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NATIONAL INSTITUTE OF MENTAL HEALTH

National Advisory Mental Health Council

Minutes of the 205th Meeting

February 6, 2004

Minutes of the 205th Meeting of the National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 205th meeting in closed session for the purpose of reviewing grant applications at 10:00 a.m. on February 5, 2004, in the Neuroscience Center, Rockville, Maryland, and adjourned at approximately 5:00 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened in open session at 8:40 a.m. on February 6, in Building 31C, Conference Room 10, on the main campus of the National Institutes of Health, Bethesda, Maryland. In accordance with Public Law 92-463, this policy meeting was open to the public until its adjournment at 1:00 p.m. Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH), chaired the meeting.

Council Members Present at Closed and/or Open Sessions (Appendix B has Council Roster)

Sergio Aguilar-Gaxiola, M.D., Ph.D.
Susan M. Essock, Ph.D.
Susan Folkman, Ph.D.
Faye A. Gary, Ed.D., R.N.
Megan R. Gunnar, Ph.D.
Martha E. Hellander, J.D.
Renata J. Henry
Ned H. Kalin, M.D.
Jeffrey A. Lieberman, M.D.
James P. McNulty
Eric J. Nestler, M.D., Ph.D.
Charles F. Reynolds, III, M.D.
Peter Salovey, Ph.D.
Larry R. Squire, Ph.D.
Ming T. Tsuang, M.D., Ph.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 Members Present at Closed and/or Open Sessions

Elspeth Cameron Ritchie, M.D., Department of Defense

Others Present at Open Policy Session

Michelle Alonso, Anxiety Disorders Association of America
Lydia Bernik, Suicide Prevention & Advocacy Network USA
Jim Bernstein, American Society for Pharmacology & Experimental Therapeutics
Lizbet Boroughs, American Psychiatric Association
Jane Browning, Learning Disabilities of America
Perry Cohen, Parkinson's Disease Foundation
Sharon Cohen, Biotechnology Industry Organization
Christine deVries, American Association for Geriatric Psychiatry
Jill Egeth, Federation of Behavioral, Psychological and Cognitive Services
Cynthia Folcarelli, National Mental Health Association

Ranen Forzigen, J&J
Iconne Fuller, National Medical Association
Anoop Ghuman, American Academy of Pediatrics
Michael Greer, Academy for Educational Development
Laura Lee Hall, National Alliance for the Mentally Ill
Lee Herring, American Sociological Association
David Kaplan, American Counseling Association
Alan Kraut, American Psychological Society
Anand Kumar, American Association for Geriatric Psychiatry
Scott Jenkins, *The Blue Sheet*
Alan Leshner, American Association for the Advancement of Science
Sue Levi-Pearl, Tourette Syndrome Association
Sherry Marts, Society for Women's Health Research
Noel Mazade, National Association of State Mental Health Program Directors Institute, Inc.
Mary Ann McCabe, Society for Research in Child Development
William Northey, American Association for Marriage and Family Therapy
Millicent Plotkin, National Association of Anorexia Nervosa and Associated Disorders
Valerie Porr, Treatment and Research Advancements: National Association for Personality Disorder
Stephanie Reed, American Association for Geriatric Psychiatry
Darrell Regier, American Psychiatric Association Research Institute
Tina Renneisen, Bazelon Center for Mental Health Law
Dan Romer, Mental Health Media Partnership Annenberg Public Policy Center
Anita Rosen, Council on Social Work Education
Mercedes Rubio, American Sociological Association
Mary Ruffalo, Society for Social Work and Research
Paul Seifert, International Association of Psychosocial Rehabilitation Services
Angela Sharpe, Consortium of Social Science Associations
Deborah Shelton, International Society of Psychiatric-Mental Health Nurses
Lisa Shuger Hublitz, American Orthopsychiatric Association
Patricia Smith, MasiMax Resources, Inc.
Joel Streim, American Association for Geriatric Psychiatry
Karen Studwell, American Psychological Association
Marjorie Vanderbilt, American Association for Geriatric Psychiatry
Karen White, Children & Adults with Attention Deficit Disorder
Ronita Wisniewski, Autism Society of America/Autism Society of America Foundation
Joan Zlotnik, Institute for the Advancement of Social Work Research
Matt Zonarick, American Society for Cell Biology

OPEN POLICY SESSION: Call to Order/Opening Remarks

Thomas R. Insel, M.D., Director, NIMH, and Chairman, NAMHC, convened the open policy session of the 205th Council meeting at 8:40 a.m. on February 6, in Conference Room 10, Building 31C, on the campus of the National Institutes of Health (NIH) in Bethesda, Maryland. After welcoming those present, Dr. Insel asked the six newly appointed Council members to introduce themselves.

Dr. Sergio Aguilar-Gaxiola is Professor of Psychology at California State University in Fresno and specializes in cross-cultural psychiatric studies.

Dr. Faye Gary is the Medical Mutual of Ohio Professor of Nursing for the Care of Vulnerable and At-Risk Persons at Case Western Reserve University. She has a special interest in the care of children and adolescents and a research focus on violence, intimate relationships, and attention deficit hyperactivity disorder in children.

Ms. Martha Hellander is the Executive Director of the Child and Adolescent Bipolar Foundation, a parent-led, Web-based organization in Wilmette, Illinois. Ms. Hellander has a special interest in the early diagnosis and treatment of children with major psychiatric disorders.

Dr. Ned Kalin is Professor and Chairman of the Department of Psychiatry at the University of Wisconsin Medical School and has a research interest in the relationship of stress to the onset and maintenance of psychopathology.

Dr. Peter Salovey is Professor of Psychology and Epidemiology and Dean of the Graduate School of Arts and Sciences at Yale University and focuses on the study of human emotions and emotional competencies as well as health communication strategies.

Dr. Stephen Warren is Professor and Chairman of the Department of Human Genetics at Emory University School of Medicine and specializes in research on the genetics of cognitive deficits.

Approval of the Minutes for the Previous Council Meeting

Dr. Insel requested and received a motion to approve the minutes for the September 12, 2003, NAMHC meeting. The motion passed unanimously without further discussion.

NIMH DIRECTOR'S REPORT

For his Director's Report, Dr. Insel focused on three topics: NIMH activities in response to recent Council workgroup recommendations, priority setting at NIH, and exciting discoveries reflecting new directions in the science of mental health.

Update on NIMH Activities

Since the May 2003 Council session when Dr. Charles Reynolds, III, presented the final recommendations of the Council's Aging Research Workgroup contained in its report "Mental Health For A Lifetime: Research for the Mental Health Needs of Older Americans," several significant changes have occurred at NIMH.

To meet the need for a structure that would provide a focal point on aging issues and would be well positioned to coordinate NIMH's efforts across NIH and other Federal agencies, the Institute has formed an Aging Treatment and Preventive Interventions Research Branch under the direction of Dr. Barry Lebowitz. He also will assume responsibility for the Aging Consortium, which Dr. Bruce Cuthbert has ably led for the past several months. Dr. Lebowitz is a national figure in aging research and has a reputation for promoting the development of new investigators in the field of aging research, having initiated the popular summer workshops for geriatric psychiatry that have attracted many young researchers.

In response to Council's advice on maximizing the opportunities for international mental health research, NIMH has formed a new Office of Global Mental Health under the direction of Dr. Karen Babich. An internal review of NIMH collaborations with other countries and with NIH's Fogarty International Center revealed that 25 percent of the Institute's international grants pertain to human immunodeficiency virus (HIV) in mostly developing countries. The Office of Global Mental Health will administer non-HIV international programs and activities and seek opportunities to engage in global clinical and services research that aids in understanding shared and culturally unique attributes of mental disorders, providers, and delivery systems; to build the capacity of U.S. and foreign researchers to conduct global mental disorders related research; and to work with international organizations and institutes of mental health on shared goals and exchange of resources, ranging from neuroinformatics to studies of the burden of disease. Dr. Insel acknowledged the assistance of former Council member Dr. Javier Escobar in establishing this new office.

At the Intramural Research Program, the schizophrenia initiative that Dr. Daniel Weinberger announced at the last meeting is well underway. The new Genes, Cognition, and Psychosis Program is recruiting scientists in the cell biology arena to explore how variations in mutations and alleles of recently identified susceptibility genes for schizophrenia alter cellular functioning and then alter brain functioning at the systems level. Dr. Insel reported that the Director's Office is developing an electronic forum to inform investigators, patients, family members, and others about important new findings and to spur the pace of discovery in this arena. The forum will be similar in format to the Web site for Alzheimer's disease (http://www.alsforum.org/) and likely operated under an NIMH contract.

Update on the NIH Roadmap

The NIH Roadmap provides opportunities for NIH Institutes to work collaboratively to accelerate the pace of medical research in targeted areas. With a fiscal year (FY) 2004 budget of nearly $129 million, which will increase to $238 million by FY 2005, more than 15 Requests for Applications (RFAs) (see http://nihroadmap.nih.gov/grants/index.asp) have been issued. Each Institute has a designated liaison to the Roadmap, and Dr. Mayada Akil is the NIMH liaison. NIMH has representatives on eight of nine implementation groups and is the lead Institute on the Molecular Libraries initiative.

Conflict of Interest Issues

There has been recent concern expressed in the press about possible conflicts of interest involving senior scientists at NIH who are working with industry and other private organizations. While this perception has caused concern, an internal review of the charges has provided no evidence that any rules or regulations were violated or that any decisions or policies were affected by the these

investigators' relationships with private industry. Nonetheless, since questions were raised about whether the rules and policies pertaining to conflict of interest that were promulgated in 1995 are appropriate for 2004, Dr. Zerhouni is convening a blue ribbon panel to review this issue. Drs. Bruce Alberts and Norman Augustine will lead the panel, which is expected to make recommendations in the next few months. Although issues of transparency and integrity require urgent attention, Dr. Zerhouni and the Institute directors agree that public-private partnerships must continue as a crucial aspect of the NIH Roadmap activities.

The FY2004 and FY2005 Budgets

After 4 months of continuing resolutions, which held NIH funding to FY 2003 levels, the FY 2004 budget was approved on January 22 as part of the Omnibus Appropriations Bill. The NIMH FY 2004 appropriation of $1.38 billion represents an increase of 3.1 percent over the FY 2003 appropriation. The President's budget request for FY 2005, which was submitted to Congress on February 2, requests $1.42 billion for NIMH—a 2.8 percent increase over the FY 2004 level. If approved, this FY 2005 budget will allow a slowed but continuing increase in the number of grants that can be funded—projected at a 10 percent increase over the FY 2002 funding levels for non-competing continuation and new competing applications. Part of the anticipated increase will come from monies that become available when several large grants and contracts are completed.

