholarly careers of the junior investigators. Dr. Joe said that the K01 gave him both protected time for research and access to very skilled investigators who served as mentors. In addition, this award gave him the time to develop his own research agenda, and it put him in touch with NIH program staff who helped to shape his research. Dr. Hahn stated that his K award was critical to his development as a researcher as it allowed him time to conduct research. Dr. Simpson agreed and added that had the new K99 mechanism been available, it would have helped her make the transition from a junior to a full-fledged investigator. Dr. Insel said that one of the goals of the K99 is to allow junior investigators to leave their training institutions and find a position elsewhere by providing up to 3 years of support to transition as an independent scientist to an extramural sponsoring institution at which the individual has been recruited. Recognizing the difficult budgetary constraints, Dr. Simpson suggested that money and time are essential in making the transition from trainee to full-fledged investigator.

Dr. Cohen asked the presenters how well their training covered the range of subjects needed to understand the neural basis of psychopathology–from genetics, to molecular and cellular biology, through to behavior. He asked whether there were gaps in the intellectual landscape of their training for bridging these various disciplines. Dr. Kuan Wang said he was trained as a molecular biologist, and he finds the exposure to translational and clinical research in the NIMH intramural program very helpful in making the link between the basic molecular and cellular mechanisms and human functioning. Dr. Joe said that as a social behavioral scientist, he found it difficult to get brief training in the methodology of biological mechanisms or biomarkers. While he is interested in all the risk processes related to the onset of suicidal behavior and eventual suicide, he said that his training in biological markers has been limited. The focused suicide research centers, which became available after his training, could be very useful for learning

about a range of subjects and methodologies.

Dr. Insel asked the presenters with M.D./Ph.D. degrees for their perspective, because NIMH has few of such grantees. Dr. Hahn said that a major struggle for him was figuring out a way to navigate through the huge amount of information spanning subjects from molecular to clinical research. The field has been in the process of putting together an intellectual paradigm for approaching psychiatric illnesses from a translational standpoint. He hopes that this kind of integrated perspective will be incorporated more frequently into training programs, such as the K program. Dr. Akbarian said he chose a mentor who was a stem cell biologist because he wanted to learn the newest methodologies. He said that neuroscientists might be encouraged to expand their perspectives and continue to learn new principles of basic cellular mechanisms, which seem to be of profound importance for the nervous system. Dr. Simpson said her original work with the brain circuitry underlying bird song vocalization was critical training for her as a clinical researcher because it taught her to consider the brain mechanisms underlying treatments and patient behavior. She also endorsed the emphasis on translational models showing the public health significance of research.
Dr. Gur commented that the junior investigators who presented at this meeting have been quite successful in tapping the institutional resources (including intellectual resources) available to them.

Ms. Hellander encouraged more work with children in both preclinical and clinical research. Mental disorders begin in childhood, and therefore she believes this piece is essential for research endeavors. The investigators agreed and said that they would like to include children in greater numbers but that several factors made it difficult, including the need for more child psychiatrist clinical researchers, the ethical questions regarding the use of some brain imaging technologies in children, and the difficulty in recruiting sufficient number of participants.

Dr. March said that the development of an independent scientist hinges not only on the transition from a K award to the first R01 but also from the first to the second R01. It is only then that resources are stable enough to develop a program of research.

Dr. Kalin encouraged collaborative brainstorming between NIMH and the leaders of psychiatry departments to address the development of junior investigators. The issues include not only obtaining grant funding but also supporting, mentoring, and freeing up time, even at some cost to the institutions. Dr. Insel agreed on the importance of encouraging academic institutions to do more in supporting the development of their researchers.

Concept Clearance: National NeuroAIDS Tissue Consortium

Dr. Kathy Kopnisky, Chief of the NIMH HIV Therapeutics and Psychiatric Pathogenesis Program, described the concept clearance request for the proposed National NeuroAIDS Tissue Consortium (NNTC) initiative. The NNTC is a brain tissue and fluid bank established in 1998 designed to serve primarily as a research resource. Its purpose was to provide investigators with high-quality brain tissue and fluids on well-characterized patients who were considered to be at the end stage of illness. Patients were characterized by several measures: degree of neurobehavioral impairment; neurological and other clinical diagnoses; history of alcohol and drug abuse; antiretroviral treatments; blood and cerebrospinal fluid (CSF) viral load; neuropsychiatric diagnoses; and ultimately, postmortem neuropathological tissue assessments.

The current consortium is located in four different sites: Mount Sinai Medical Center in New York, the University of Texas at Galveston, and the Universities of California in San Diego and Los Angeles. The database coordinating center, located in Rockville, Maryland, provides administrative support to the brain banks. It is responsible for designing and maintaining the Web site used by the public and the consortium members, providing descriptive statistics on the cohort and technical assistance related to data and data-integrity issues.

Approximately 2,000 patients have been enrolled into the brain bank program. More than 600 brains have been collected; more than 1,000 brain specimens, 600 CSF samples and several thousand plasma samples are readily available. This resource is available to the scientific community without charge. In addition, the NNTC has longitudinal data on a unique cohort of well-characterized individuals.

The purposes of this solicitation is to authorize continued support for clinical assessments and brain banking operations, to incorporate a Principal Investigator with statistical, HIV, and genetic epidemiology expertise, and to charge the consortium with the development of a scientific agenda that capitalizes on the data and the unique cohort.

Dr. Kopnisky said that she and her colleagues believe that the collection of well-characterized brains and fluids from the HIV population will continue to be an important research resource for the community. Although much is known about the neuropathogenesis associated with neuroAIDS, more needs to be learned about the evolving disease and brain-related changes in response to new treatments.

Currently, the National Institute of Neurological Disorders and Stroke (NINDS) and NIMH together fund the tissue consortium. The National Institute of Drug Abuse (NIDA) is considering supporting one of the sites.

Dr. Kraemer asked whether any attention had been given to the issues of sampling and the representativeness of the materials being collected. Dr. Kraemer said that it might be helpful to have someone determine how subjects are selected. Many kinds of biases enter into a sample that cannot be corrected by subsequent analysis, she noted. Dr. Kopnisky said that this is one of the goals and hopes that both the addition of a Principal Investigator and the development of a scientific agenda into the brain banking functions might address this as well as other questions.

The Council then voted to approve the concept clearance.

Public Comment

Dr. Bernard S. Arons introduced himself as a psychiatrist and Executive Director and CEO of National Development and Research Institutes, Inc. (NDRI), a New York City-based, freestanding behavioral health research organization. He said that discussion among the approximately 60 NDRI-supported investigators has led him to question whether shortening the page requirements for applications is a good idea. He encouraged the Council to make certain that the page-limit decision is based on what would produce the best science and not limit the ability of new and innovative researchers to clearly explain their research plans.

Dr. David L. Shern, President of Mental Health America, formerly known as the National Mental Health Association, first explained the name change of his organization was made, in part, to underscore the central nature of mental health to the health of all Americans, to start a new campaign to educate the public, and to develop a political consensus that treatment for mental disorders is integral to overall public health. He applauded the Institute's translation efforts and encouraged the Council to continue to be concerned about the relevance of research for those who suffer from mental disorders.

Dr. Insel reminded Council members that the next meeting would be held May 10-11, 2007. With that, he adjourned the meeting.

ADJOURNMENT

Dr. Insel adjourned the 214th meeting of the NAMHC at 12:32 p.m. on May 11, 2007.

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

Appendix A

REVIEW OF APPLICATIONS — January 2007 Council*

Category	IRG Recommendation							
	Scored #	Scored Direct Cost $	Not Scored (NRFC) #	Not Scored (NRFC) Direct Cost $	Other #	Other Direct Cost $	Total #	Total Direct Cost $
Research	734	$957,128,862.00	486	$399,923,145.00	29	$28,460,620.00	1249	$1,385,512,627.00
Research Training	200	$93,631,837.00	24	$18,103,482.00	4	$0.00	228	$111,735,319.00
Career	83	$59,137,598.00	29	$20,297,081.00	1	$757,890.00	113	$80,192,569.00
Other	0	$0.00	0	$0.00	0	$0.00	0	$0.00
Totals	1017	$1,109,898,297.00	539	$438,323,708.00	34	$29,218,510.00	1590	$1,577,440,515.00

*Applications with primary assignment to NIMH

APPENDIX B: COUNCIL ROSTER
DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF MENTAL HEALTH
NATIONAL ADVISORY MENTAL HEALTH COUNCIL
(Terms end 9/30 of designated year)

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Bethesda, MD

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Jane A. Steinberg, Ph.D.
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