While budget increases level off, the number of submitted applications continues to increase at a rapid pace: 2,238 applications were reviewed in FY 2002, compared to 2,497 applications in FY 2004 and to a projected 2,587 applications in FY 2005. This increase may be due to a perception in the field that the smaller budget increases seen in recent times results in fewer funding opportunities as paylines go down. In fact, the Institute's paylines were already dropping in FY 2001 and FY 2002, and as budget increases now hover around 3 percent per year, the payline, which has been around 20 percent, likely will drop even further. Other Institutes are experiencing payline reductions: the National Institute of Child Health and Human Development is facing a 13th percentile payline for this round of applications, and the National Institute on Drug Abuse and the National Institute of Neurological Disorders and Stroke are nearing the 19th to 20th percentile.

Autism Summit

As the NIH-designated lead agency for the Interagency Autism Coordinating Committee (IACC), NIMH played a critical role at the conference "Autism Summit Conference: Developing a National Agenda," which was held in November 2003, in Washington, DC (see http://www.nimh.nih.gov/events/prautismsummit.cfm). The summit, which was a joint effort of the Department of Health and Human Services and the Department of Education, addressed three major areas of emphasis: biomedical research, implementing early screening and diagnosis, and improving the accessibility and coordination of services. The involvement of members of Congress, public officials, scientific investigators, practitioners, and community members provided a forum for highlighting the Federal Government's interest in autism and for the mobilization of resources. Speakers included several members of Congress, the Secretary of Health and Human Services, and the Secretary of Education. A key focus of the meeting was the introduction of a 10-year national research agenda, developed by an IACC-appointed science panel. A review of the Autism Summit was published in the *Journal of the American Medical Association* 291:29-31, 2004.

Science Lists Mental Illness Genetics Among Ten Top Breakthroughs for 2003

Each December, *Science* magazine announces the ten biggest scientific breakthroughs for the year, and research on the genetics of mental illness was named the number two scientific "breakthrough of the year" in its December l9, 2003, issue. Most of the studies listed were conducted by either the Institute's intramural scientists or NIMH-funded investigators. The journal selected the mental health studies collectively as the first of nine runners-up, second only to newfound insights into the nature of the cosmos. It cited progress in identifying genes that increase one's risk of developing schizophrenia, depression and bipolar disorder, as well as advances in "unraveling" how the genes work in the brain to influence vulnerability.

Role of the 5-HT1A Receptor in Human Anxiety

An important scientific discovery relates to the role of the 5-HT1A receptor in anxiety. Initial studies by investigators at Columbia and members of the Pediatrics Department at Children's Hospital in Philadelphia demonstrated that a strain of "knockout" mice without 5-HT1A receptors show many hallmarks of anxiety. Also, mice with a conditional knockout—that can be controlled in time and space—display anxiety symptoms if the gene is removed from the forebrain but not in the brain stem. Moreover, mice whose 5-HT1A receptors are "knocked out" during critical early development exhibit a lifetime phenotype of anxiety. Recently, members of the NIMH intramural program extended these findings by using a new radioactive probe and positron emission tomography to identify the major sites of 5-HT1A receptors in living humans' brains. Most intriguingly, patients diagnosed with panic disorder—with or without depression—have about a 30 percent reduction of 5-HT1A receptors in the anterior and posterior cingulate areas of the forebrain and less significant reductions in the raphe and the brain stem (see Neumeister, A., Bain, E., Nugent, A.C., Carson, R. E., Bonne, O., Luckenbaugh, D.A., Eckelman, W., Herscovitch, P., Charney, D.S. and Drevets, W.C. "Reduced Serotonin Type 1_A Receptor Binding in Panic Disorder." *Journal of Neuroscience* 24**:**589-591, 2004). This is an example of how animal research has laid the way for human studies and may help explain how genes influence vulnerability to anxiety.

Changes in Brain Metabolism Among Persons Receiving Different Depression Treatments

A group of investigators led by Dr. Helen Mayberg have been investigating the question of how brain metabolism and activation of different regions of the brain change as patients with depression recover with the help of two treatments that have approximately equivalent and positive outcomes: an antidepressant medication and cognitive behavioral therapy (CBT). When the investigators used functional magnetic resonance imaging to examine increases and decreases in the brain activation of two groups of patients with depression who responded equally well to either paroxetine or CBT, they found markedly different brain changes between the two cohorts. Only certain parts of the frontal cortex showed a reduction in activity for both groups. The intriguing finding suggests that CBT may work through a particular pathway that differs noticeably from that of medications. Researchers are now mapping these different responses in an attempt to understand the whole neurobiology of the antidepressant response and to highlight the specific networks that respond to these two treatments with either increased or decreased activity.

Discussion

Dr. Tsuang asked about NIH's response to the recent report in the *Los Angeles Times* about conflict-of-interest allegations for some senior NIH investigators. While NIH is apparently investigating the charges and has found no evidence of rule breaking, the general public perception is important to consider. Dr. Insel referred Council members to a recent article in the *New England Journal of Medicine* about the history of this issue (see Steinbrook, M. "Financial Conflicts of Interest and the NIH." *New England Journal of Medicine* 350:327-330, 2004) and
Dr. Zerhouni's January testimony before the Appropriations Committee that is in the public record.

Ms. Hellander, on behalf of families affected by mental illnesses, commended NIMH for its work on the genetic components of mental illness. Recent findings, she said, offer great hope to future generations that will not have to suffer for many years from misdiagnoses and ineffective treatments.

UPDATE ON COUNCIL WORKGROUP ACTIVITIES

Workgroup on Setting Priorities for the Basic Sciences of Mental Health

Dr. Insel introduced Dr. Alan Leshner, former Director of the National Institute on Drug Abuse (NIDA) and Acting Director of NIMH, who currently is Chief Executive Officer of the American Association for the Advancement of Science and Executive Publisher of *Science* magazine, to report on the activities of the recently created Council Workgroup on Setting Priorities for the Basic Sciences of Mental Health (see http://www.nimh.nih.gov/council/bsworkshop.cfm).

Dr. Leshner began his presentation by noting that in the context of slowed budget growth at NIMH and less available funding for new and competing grants, the momentum achieved over the past 5 years by unparalleled advances in basic scientific discoveries of relevance to mental health will be impossible to maintain unless priorities are set that encourage innovative initiatives. Hence, this Workgroup's fundamental charge is to help NIMH set priorities in the domains of molecular, cellular, and genomic neuroscience, behavioral neuroscience, and basic behavioral and cognitive science. The Workgroup is large to include broad representation from the scientific community as well as the participation of several Council members. The Workgroup has been divided into two subgroups, with Dr. Eric Nestler chairing the basic molecular, cellular, and genomic research group and Dr. Richard Davidson heading the basic behavioral and behavioral neuroscience group.

The Workgroup is addressing three major issues: (1) how to build a basic science foundation that integrates the multiple levels of brain analyses with complex analyses of behavior and the environment to ensure integrative approaches of most relevance to mental and behavioral disorders; (2) how, in fulfilling NIMH's mission to reduce the burden of mental illness, to accelerate the translation of knowledge about basic sciences to clinical research and ultimately to improved pharmacologic and behavioral treatments and better systems of care; and (3) how to capitalize on the array of recent advances in the life sciences and achieve an optimal balance between "discovery-based research" that utilizes new technologies such as neuroimaging or microarrays, and traditional hypothesis-driven research.

The Workgroup has been reviewing NIMH's existing basic science portfolio to ascertain areas of potentially high-impact research that are not currently being investigated as well as imbalances in the portfolio and areas that may be over-represented or better suited to the mission of other NIH

Institutes. Three criteria are being applied during the portfolio review: (1) relevance to the NIMH mission; (2) potential traction or payoff from a significant investment; and (3) innovation. After the portfolio review, the Workgroup will recommend research areas with the highest priority for advancing basic research pertaining to mental disorders and suggest approaches to filling identified gaps. The Workgroup plans to present its recommendations at the May Council meeting.

Discussion

Several Workgroup members reported their perspectives on the tasks and challenges facing the Workgroup before the discussion was opened to other Council members.

Dr. Nestler reported that the basic molecular, cellular, and genomic subgroup is composed of eight scientists representing broad areas of cellular and molecular neuroscience, developmental neurobiology, and clinical science and that the group reviewed over 400 grants in the NIMH cellular and molecular neuroscience portfolio at its first meeting. Tentative consensus was rapidly achieved about areas of greatest relevance and promise for continuing research, and a few areas were identified where some de-emphasis could be afforded. Overall, the subgroup was struck by the awesome opportunities currently available in the NIMH basic cellular and molecular neuroscience portfolio.

Mr. McNulty commented that clearly basic neuroscience research has led to developments in the clinical arena that have improved the lives of many patients suffering from mental illness. However, he noted, it is important that the translation of findings and communications among clinicians and scientists in these areas be bi-directional so that, for example, the search for explanations that may arise from observed clinical phenomena would be directed to basic scientists, which may subsequently lead to new research. He commended Dr. Nestler's emphasis on the opportunities for new basic research that would be generated from the Workgroup's deliberations rather than questioning the relevance of the existing basic neuroscience portfolio.

Dr. Gunnar agreed that the Workgroup's primary motivation is setting priorities for soliciting and funding new and innovative grants. It would be helpful, she said, if the Workgroup provided guidelines for investigators about how to frame applications so they have relevance for NIMH.

Dr. Salovey noted that, as a member of the basic behavioral and behavioral neuroscience group that meets in March, he has been reviewing the portfolio and has seen excellent science. In his view, relevance, traction, and innovation are good criteria for thinking about impact. He anticipated quick agreement among subgroup members about traction and innovation, but more discussions about mission relevance and setting priorities may be required. While everyone agrees that NIMH's primary goal is to reduce the burden of mental illness, it is more difficult to balance the value of research with an immediate and obvious payoff against initiatives with a potentially greater, but more remote, impact. Just how a research project may translate into reducing the burden of mental illness may not be known at its start but may only be revealed over time. It will be necessary to balance both long and immediate views to maximize the chances that truly innovative research becomes part of the NIMH grant portfolio.

Dr. Leshner replied to a question from Dr. Lieberman about how the Workgroup would address the challenging issue of determining relevance to NIMH's mission that, although the Institutes he has directed support a broad array of basic science, the relevance question has not been adequately addressed. The Workgroup's report will recommend priority areas of research with the highest

relevance to NIMH's mission. For example, NIMH and the rest of NIH have invested little in developmental neurobiology; however, given what is known about the relationship between mental illness and the developing brain, this is an area of research that likely will be emphasized in the Workgroup's recommendations.

Dr. Ritchie, as the representative of the Department of Defense (DOD), asked what kind of basic research is envisaged to take advantage of the natural experiment that is occurring with the return of approximately 145,000 Iraqi War veterans after exposure to fighting that has caused great distress and, occasionally, mental illness. While the Department of Veterans Affairs (VA) and DOD are already engaged in this type of work, discussions are ongoing regarding how to ally more closely with the NIMH to stimulate basic research exploring the impact of combat and stress on the brain.

Dr. Leshner responded that in his view, a lot of research is already addressing the effects of stress per se. While it would be a shame not to capitalize on this natural experiment and undertake a set of clinical studies, legitimate questions pertain to which agency should assume responsibility for leading such an effort.

Dr. Tsuang added that the VA is already studying veterans of both the Vietnam and the Gulf Wars with a view to learn more about the prevention of post traumatic stress disorder (PTSD) and other illnesses. Data are being collected about the way in which the Gulf War impacted participants' physical and mental health. The VA might consider organizing a similar study, in conjunction with NIMH, of returning Iraqi War veterans.

Dr. Insel commented this is precisely the type of question the Workgroup was organized to address. However, the Institute also must consider how to partner with other agencies to maximize research efforts and resources to address shared research questions. For example, NIMH has supported approximately 60 grants in the area of developmental neurobiology, and NINDS has three to four times that number. These 60 developmental neurobiology grants cover all aspects of that area, with some areas more fully covered than others. Hence, the Workgroup may determine that the issues of most relevance to NIMH do not pertain, for example, to the earliest stages of differentiation or how the spinal cord is formed but should focus on the later regressive aspects of neural development that seem not to be working in autism or may have gone awry in schizophrenia. This type of review could suggest that NIMH and NINDS should parse the field of developmental neurobiology so that NIMH focuses on the sub-areas of most relevance to its mission, while NINDS focuses on research issues that are more relevant to its goals. Dr. Insel continued that he would soon be discussing priority setting with the NINDS Advisory Council and expected to stimulate discussion on developing referral guidelines that differentiate areas of particular interest to each Institute.

Dr. Essock expressed her enthusiasm for the emphasis on translating findings from clinical research into practice, reducing the burden of mental illness, and improving the service delivery systems where patients with mental illness receive care. She reminded the audience that this will require more focus on aspects of the portfolio that pertain to administrators, Medicaid directors, and other practitioners who are implementing systems of mental health care.

Clinical Trials Workgroup

Dr. Jeffrey Lieberman, Professor and Vice Chair of the Department of Psychiatry at the University of North Carolina at Chapel Hill, updated Council about ongoing activities of the Clinical Trials

Workgroup. The Workgroup has been engaged in a similar endeavor to that described by Dr. Leshner and colleagues but reviewing the portfolio of the Division of Intervention and Services Research (DISR). Although the Workgroup was initially formed to review the clinical trials grant portfolio in DSIR, the Workgroup's charge was broadened to include consideration of contracts and cooperative agreements, with respect to how well the funded clinical treatment studies map to the country's public mental health priorities and treatment needs.

The Workgroup has been working to identify critical knowledge gaps as well as scientific opportunities that may not have been fully incorporated in the portfolio and to recommend ways to address any deficiencies. The Workgroup has been assessing the progress achieved by the funded trials and will recommend potential strategies to enhance performance and achieve greater efficiencies in their execution.

The preliminary impressions of the Workgroup are that DSIR's research portfolio is scientifically of good quality and reflects a reasonable balance and proportional diversity in covering an appropriate range of mental disorders, age-relevant populations, and currently indicated pharmacological and psychosocial treatment modalities for mental disorders and behavioral disturbances. However, the portfolio lacks breadth and depth across some of the major disorders and may be deficient in other areas pertaining to public mental health care. Finally, the Workgroup discovered that some funded studies are experiencing difficulties in achieving their subject enrollment goals and delivering the results that they were designed to accomplish. The Workgroup is considering a set of procedures or infrastructures for supporting the implementation of funded treatment studies.

The Workgroup observed that services and intervention research are inherently different from other NIMH-funded initiatives with respect to the scale and cost of projects. NIMH must be proactive in setting a public mental health research agenda and in ensuring that it is carried out. The NIMH is engaged in large-scale treatment development activities under the direction of Drs. Ellen Stover and Wayne Fenton and must determine how best to balance these activities with the clinical trials program.

The Workgroup's final report will summarize the strengths and limitations of the current portfolio and will enumerate goals and targets for better aligning the portfolio with NIMH's mission. The report also will describe the difficulties inherent in organizing studies of sufficient size and complexity to address major public mental health issues. Finally, the report will outline an ideal portfolio of treatment studies for NIMH to oversee as the Nation's steward for research efforts in the treatment and prevention of mental illness and the delivery of services. The Workgroup's recommendations can provide an action blueprint for funding crucial treatment and services research.

Discussion

Dr. Essock commended the Workgroup's efforts to identify areas where NIMH might assume a leadership role in pushing the field to produce research results with a more immediate impact on mental health care practices.

Ms. Henry remarked that she has been working to expand the role of the 50 State Mental Health Authorities through the National Association of State Mental Health Program Directors to tie the treatment systems they oversee into this priority-setting process. The Directors have questions about the best treatment practices for various populations and the associated costs for their implementation,

especially given the current environment of limited funding. She commended NIMH's focus on the relevancy of research to practice settings. The Workgroup's final report will offer guidance, she said, to public health administrators in formulating questions that require the answers to be delivered through research.

Dr. Gary asked if the Workgroup members had considered the Nation's public health goals for 2010—to address and resolve mental health care disparities and alleviate the poor quality of life endured by certain subgroups in the United States—as they outline the blueprint for future treatment research priorities. Dr. Lieberman replied that the Workgroup was mindful of the need for representative patient samples in the various studies to ensure that results are generalizable as well as informative about the most effective treatments for different populations. Disparities in service delivery, he said, is an important issue that is beyond the purview of the Clinical Trials Workgroup but clearly one that must be addressed.

Dr. Nakamura commented that NIMH, in trying to ensure that the clinical trials are generalizable to real-world settings, has recognized that research participants recruited by traditional academic health centers tend to fit a limited demographic population. Hence, subject recruitment efforts have been expanded to include community mental health centers and other clinics that treat a diverse group of patients representing a full range of ethnicities as well as economic conditions, insurance types or payment options, culture, and comorbidities. The NIMH Office of Communications is engaged in efforts to destigmatize participation in clinical trials among some minority groups.

Mr. McNulty reinforced the importance of strengthening the partnership between NIMH and public mental health systems since mental illness accounts for a large percentage of public expenditures for disability by the Center for Medicare and Medicaid Services and the Social Security Administration.

Ms. Hellander asked whether NIMH invests in the development of Internet-based screening tools for parents as a potential service delivery method since many parents now turn to the Internet as an information resource. At Dr. Insel's request, Dr. David Chambers reported that NIMH is trying to forge a link, for example, between telemedicine and autism through the Mind Institute at the University of California, Davis. Additionally, many recent grant applications include Internet-based components, and NIMH sponsored a workshop on the efficacy and safety of Internet-based interventions (see http://www.nimh.nih.gov/research/interventionsJuly03.cfm). Although the ideas are promising, much work remains to adequately develop this area. Ms. Hellander added that the studies she is familiar with show that patients and families may like Internet-based interventions but that often providers do not support them. Dr. Insel replied that Ms. Hellander's question is a good example of an innovative opportunity that needs investigation.

Dr. Wagner underscored the compelling need for the Clinical Trials Workgroup to consider effective treatments for childhood mental disorders and to ascertain whether the NIMH portfolio adequately addresses current and future needs in this area.

Dr. Salovey asked if the Workgroup would be considering both the biological and the psychological mechanisms that help explain patient outcomes. While it is important to learn what treatments work, it also is crucial to understand the factors that contribute to the success or failure of treatment—information that may guide the future development of innovative therapies.

Dr. Lieberman replied that for practical purposes, the Workgroup's review was directed at examining the representativeness of treatment modalities used for various conditions and did not include such issues as mechanism of action and the range of outcomes that might be evaluated.

To a question from Dr. Nestler about whether the Workgroup is considering the utility of the large contracted clinical trials, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (see http://www.nimh.nih.gov/studies/catieschiz.cfm) and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (see http://www.nimh.nih.gov/studies/3mooddisordersseq.cfm), Dr. Lieberman answered that the Workgroup is evaluating the contracts as part of the portfolio. These large mechanisms provide strong incentives, he said, for successful completion of the contracted work in a timely manner.

Dr. Aguilar-Gaxiola expressed his enthusiasm for efforts to link science to specific services for populations that often do not participate in clinical trials. More emphasis needs to be given, he said, to translating findings derived from population-based studies into practical interventions.
Dr. Lieberman responded that a logical and necessary corollary to the Workgroup's charge is to evaluate research addressing treatment quality and the configuration of service delivery systems.

Dr. Insel noted that NIMH is participating with the Substance Abuse and Mental Health Service Administration in a science-to-service initiative that deals specifically with the dissemination of evidence-based discoveries. That initiative will be described at a future Council meeting. As readers of the *New York Times* and other sources recognize, the public must be provided with objective and unbiased research-based information about the prescription of selective serotonin reuptake inhibitors or SSRIs for adolescents and the advantages and disadvantages of atypical versus conventional antipsychotics. The results from some of the large clinical trials, including the Treatment for Adolescents with Depression Study (TADS) (see http://www.nimh.nih.gov/studies/tads.cfm) and the CATIE study, will inform these questions.

THE NEUROBIOLOGY OF ATTENTION AND EXECUTIVE CONTROL

Dr. Robert Desimone, Scientific Director of the NIMH Division of Intramural Research Programs, spoke about the aspect of attention and executive control that allows someone to concentrate on a particular task while blocking out intervening distractors. Psychologists divide this cognitive task into several subcomponents: sustained attention to the task goal, inhibition of competing internal and external distractors, resolution of conflicts between responses, and maintenance of the task goal and working memory.

Impairments in attention vigilance, executive functioning, and working memory are the most severe and enduring cognitive impairments found in patients with schizophrenia. Increasingly, researchers are realizing that these cognitive impairments are found in a wide variety of psychiatric disorders, including attention deficit disorder, various behavioral disorders, borderline personality disorder, major unipolar depression, and bipolar disorder—especially among adolescents with this diagnosis and in the manic phase of adults with bipolar disorder.

Neuropsychologists recently have been studying the neural circuitry underlying these types of cognitive disabilities. Dr. Michael Posner and colleagues found that different neuropsychological tasks (e.g., a flanker task) activated large areas of the prefrontal cortex as well as parts of the parietal lobe (see Fan J., Flombaum J.I., McCandliss B.D., Thomas K.M., and Posner M.I. "Cognitive and

Brain Consequences of Conflict." *Neuroimage* 18:42-57, 2003). Even a very simple task such as having subjects maintain attention to the blank part of a screen while waiting for a stimulus shows widespread prefrontal and parietal cortex activation. In fact, a meta-analysis of findings from numerous studies of neuropsychological tasks in different laboratories concluded that the same circuitry is involved in all similar top-down tasks—the parietal-prefrontal network seems to provide top-down biasing signals to circuitry and the extrastriate cortex, at least for visual processing (see Kastner, S., Pinsk, M.A., De Weerd, P., Desimone, R., and Ungerleider, L.G. "Increased Activity in Human Visual Cortex during Directed Attention in the Absence of Visual Stimulation." *Neuron* 22:751-761, 1999). The output from competition among these different aspects of the extrastriate cortex is forwarded from memory and affective and motor systems.

To depict this process, Dr. Desimone showed slides with lateral views of monkey brains. The extrastriate network representing stimuli appears as a circuit that begins in the primary visual cortex and continues down through the temporal lobe. In this circuit, the visual scene is broken into receptive fields—little regions in space that are analyzed by neurons that increase in size as they move along the pathway. The neurons with small receptive fields converge on neurons with large receptive fields. Both physiological and brain imaging studies have shown that distracting information is filtered out at every stage of this pathway until, by the time an endpoint is reached, only the representation of a behaviorally relevant object remains.

Researchers now are attempting to determine how behaviorally relevant stimuli gain preference along this pathway and how distractors are filtered out. Until recently, much work has focused primarily in the amount of neural activity in this pathway, which escalated or diminished with attention. Recently, work has examined what role modulation of processing played in cognition, particularly the role of temporal synchrony—or the timing at which cells communicate information. Temporal synchrony evokes the concept of temporal binding proposed by Dr. Wolf Singer and colleagues at the IRP where information is bound together in the brain by synchronizing the activity of neurons that code different components. For example, a person who sees a red car synchronizes the activity of red coating cells with car coating cells to get the unified percept. While this theory of temporal binding is not yet established, neuroscientists are accumulating a wealth of evidence that temporal synchrony plays a very broad role in neural processing.

More specifically, studies of the hippocampus in which cells outputs were measured as a function of the timing of inputs found that cells only fire if the inputs arrive within a few milliseconds of each other—in a very narrow temporal summation window. Studies by Drs. Bi and Poo (see Bi, G. and Poo, M. "Synaptic Modifications in Cultured Hippocampal Neurons: Dependence on Spike Timing, Synaptic Strength, and Postsynaptic Cell Type." *Journal of Neuroscience* 18: 10464-10472, 1998) further demonstrate that plasticity in neural circuits only occurs when there is high temporal precision between inputs to the cell and outputs from the cell.

Studies of the hippocampus also have shown that individual neurons can synchronize their activity with respect to global network oscillations. The very low frequency network oscillation in the hippocampus known as a feta wave is stimulated by cholinergic inputs. Research by Dr. Gyorgy Buzsaki and others demonstrated that individual cells in the hippocampus in different population groups synchronize their activity to different phases of the global network oscillations (see Csicsvari, J., Jamieson, B., Wise, K.D., and Buzsáki, G. "Mechanisms of Gamma Oscillations in the Hippocampus of the Behaving Rat." *Neuron* 37:311-322, 2003). An even greater range of temporal processing occurs in the cortex. Drs. Gray and McCormick and colleagues have discovered that

cortical cells have a wide variety of timing characteristics that seem to be associated with morphologically distinct types of neurons (see Nowak, L.G., Azouz, R., Sanchez-Vives, MV., Gray, C.M., and McCormick, D.A. "Electrophysiological Classes of Cat Primary Visual Cortical Neurons In Vivo as Revealed by Quantitative Analyses." *Journal of Neurophysiology* 89:1541-1566, 2003).

The concept that timing plays an important role in all aspects of neural processing has led to a theory that behaviorally relevant stimuli gain an effective advantage in the processing pathways because the cells that carry behaviorally relevant information synchronize their activity to increase momentum at each stage along the pathway. Studies of the neural activity of monkeys corroborated the hypothesis that timing frequency gives effective stimuli an advantage since the gamma range showed spikes within about a 25-millisecond time window—the optimum spot for increasing gain on the postsynaptic cells.

Investigators are now discovering where synchronized activity with attention is initiated and have found temporal synchrony in the cortex along the whole neuroanatomy, reaching back as far as areas V1 and V2. In V4, attention increases high-frequency synchronization in the gamma band although the deep layers show very little high-frequency synchronization. In the low-frequency band, more synchronous activity actually occurs when the animals ignore the stimulus within the receptive field. When the neuroanatomy of cells in the different layers was considered, the deep layer cells were found to project to many visual motor structures, including the spirit colliculus, thalamus, and the striatum, at later stages of the pathway.

Researchers also have found that low-frequency synchronization is associated with the time at which laboratory monkeys inhibit a behavioral response to an inappropriate stimulus. At the particular moment when an animal suppresses a response to a distracter stimulus, a large increase in low frequency synchronization of the cells occurs (see Donoghue, J.P., Sames, J.N., Hatsopoulos, N.G., and Gaal, G. "Neuroal Discharge and Local Field Potential Oscillations in Primate Motor Cortex." *Journal of Neurophysiology* 79:159-173, 1998).

Investigators are now examining whether the top-down signals from the parietal/prefrontal attentional network are responsible for inducing the synchronous activity. In earlier work, Dr. Richard Nakamura and colleagues studied the local field potential of synchronous activity across different brain areas when monkeys were performing a complex task involving visual stimuli and motor responses. Although these early studies were not examining the relationship between spikes and local field potentials, they did show synchronous activity during the motor phase of the task between the visual and motor cortex. By contrast, there was synchronous activity between the prefrontal and visual cortex during perceptual stages of the task. An unresolved question is whether these findings are relevant to the executive control deficits in psychiatric disorders since clinical studies have largely ignored high-frequency activity. A recent study that provided some positive evidence (i.e. Spencer, K.M., Nestor, P.G., Niznikiewicz, M.A., Salisbury, D.F., Shenton, M.E., and McCarley R.W. **"**Abnormal Neural Synchrony in Schizophrenia." *Journal of Neuroscience* 13:7407-7411, 2003) used scalp-recorded electroencephalogram to examine the synchronization of neural circuits in schizophrenia. The normal control subjects, but not those with diagnosed schizophrenia, displayed gamma frequency synchronization across cortical areas when they perceived the illusory square. Studies using such techniques as magnetoencephalography combined with functional magnetic resonance imaging may be able to localize the time signals to different areas in the human brain.

In sum, the simple task of attending to something while ignoring distractors seems to involve virtually the whole brain in attention and executive control functions. Widespread interactions between several cortical areas across the cortex are apparent, without even examining subcortical structures, which are almost certainly involved as well. It is not just gross activity that is coordinated across these areas. Rather, attention and executive control are more analogous to a symphony orchestra where all the instruments must be precisely coordinated to the same timing to convey the intended message.

Discussion

Dr. Nestler, praising Dr. Desimone's research, asked whether the model could be used to understand how subcortical motivational circuits affect an animal's attention to behaviorally relevant stimuli. Dr. Desimone replied that Dr. Wolfram Schultz, in examining the influence of reward and motivation in monkeys' dopaminergic circuits, found that the dopamine cells were projecting into the cortex and probably modulating activity. However, much of the explanation may have been missed by looking for gross changes in the cortex's firing rate with dopaminergic modulation. Actually, the changes are probably very subtle, requiring a closer examination of whether dopamine is affecting timing, especially since almost all psychoactive drugs affect neural timing.

Dr. Tsuang, reflecting on the intriguing concept of orchestrating cells in relation to behavior, asked if the same concept might be applied to gene expression interacting with the environment. Since limiting research to one gene is not going to solve the puzzle of schizophrenia or affective disorder, a more concerted effort may be required to integrate the concepts of genes, timing, and behavioral manifestations. The presentation provided tantalizing insights into future genetic studies of behavior that use these concepts of orchestration and timing. In response, Dr. Desimone recalled that early brain imaging and neurophysiological studies focused on the neuron by asking how separate genes acted. He agreed that scientists are now thinking more about coordination and how genes interact with each other and the environment to impact behavior. Dr. Nakamura added that the search for disease endophenotypes has hindered an understanding of thinking and defects of thinking. This research points directly to the possibility of developing techniques and devices that identify defects in these circuits and see what spatial and temporal resolutions are needed.

Ms. Hellander asked how early neurocircuitry patterns in the brain can be detected and if there is some window of opportunity for correcting any deficits. Many parents of children who are later diagnosed with bipolar disorder recall that they seemed to “hit the wall” during third grade when materials they were expected to learn becomes more complex. Dr. Desimone replied that this issue can be examined in two ways. Neuropsychological testing of young children can predict later problems. At the neural end, however, the developmental work of researchers such as Dr. Carla Schatz, show that the timing of an activity determines, to a large extent, how the brain gets wired up.

Dr. Kalin recalled that this concept was not initially recognized as relevant, although the fruits are now obviously important for mental illness. He remarked that a thoughtful approach to these issues in relation to priority setting is going to be very important from a translational perspective.

Dr. Insel added that this line of questioning underscores the opportunity to move investigations in other directions by examining the development of this process. How does temporal synchrony happen? What consequences and implications of temporal synchrony are not yet understood? Only a

few researchers are studying primate neurophysiology and development, although the research that originated in Dr. Charles Gross's laboratory has tremendous implications for understanding the process of visual development. The time is ripe for studies of developmental neurobiology, developmental neurophysiology, and developmental behavior to come together.

Dr. Gunnar asked about the effects of high arousal, quick acting, and constant stimulation on children with respect to differentiating what they should and should not attend to. A salient question, she said, is whether these experiences are impacting the process of timing when stimuli have smaller discrepancies. In other words, are children getting much less experience in focusing their attention on less-intense variations, and is that doing something to their capacity to couple timing when the stimulus is not as large as a video game? These are important issues that may have significant implications for children suffering from mental illness.

ALCOHOLISM AND CO-OCCURRING MENTAL DISORDERS

Dr. T.K. Li, Director of the National Institute of Alcohol Abuse and Alcoholism (NIAAA), reviewed some interesting aspects of alcohol use patterns and disorders, as well as NIAAA's current mission and activities, before elucidating similarities in the developmental trajectories of alcoholism and mental illnesses.

- The cost of alcohol-related problems in the United States is an estimated $185 billion annually. Nearly 14 million Americans suffer from alcohol abuse or dependence and 100,000 die annually. One in four children under the age of 18 is exposed to alcohol problems in the family—a recognized predictor of similar problems in the child's future. Between 20 and 40 percent of hospital admissions are alcohol related, depending on the type of hospital studied.

- While half the U.S. population drinks little or nothing, 10 percent of Americans consume 60 percent of the alcohol sold. The drinking patterns that cause problems can be summarized as drinking too much too fast or too much too often.

- Alcohol abuse is a pattern of high-risk drinking that results in a variety of adverse personal, interpersonal, and social problems. High-risk drinking for males entails repeated consumption of four or more drinks on any day or more than 14 drinks a week. For women, the risk begins at a slightly lower consumption level: more than seven drinks a week or more than three drinks on any day. In the personal arena, drinking-related problems include injuries and death, impact on memory and cognition, loss of employment, family and friends, and increased risk for health problems and organ damage. The interpersonal problems caused by high-risk drinking include homicide, sexual assault, and other types of crime and violence. Increased health care costs, lost productivity, and highway injuries and deaths are among the social problems associated with alcohol abuse.

- Alcohol dependence or alcoholism is a common, complex disease that is characterized by a persistent and progressive pattern of abnormally intense alcohol-seeking behavior that, over time, leads to impaired control over drinking, preoccupation with drinking, and the development of tolerance and dependence.

- The drinking pattern an individual adopts over time is influenced by familial and non-familial environmental factors, personality-temperament differences, and the pharmacological properties

of alcohol itself. Twin studies demonstrate that drinking initiation is strongly influenced by the environment, especially peers. The genetic personality-temperament dimension begins to interact more with environmental influences as drinking continues, as do the pharmacological effects of alcohol. The development of tolerance is important for drinking large amounts of alcohol and becoming dependent.

- Both humans' and animals' reactions to alcohol have significant genetic components and reflect large between-individual variations that are due to alcohol's pharmacokinetic and pharmacodynamic effects. There may be a three- to fourfold variation from person to person in the absorption, distribution, and metabolism (pharmacokinetics) of alcohol that is, in humans, mostly consumed orally. As much as a twofold variation also can exist within one person, depending on what he/she has eaten or taken as medications. Large, two- to threefold variations in subjective and objective responses to alcohol have been found in experimental conditions when alcohol is administered at a prescribed level.

- NIAAA's mission is to increase an understanding of normal and abnormal biological functions and behavior related to alcohol use; improve the diagnosis, prevention and treatment of alcohol-related problems and alcoholism; and enhance access to quality care.

- NIAAA's multi- and transdisciplinary research portfolio includes studies of genetics, neuroscience, pharmacokinetics and metabolism, as well as treatment and recovery, prevention, and epidemiology. Translational research includes animal models with good predictive validity that are useful for studying mechanisms as well as medications development. The Institute's current research priorities include the neurobiology of adolescent drinking, rural underage drinking, alcohol metabolism and markers, medications development, and co-occurring behavioral disorders.

Dr. Li then focused on one of NIAAA's highest priorities—adolescent drinking and its impact on the onset of alcohol use disorders and presented the following information.

- Data from a 2001 World Health Organization (WHO) study involving young persons between the ages of 15 and 44 years of age in the United States, Canada, and Western Europe, "Burden of Disease Statistics," show alcohol use disorders (14%) ranked second only to unipolar depressive disorders (18%) as causing the highest disease burden for this age group.

- Recent data (2003) from Wave 1 of NIAAA's National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which includes data on 43,000 subjects, reflect the very high odds of a DSM-IV-diagnosed alcohol-dependent individual having a co-occurring disorder during a 12-month period. More specifically, an alcohol-dependent person is 3 times as likely to also have generalized anxiety disorder, 3.7 times as likely to also have major depression, 5.7 times as likely to also have mania, 36.9 times as likely to also have drug dependence, and 7.1 times as likely to have antisocial personality disorder.

Dr. Li then presented information on the early onset of alcohol use and mental disorders, which serves as the underpinning of NIAAA's initiative on adolescent drinking. This information included:

- An illustration adapted from the January 20, 2003 issue of *Time* (page 82) showing the age of onset or developmental trajectory of various brain disorders. Autism and attention deficit

hyperactivity disorder are usually manifested within the first 5 years of life; anxiety, childhood depression, conduct disorder, and antisocial behavior become apparent between 5 and 10 years of age; symptoms of eating disorders and obsessive compulsive disorders are first noticeable between 10 and 13 years of age; and social phobias, panic disorder, and bipolar disorder usually become evident between 13 and 20 years of age. Symptoms of alcohol and drug use disorders also manifest in the later stages of this developmental trajectory.

- Data from a NIAAA epidemiological study (Grant, B.F. and Dawson, D.A. "Age of Onset of Drug Use and Its Association with DSM-IV Drug Abuse and Dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey." *Journal of Substance Abuse* 10:163-173, 1998) that demonstrate that the earlier a person begins to drink, the more likely he/she is to develop alcoholism in later life. Youngsters who begin drinking at age 13 have a 4 times greater risk for becoming alcohol dependent at a later age; those with a family history of alcoholism are even more likely to become alcoholic. Both age of drinking onset and genetic load are important predictors for lifetime development of alcohol dependence.

- Data from the 2003 National Epidemiological Survey on Alcohol and Related Conditions (NESARC), which examine hazard rates or the likelihood for an initial DSM-IV diagnosis of alcohol dependence, show a sharp spike at age 18 (1.7%), with decreasing percentages at age 21 (1.3%) and 25 years (0.7%). After age 25, onsets of alcohol dependence diminishes dramatically. The NESARC also shows the trajectory for developing major depression, with onsets of this diagnosis also beginning between ages 15 and 18 years (0.6-0.7%), but higher peaks at ages 25, 30, and 35 (0.8%) and additional spikes at age 40 and 45 before diagnoses taper rapidly. A similar graph depicting onset age for panic disorder shows smaller spikes around age 25 (0.3%), a series of similar peaks at ages 30, 35, 40, with onsets peaking around age 50 years (0.35%).

- Data from the 7 year Collaborative Study on the Genetics of Alcoholism (COGA), which incorporates genetic analyses of alcoholic probands with information from other family members, including children, depict similarities between alcohol dependence and major depressive disorder. The cumulative incidence rate for developing alcohol dependence as an asymptote is nearly 60 percent by age 25 years. The alcohol dependent controls have a similar trajectory, although the incidence is much lower. The trajectories for developing drug dependence plateau a little earlier (around age 20) than for alcoholism in both probands and controls but follow a very similar path. The cumulative incidence rate for developing major depressive disorder increases more gradually through age 29 in probands (55%) and controls (37%). These disease developmental trajectories offer professionals some guidance for treatment and prevention efforts.

Dr. Li followed the discussion on developmental trajectories with research on genetic influences in alcohol dependence. Research has focused on two genes that seem to predispose drinkers toward or protect against high-risk consumption patterns. Repeated association studies in different populations have produced similar and robust findings with regard to the role of alcohol dehydrogenase (ALDH2) and aldehyde dehydrogenase (ADH2) in alcohol metabolism. These gene polymorphisms are found almost entirely in Asian, Polynesian, and Jewish populations. The genes for protective effects cross ethnic groups. One of the chromosomes that maps to alcohol dependence is in the cluster of alcohol dehydrogenase.

- The COGA studies and other research also have found genes for endophenotypes and/or disorders that co-occur with alcoholism. The research associating COMT and the serotonin transporter

val158met with alcohol dependence, heroin addiction, schizophrenia, cognitive dysfunction, lower frontal P300 amplitude, and diminished response to pain and stress has been widely publicized. The COGA study also found that alcohol dependence maps to the GABA receptor alpha 2 site on chromosome 4 (GABRA2) and to the beta frequency of the EEG. This is important for understanding disinhibition and its impact in the frontal cortex.

- Another gene of particular interest is the cholinergic muscarinic receptor (CHRM2) on chromosome 7 that has been found in the families from COGA. An article describing significant linkage and linkage disequilibrium for the frontal theta event-related oscillations that underlie P3 at this site is in press (Jones, Porjesz, Almasy, et al. *International Journal of Psychophysiology*). The research indicates that this gene may contribute to the development of major depressive disorders in the COGA families. A study lead by Dr. Laura Bierut, at the Washington University COGA Group, has also found significant linkage and linkage disequilibrium for CHRM2 with alcohol dependence.

In sum, longitudinal studies of cohorts at high risk for alcohol dependence, as well as for drug abuse and co-occurring mental disorders, are very useful for tracing gene involvement if large numbers of subjects are initially phenotyped and assessed with recently developed SNIP technology. The understanding of alcoholism and co-occurring mental disorders is enhanced by studying the longitudinal developmental trajectories of preadolescents, adolescents, and young adults. Newly available tools that assist this effort include electrophysiology for endophenotyping, neuroimaging, and mechanisms that allow animals to self-administer alcohol, not only orally but also intravenously and intracranially, into specific brain regions. The effects of alcohol also can be studied with the tools of genomics and proteomics as well as metaboleomics. Alcohol is an interesting probe to study brain functioning and how this relates to basic and clinical neuroscience.

Discussion

Dr. Tsuang remarked that Dr. Li's presentation on co-occurring disorders reflects areas of common interest to NIAAA and NIMH, especially at the behavioral level among adolescents who are at risk for depression, schizophrenia, and substance abuse, which can lead to higher suicide rates, violence, traffic accidents, assaults and other negative behaviors with significant public health implications.

In agreeing with this assessment, Dr. Li recalled a perspective on genetics expressed by Walter Willet in an article in *Science* a few years ago. Since most of the common complex disorders can be treated by environmental manipulations, many of the Institutes within NIH, and not just NIAAA, NIMH, and NIDA, have a responsibility to collaborate where their interests intersect. This includes the Institutes concerned with obesity, child health, and cancer.

CONCEPT CLEARANCES

Dr. Insel explained that the following five concepts were being introduced to Council for members' comments and approval prior to issuing Requests for Applications, should monies be available to support them (see http://www.nimh.nih.gov/council/conceptindex.cfm for information on approved concepts).

Cooperative Drug Development Group

Dr. Wayne Fenton, Deputy Director for Clinical Affairs, DMDBA, described a Cooperative Drug Development Group (CDDG) concept that would encourage academic investigators who have identified what they believe is an effective compound to partner with private sector industrial or biotechnology collaborators in conducting proof-of-concept studies for promising novel-mechanism drug candidates and IND-ready medications to treat severe mental illnesses. The proposed work would facilitate studies to determine whether a drug candidate is sufficiently safe and tolerable to warrant further commercial development and to ascertain the medication's optimal dosage as well as its pharmacokinetics, pharmacodynamics, and preliminary clinical efficacy.

The CDDG would bridge the gap between the National Drug Discovery Groups for the Treatment of Mood Disorders and Nicotine Addiction supported in the Division of Neuroscience and Basic Behavioral Science (DNBBS), which focus on identifying potential medications in preclinical models, and the clinical effectiveness trials that are supported in the Division of Services and Intervention Research (DSIR). A variety of cooperative agreements, contracts, and R01s are envisaged, with DNBBS responsible for studies that focus on pharmacokinetics, pharmacodynamics, dose finding, *in vivo* receptor occupancy, and biomarkers or imaging endpoints, and DMDBA supervising studies that focus on preliminary clinical endpoints.

Discussion

In response to Dr. Nestler's question about plans for proof-of-concept studies, Dr. Fenton explained that the CDDG is not meant to support preclinical proof-of-concept studies that are already the responsibility of DNBBS but to fund first-time-in-human studies that use either biomarkers, psychophysiology, or clinical endpoints.

Children Affected by HIV/AIDS in International Settings

Dr. Andrew Forsyth, Program Director for Primary HIV Prevention and Behavior Change in the Center for Mental Health Research on AIDS, DMDBA, presented the concept pertaining to children affected by HIV/AIDS in international settings. The proposed initiative would support research to enhance the provision of psychosocial support to children affected by HIV/AIDS in international settings. At present, approximately 13 million children age 16 or younger have lost one or both parents to HIV/AIDS. The number of children in sub-Saharan Africa who are orphaned by parental AIDS deaths is expected to reach 25 million by 2010 (UNAIDS, *Children on the Brink*, 2002).

These children suffer psychological distress, even before a parent succumbs to HIV disease. This stress may manifest as symptoms of depression, anxiety, PTSD, or aggressive behavior. After parents die, many of these children quit school to work and support their siblings. Without parental protection, they become vulnerable to exploitation, sexual abuse, and violence, which ultimately may increase HIV risk behaviors. AIDS-related parental illness and premature death also brings to families and communities severe economic hardship, stigma, and discrimination.

Guidance in developing this concept was sought from the NIH Office of AIDS Research (OAR), which sets priorities for and supports AIDS-related research pertaining to adults and children in resource-poor settings. The concept also dovetails with the President's Emergency Plan for AIDS Relief (PEPFAR), a $15 billion initiative that funds medical treatment, care, and support, but not

research. The NIMH effort could fill an important gap by supporting basic and applied prevention research to develop, implement, and evaluate a variety of interventions that draw on findings from NIMH's portfolio of HIV-related domestic studies.

The proposed initiative aims to stimulate the development of culturally appropriate, effective, and sustainable psychosocial supports for children facing the loss of parents to HIV disease. The research priorities may include development and evaluation of such interventions as peer supports or school retention efforts that minimize psychological distress. Interventions for children may also be incorporated into parental HIV treatment services, particularly as medications become available. Planning custody arrangements may be increasingly important to prevent orphaned children from living on the street, participating in risky behavior, and becoming HIV infected.

A priority-setting meeting scheduled for April 2004 will convene experts from relevant content areas, including child bereavement, HIV prevention, science, and community-based interventions. Feedback from those discussions is expected to inform an RFA to be issued in fiscal year 2005. Solicitation of collaborative research applications is expected to begin in the fall of 2005.

Discussion

Dr. Folkman commended this desperately needed initiative, which aims to reduce the terrible impact of HIV/AIDS on sub-Saharan Africa. It also exemplifies translational research.

To a question from Dr. Ritchie about whether representatives from sub-Saharan Africa will be invited to offer their advice regarding the appropriateness of the mental health interventions, Dr. Forsyth elaborated that not only will experts who are implementing similar programs in sub-Saharan Africa attend the planning meeting but NIMH is also developing a satellite conference for the International AIDS Conference that will bring together representatives from Eastern and Southern African, Asia, South America, and Central America to help ensure that planned interventions are culturally appropriate, effective, and sustainable for the context in which they will be applied.

To Dr. Salovey's query about coordination on this initiative between NIMH and such worldwide service organizations that already serve children as UNAIDS and UNICEF, Dr. Forsyth replied that the satellite meeting being considered for the International AIDS Conference has already involved collaborations with USAID, UNICEF, and UNAIDS.

State Implementation of Evidence-Based Practices II

Dr. David Chambers, Chief of the Dissemination and Implementation Research Program for the Services Research and Clinical Epidemiology Branch, DSIR, described plans for a second phase of the initiative "Bridging Science and Service: State Implementation of Evidence-Based Practices." The proposed effort will provide States with funding for research planning grants related to the implementation of evidence-based practices (EBPs) and for introducing carefully targeted and appropriate EBPs into local mental health care settings.

The new concept builds on a current effort that is jointly sponsored by NIMH and the Center for Mental Health Services (CMHS), a part of the Substance Abuse and Mental Health Services Administration. This first phase, which evolved from State Mental Health Commissioners' concern about the relevance of federally sponsored research to State systems, offered 1 year planning grants

to enable State agencies to develop their own research agendas and identify factors that facilitate or impede statewide implementation of EBPs. Nine States are current recipients of Phase I planning grants to build consensus among their stakeholders, conduct pilot studies of proposed EBPs, survey providers, consumers, and policymakers, and develop partnerships with researchers before moving to State-led research activities. Since the grants have only been funded for 4 months, it is too early to predict the success of this initiative. However, it has already increased the number of NIMH discussions with States about applying for other funding mechanisms. Some consensus conferences have been held; pilot work is underway in several States, and applications for new research are being submitted.

Phase II of this State initiative has two goals: (1) to develop a new cohort of States that will undertake similar planning activities for EBPs as those in Phase I and (2) to advance States' science-to-service capabilities through State-led implementation trials to test a carefully selected EBP that meets an identified State need in small sites and that will ultimately become part of a statewide implementation effort. The research activities for Phase II may include exploratory/developmental research (R34s) on the dissemination and implementation of an EBP, evaluation of training models for disseminating information on EBPs, and similar activities that evaluate changes in State mental health systems. The kickoff for Phase II, as for Phase I, will be a technical assistance workshop in the near future to introduce interested participants to NIMH procedures and to offer whatever may be needed in preparing applications. It is anticipated that the Phase II initiative will continue NIMH's partnership with CMHS.

Discussion

To a question from Ms. Hellander about potential problems in getting consent to conduct research in foster care populations if a State wants to focus on suitable EBPs for children and adolescents, Dr. Chambers replied that this issue would apply to any NIMH-supported research conducted in foster care sites. Since each State decides the focus for proposed research, a State that wanted to emphasize foster care could request technical assistance from NIMH staff regarding such concerns.

Mr. McNulty noted that, since some State Mental Health Authorities have not established exemplary collaborations with academics who could undertake this type of activity, NIMH might need to find ways to encourage academics to cooperate on such an initiative. Dr. Insel noted that NIMH is considering ways to improve triangular collaborations involving the Institute, academia, and the States.

Gene/Environment Interaction and Epigenesis in Depression

Dr. Steven Moldin, Director of the Office of Human Genetics and Genomic Resources and Associate Director, DNBBS, presented a concept pertaining to the effects of epigenetics and gene-environment interactions on depression. After noting that the search for genes affecting depression risk has produced inconsistent results, he explained that this lack of progress may be due to complexities at the molecular genetic level and to the interaction of genes with other environmental factors. Hence, the two-fold focus of the proposed initiative is on epigenetic mechanisms and a variety of environmental risk factors that may interact with these epigenetic abnormalities to produce vulnerability to depression.

Epigenetics are heritable aberrant mechanisms that are not dependent on alterations in DNA sequence per se, but have important biological and clinical impact and are operative in other CNS disorders (e.g., Fragile X, Prader-Willi, and Angelman syndromes) where they affect the transcription of genes involved in the regulation of neural development and differentiation. To date, the search for genes affecting risk for depression has not looked at the potential impact of these alternative molecular mechanisms.

Another complexity not fully considered in previous genetic studies of depression is gene-environment interactions where genes plus environmental exposure to a particular risk factor produce disease susceptibility. Modulation of the pathway from gene to disease by environmental influences is found in other complex disorders such as diabetes. Data from recent research confirms this possibility with regard to depression susceptibility—notably in the paper by NIMH grantees, Drs. Terrie Moffitt and Avshalom Caspi, that was cited by *Science* magazine as a breakthrough discovery for 2003 and outlines the relationship between the serotonin transporter (5-HTT), life stress in early adulthood, and depression risk.

The proposed RFA for this initiative, which is planned for publication this spring, would support several small R01s that would focus on pedigree ascertainment, gene discovery, elucidation of underlying genetic molecular mechanisms, measuring exposure to environmental risk factors, high-throughput genotyping, statistical modeling, and the whole genome or candidate genes. The estimated deadline for receipt of applications is June 2004, with a peer review in October and Council review in January 2005.

The component of the initiative that concentrates on finding alternative epigenetic mechanisms is a high-risk undertaking that will hopefully advance the field of genetic research on depression and ultimately have a significant impact on public health. Elucidating the genetic architecture that is involved in depression, as well as the contribution of environmental factors to disease susceptibility, would open the way for developing better targeted interventions to modify environmental risk and tailoring new therapeutic compounds to an individual's genetic profile.

Discussion

Dr. Warren, after remarking that the proposed study of epigenetic effects as a direct consequence of environmental variance is a good one and likely applicable to other forms of mental illness in which environmental factors might trigger the genome through epigenesis, asked whether pedigree ascertainment in the human genetic component would replace preliminary animal studies. Dr. Moldin replied that the major reason for limiting the focus to depression is the availability of funding. However, animal studies are certainly included as part of the implementation plans. Pedigree ascertainment was included to encourage investigators to include data collection efforts that focus on alternative genetic mechanisms.

Dr. Insel added that the proposed initiative is also meant to stimulate better methods for examining epigenetic changes by developing, for example, high throughput approaches that might involve the National Human Genome Research Institute (NHGRI) as well as other collaborations.

Dr. Folkman asked for clarification of the proposed timelines, noting that issuing an RFA in March or April with a deadline of June for applications seemed unrealistic. Dr. Moldin replied that the timeline

for publishing the RFA will be met, but conceded that an extension of the deadline for submitting applications may be needed to ensure innovative research approaches.

Dr. Tsuang asked if it is realistic to target the very broad spectrum of depressive disorders—from early onset depression with a large genetic component to depression that reflects more environmental impacts—rather than concentrating on one aspect. More specifically, what are the plans for diagnostic assessment of the probands? Dr. Moldin responded that past efforts that begin with the phenotype to resolve genetic or etiologic heterogeneity have not been successful in studying depression. This initiative will try to resolve heterogeneity by beginning with the genetic mechanisms and identifying different subgroups of patients whose depression stems from particular mechanisms or interactions with the environment. Hopefully, the phenotypic characteristics will evolve from initial identification of underlying genetic alterations.

mRNA Profiling of Major Psychoses

Dr. Douglas Meinecke, Chief of the Molecular and Cellular Program in the Clinical Neuroscience Research Branch, DNBBS, described a concept for accelerating the analysis of mRNA profiling of major psychoses by exploiting postmortem human brain tissue with microarray chip technology. While identification of the genetic contribution to major mental disorders is a fundamental element of research, the limited focus on perturbed or polymorphed genes in a population with a different haplotype does not explain the proximal cause of the disease until the gene function is ascertained. The research strategy promoted by the proposed initiative is to interrogate what genes are being turned on, down, up, or off in major mental disorders. Seed money hopefully will encourage investigators to conduct more postmortem studies, using gene array technology to answer the aforementioned questions as well as ascertaining whether genes are being altered from normal in either cells, circuits, groups of circuits, or a whole brain region.

Although this research strategy is widely used in many laboratories, an examination of the NIMH portfolio found that fewer than five DNBBS-funded investigators are currently using gene array technology for mRNA profiling studies of human postmortem brain samples and comprehensive mapping of disease-specific brain gene expression phenotypes. Since schizophrenia is relatively well covered already, the RFA primarily targets depression, bipolar disorder, and other major mental disorders.

Discussion

Dr. Tsuang remarked that postmortem viewing of the human brain is a sound and relatively inexpensive first step for this type of profiling. However, since postmortem tissue may not elucidate all gene expression, another approach will be needed in the future.

Approval of the Five Concepts

Following these presentations, Dr. Insel asked Council for en bloc approval of the five concepts. Accordingly, a motion was made, seconded, and unanimously accepted without further discussion.

UPDATE ON NIMH ACTIVITIES

The NIH Roadmap for Research

Dr. Mayada Akil, Senior Advisor to the NIMH Director in the Office of Science Policy and Program Planning and newly designated liaison to the NIH Roadmap activities, reported on its progress and activities. The Roadmap, she recalled, is a series of progressive and ambitious initiatives that are intended to transform and facilitate rapid progress in biomedical research. The NIH-wide initiatives target identified opportunities, gaps, and issues in biomedical research that no single Institute could accomplish alone.

This Roadmap process began in August 2002 when over 100 scientists convened to discuss current scientific challenges, roadblocks to progress and how these can be overcome, and appropriate projects for cross-Institute involvement. Based on identified areas of interest, 15 working groups were formed in March 2003 to develop a series of initiatives for presentation to the NIH leadership. Twenty-eight initiatives have now been selected and integrated into a well-coordinated implementation plan.

The NIH Roadmap has three themes: (1) new paths to discovery; (2) research teams of the future; and (3) re-engineering the clinical research enterprise. Nine groups have been established to implement these themes. The groups comprising the first theme include building blocks, pathways, and networks for metaboleomics, proteomics, etc.; molecular libraries and imaging; structural biology, including membrane protein production; bioinformatics and computational biology; and nanomedicine. The research teams of the future theme has three implementation groups: high-risk research; interdisciplinary research; and public/private partnerships. The re-engineering the clinical research enterprise theme has one implementation group, clinical research, which focuses on such activities as training clinical researchers, coordinating networks of clinical research, and creating translational cores.

The Roadmap activities have been organized into a formal structure for purposes of coordination. NIH Director, Dr. Elias Zerhouni; Deputy Director, Dr. Raynard Kington; and all Institute and Center Directors have overall authority. Dr. Dushanka Kleinman was recently named Assistant Director for NIH Roadmap coordination. Her office will coordinate the implementation of initiatives with the assistance of a committee composed of the nine implementation group chairs and six representatives from the director's office. All proposed science will be reviewed by the implementation groups. A senior advisor for clinical research under the re-engineering activities will be designated. Each Institute has named a Roadmap liaison to communicate with its staff, the research community, and the public about Roadmap activities.

Funding for this effort will be provided by all the Institutes and Centers that are committed to pooling some of their resources for this joint effort. The FY 2004 budget of $128 million came largely from the Director's discretionary fund and transfer authority as well as contributions of 0.34 percent from each Institute's current budget. The funding will increase to nearly $263 million next year with contributions of 0.63 percent of each Institute's budget. Cumulatively, funding for the Roadmap is expected to reach more than $2 billion by FY 2009.

NIMH is deeply involved in Roadmap activities, with representatives on eight of the nine implementation groups. NIMH contacts have been designated for various Roadmap RFAs and other

announcements. NIMH also heads the implementation committee for the Molecular Libraries and Imaging implementation group. Current information about initiative announcements and other Roadmap activities can be found on the Web site at http://nihroadmap.nih.gov/.

NIH Molecular Libraries and Imaging Probes Roadmap

Dr. Linda Brady, Chief, Molecular, Cellular, and Genomic Neuroscience Research Branch, DNBBS, described the Molecular Libraries and Imaging Probes Roadmap activity, which is headed by Dr. Insel, NIMH Director, Dr. Francis Collins, Director, NHGRI, and Dr. Roderic Pettigrew, Director, National Institute of Biomedical Imaging and Bioengineering. This initiative's overall goal is to speed the discovery of new molecular tools, drugs, ligands, imaging probes, and other scientific breakthroughs. The anticipated outcomes include: (1) development of new research tools—both molecular probes and novel assays—that facilitate studies of biological processes and the pathophysiology of disorders addressed by the NIH; (2) advances in biological research leading to the identification and validation of novel biological targets for therapeutics development by academic, private, and biotech sectors; and (3) discovery of novel biological markers that facilitate the monitoring of disease progression and the prediction of treatment response. More information can be found at http://nihroadmap.nih.gov/molecularlibraries/index.asp.

The molecular libraries initiative has three components: (1) a public sector repository for small molecules or compounds with a network of screening centers to test assays and the molecules within the assays; (2) a cheminformatics database, PubChem, that lists the 3-D chemical structures of the small molecules in the library, data obtained from screening compounds in biological assays, and assay protocols; and (3) associated technology development activities targeted at enhancing the chemical diversity of small molecules in the repository, facilitating the development of novel assays by the research community, stimulating robotics and miniaturization approaches that assist the implementation of more high-throughput assays, and fostering predictive bioavailability and toxicology assays that help develop more biologically active probes.

A Request for Proposals has been issued (see http://grants2.nih.gov/grants/guide/notice-files/NOT-RM-04-003.html), with an anticipated spring 2004 award date, to establish a publicly available central repository for 100,000 to 500,000 chemically diverse small molecules, which will consist of compounds that have been assembled, arrayed, and screened for potential new activities and applications at one of six proposed centers. The first of this consortium of screening centers will be an intramural effort at the NHGRI that is expected to be operational in 2004. A Request for Information was issued last November to establish a series of pilot screening centers in the extramural environment, initially for a 3-year period, but evolving into five larger extramural centers (see http://grants1.nih.gov/grants/guide/notice-files/NOT-RM-04-001.html). The centers will receive assays from the scientific community based on a peer review process. Promising hits will be prioritized across the Institutes, using some limited chemistry to optimize them for such end uses as *in vitro* probes or *in vivo* probes in animal models. The screening data will be deposited in a public database (i.e., PubChem) and made available to investigators in academic and private sectors. A separate coordinating center to oversee activities of the central repository and the screening centers will be established in 2005.

The comprehensive public sector database, PubChem, which already is being developed by the National Center for Biotechnology Information (NCBI) for release in the fall of 2004, will be a

3-D chemical structure database that is fully linked to other NCBI Entrez databases for genes, proteins, and Medline resources. PubChem also will coordinate data deposition from individual screening centers and enter these into its master database. At a future point, NIH expects to fund some data mining opportunities and cheminformatic tools to explore this database.

The plans for technology development, known as chemical diversity expansion, include further expansion of the small molecule repository at the library through an RFA to be issued in 2005 as well as a series of workshops scheduled for this summer on extracting small molecules from natural products and ways to build biologically relevant chemical diversity. Another RFA has been issued to stimulate the development of innovative, biochemical, cell-based, and phenotypic-based assays with high therapeutic potential (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-04-012.html). RFAs for robotics/instrumentation scheduled for release in 2005 will focus on developing new, robust, and reproducible screening methods that allow automation of assays to a higher throughput level. A workshop is planned in 2004 to encourage academic and private sector involvement in developing predictive absorption, distribution, metabolism and elimination (ADME)/toxicology assays through an RFA to be issued in 2005.

Another aspect of the Roadmap, Molecular Imaging, is directed at developing probes for imaging molecules in biological systems that range from individual cellular events through living organisms. This initiative also has three components: development of high-resolution probes for cellular imaging; development of an imaging probe database that is analogous to PubChem and can link imaging structures and bioactivities; and development of a core synthesis facility that will initially be established in the intramural research program and ultimately make the probes available to extramural investigators.

Discussion

In response to Mr. McNulty's question about whether NIMH and the other Institutes are assured of an adequate payoff for their monetary contributions to the Roadmap initiatives, Dr. Insel noted that this issue has generated many suggestions for informing NIMH-allied investigators about available funding opportunities. A short article that will appear in the *Society for Neuroscience Bulletin* aims to educate the neuroscience community and encourage applications. Dr. Akil added that NIMH, as part of this information effort, has added links to the NIH Roadmap to its Web site.

Dr. Salovey reflected that the Institute's 0.34 percent contribution to Roadmap funding is not trivial when annual budget increases for NIMH are currently expected to be 2 to 3 percent. Even though the Roadmap will stimulate exciting science with potentially broad applications to mental health and illness, it will be important to maximize its potential for exploring issues related to mental health.

Dr. Insel, recalling that the Roadmap was initially conceptualized as addressing the worthy goal of overcoming barriers to trans-Institute collaborations, replied that Roadmap activities entail fiscal, staff and Council staff commitments. Council will be considering grant applications for the molecular libraries component, even though only a few will be directly related to NIMH.

Treatment Development

Dr. Ellen Stover, Director, Division of Mental Disorders, Behavioral Research, and AIDS (DMDBA), explained that the update would focus on an important January meeting regarding government-industry collaboration that was chaired by Drs. Insel, Edward Scolnick and Herbert Pardes and intended to define NIMH's role in accelerating the development of new treatments for mental illness. In addition to NIMH staff, meeting participants included other researchers, 14 directors of research on the central nervous system from large pharmaceutical and biotech companies, and representatives from the advocacy community.

Dr. Wayne Fenton, Deputy Director for Clinical Affairs, DMDBA, continued the report by explaining that the drug development process is a large and expensive undertaking and that the goal of the initiative is to: (1) speed the development of new medications for mental illness by identifying a unique role for NIMH that does not duplicate activities that other entities may be more qualified to perform; (2) determine whether large clinical trial networks can be utilized within a public-private partnership; and (3) determine the major barriers to government-academic-industry collaboration and how they might be overcome.

Dr. Fenton reported that industry's efforts to produce profitable medications typically have been based on familiar mechanisms of action or slight refinements rather than on innovative targets or proteins as demonstrated by the large number of new molecular entities registered with the FDA from 1993 to 2001 (see Zambrowicz, B.P. and Sands, A.T. "Knockouts Model the 100 Best-Selling Drugs--Will They Model the Next 100?" *Nature Reviews Drug Discovery*, 2:38-51. 2003). As a result, over the past 15 years only a few new medications for mental illness have come to market, and clearly a ceiling has been reached with respect to the therapeutic effects that can be expected from current targets.

Several themes emerged from the January meeting described by Dr. Stover: (1) NIMH must support basic research to elucidate the pathophysiology of mental illness. NIMH should concentrate its efforts in the proposed molecular libraries on developing new ligands, radiotracers, and small molecules for preclinical research that will help articulate new targets and new mechanisms of disease. (2) Pharmaceutical companies already have a well-developed competency to move a compound that has been identified as interacting with a receptor to a lead compound and then to a drug. (3) NIMH should continue clarifying disease phenotypes for genetic studies and defining clinical targets for treatment development as other organizations are unlikely to assume responsibility for this work. Dr. Fenton said that current medications target symptom complexes rather than DSM diagnoses and the MATRICS process might be used as a paradigm for defining non-DSM clinical endpoints and refining measurement of psychopathology as dependent variables for clinical trials. He said that it is critical that the large clinical trials networks focus on important public health questions and that grafting longitudinal studies, studies of biomarkers, and pharmacogenetic studies onto large pragmatic trials may be a useful strategy for government/industry partnership. He also commented on the need for a sustained forum for communications between NIMH and the pharmaceutical industry to facilitate future collaboration.

Dr. Fenton concluded that NIMH must take the lead in partnering with the academic community and with industry to ensure that the resources and strengths of each contribute more rapidly to developing new treatments that target the symptoms of mental illness.

Discussion

Mr. McNulty reinforced the support of the advocacy community for NIMH's treatment development work.

Dr. Tsuang asked if the pharmaceutical industry might provide some funding to hasten the development of medications that will ultimately lead to company profits. Dr. Insel replied that the major shared interests at the January meeting were in the identification of biomarkers or new indications for treatment and having NIH convene groups involving academics, industry, FDA, and other scientists to look at potential new needs and ways to optimize treatments.

Intergenerational Research

Dr. Susan Swedo, NIMH Associate Director for Child and Adolescent Research, reported on an October 2003 Workshop on Intergenerational Research that was co-sponsored by NIMH and the National Institute on Drug Abuse and prompted by a review of the NIMH portfolio on child research, which revealed that about $5 million a year is being spent on intergenerational studies.

The workshop focused on the small subgroup of longitudinal research known as intergenerational studies that examine the transmission of psychopathology from parents to children by comparing the longitudinal course of a pathological group with a control group. These studies take either a top-down approach, comparing affected parent probands with healthy parents at baseline and determining what happens to the children, or a bottom-up approach that starts with affected child probands and then examines their parents and parent-child interactions. Some of the studies involve grandparents, parents, and children. Interim and long-term comparisons are made for a variety of psychosocial risk and protective factors as well as outcome measures of psychopathology. Transmission of psychopathology is defined as finding a disorder in the child that is equivalent to that in the parent(s). The presence of symptoms in a child is assumed to be influenced by risk factors, whereas protective factors are assumed to be associated with the absence of symptoms in a child.

The Intergenerational Research Workshop had three goals: (1) to determine the unique value of intergenerational studies in reducing the burden of mental illness; (2) to explore strategies for linking these studies with newly developed biological and genetic research methodologies; and (3) to determine best methods for translating research results into meaningful intervention and prevention strategies.

The first day of the workshop was spent in reviewing the current NIMH portfolio in this field and categorizing the studies into three types: (1) systematic and comprehensive descriptions of symptom domains and the contextual environment in which they occur; (2) in-depth examinations of parent-child interactions and their influence on the development of psychopathology; and (3) documentation of risk and resilience factors that appear to be associated with transmission of the disorder as well as the moderators and mediators of psychopathology.

Specific examples of currently supported NIMH research in this area include:

- Transmission of childhood and adolescent antisocial behavior across three generations—a study initiated in the 1960s with a group of children who are now parents of adolescents and young adults. The study has collected extensive information about family interactions.
- Contextual factors affecting antisocial behavior, delinquency, and substance abuse.
- Effects of parental depression on offspring.
- Developmental trajectory of externalizing versus internalizing symptoms.
- Influence of childhood adversity on adult mental health.
- Impact of parenting and grandparenting on psychopathology.

The second day of the workshop focused on crucial issues pertaining to the future of these studies. While intergenerational research has contributed to the mental health knowledge base over the years, many unanswered issues pertain to whether this type of research is asking appropriate questions, utilizing the best methodologies, incorporating adequate data for addressing critical transmission questions, and optimizing the cost-benefit ratio. The review found that these psychosocial studies primarily collected information about behavior and did not examine the role of genetic factors in familial transmission of psychopathology.

Four goals were developed for new intergenerational research: (1) to test in a third generation the hypotheses that were generated by studies of first and second generations; (2) to determine mechanisms of disease transmission, especially gene-environment interactions; (3) to identify disease predictors, including biological markers and prodromal symptoms; and (4) to develop and test prevention and intervention strategies, especially for such areas as the impact of maternal depression on children where adverse outcomes are well known, and increase the emphasis to engaging mothers in treatment and reducing the consequences of parental illness on children. Participants agreed that future intergenerational research must address three unresolved questions: (1) Why is one child spared who presumably should have been affected? (2) Why is another child affected who might have been spared? (3) How can other children who should be affected be spared?

In conclusion, Dr. Swedo paraphrased the comments of workshop participant Dr. Jane Costello, who noted:

> Longitudinal studies, to be worth continued support, must address new questions as well as the ones they were designed to answer. Investigators in this arena may need to recruit new colleagues with new skills who can take advantage of the wealth of data already collected. NIH may need to foster such collaborations to ensure that valuable data resources remain useful.

Discussion

Dr. Tsuang remarked that an important research opportunity was missed when, for example, blood samples were not collected at the beginning of an intergenerational study involving more than 15,000 children who were born 50 years ago and have now become mothers and grandmothers. To capitalize on available data sets, it would be fruitful, when possible, to get blood samples and add a biological component.

Ms. Hellander commented on the importance of looking at the third generation in transmission of psychopathology since many families report that a disorder skipped a generation. She added that Dr. Barbara Geller, an NIMH-funded researcher, found that prepubertal children with depression eventually convert to mania if they have a parent or grandparent with bipolar disorder.

Dr. Gunnar was concerned that many investigators who conduct intergenerational research may not be biologically oriented and that incentives such as contracts with related intramural work at NIMH may be required to encourage collaborations that take advantage of the excellent cross-generational data already collected. Dr. Swedo agreed and elaborated that the meeting participants were urged to go back to their home institutions and look for opportunities to expand the breadth of their investigations. In particular, studies would benefit from the inclusion of genetics and biological assays as additional means of predicting risk.

Dr. Insel complimented Dr. Swedo for taking on this challenge, and Ms. Henry added that this type of research will be helpful in making decisions about prevention and treatment interventions across systems, especially when State Mental Health Agencies try to collaborate with child welfare agencies and departments of education to treat more than the mental health needs of a family. Dr. Swedo responded that the development of prevention and intervention strategies is an important component of intergenerational research.

PUBLIC COMMENTS

Dr. Joel Streim, President of the American Association for Geriatric Psychiatry (AAGP), applauded NIMH for establishing the new aging branch and suggested three ways to ensure that it has the intended impact: (1) expand the Branch's scope beyond services and interventions to include translational research; (2) staff it appropriately with persons who have special expertise in mental health and aging; and (3) implement the recommendations of the Council's Aging Research Workgroup to intensify recruiting and training efforts for new investigators who undertake careers in this field.

Dr. Anand Kumar, President-elect of AAGP, also pledged the organization's commitment to helping NIMH recruit and train new geriatric psychiatrists and specifically asked that more first-level K awards be made since support for investigators entering the field of aging and mental health over the past 10 years has not grown at the rate cited for other specialties.

Ms. Sue Levi-Pearl, Director of Research and Medical Programs for the Tourette's Syndrome Association, reported that members of this group frequently experience the common medical practice of prescribing an array of medications on a trial and error basis and mostly for off-label uses; however, the group had been only minimally successful in encouraging investigators to evaluate drugs' efficacy for treating special disorders. Because the numbers of affected patients are often small and profits from medication development would be minimal, the pharmaceutical industry targets its resources to areas where there are greater numbers of patients. Since the government is the only major source of research support in Tourette's illness, Ms. Levi-Pearl offered to provide the Council's Clinical Trials Workgroup more specifics about this issue.

Dr. Perry Cohen from the Parkinson's Disease Foundation remarked that his group shares a concern with NIMH about the lengthy evaluation and approval process a newly discovered treatment must undergo before it is available to patients. To assist with this effort, the Parkinson's Pipeline Project

was established to recruit subjects for clinical trials, help retain and protect human subjects, advise pharmaceutical companies on the design and endpoints for their studies, and provide patient advisors to FDA's Neuropharmacological Division. Since it behooves industry to speed new drugs to the marketplace, he noted, some industry consortia concerned with Alzheimer's and arthritis are apparently funding research to identify more precise measures.

Ms. Valerie Porr, President of Treatment and Research Advancements, National Association for Personality Disorder (NAPD), endorsed NIMH-supported research on mental illnesses that begin during adolescence since more than a quarter of the phone calls to NAPD's national helpline come from adolescents and children as young as 9 to 13 years of age. She expressed her concern about the emphasis that NIMH is placing on medication development rather than research on behavioral therapies. In her opinion, more attention needs to be given to educating families about how to help their children, particularly since psychoeducation is one of the five evidence-based practices that NASMHPD recognizes and that Medicaid will fund. In response, Dr. Insel clarified that the NIMH's treatment development activities are focusing on pharmacological, psychosocial, behavioral, and cognitive interventions and that the Institute's portfolio contains a number of studies in these areas.

Dr. Joan Levy Zlotnik, Executive Director of the Institute for the Advancement of Social Work Research, thanked Dr. Insel for participating in the January meeting of 1,200 social work researchers in New Orleans, commended the NIMH for addressing sub-Saharan African children's desperate needs for psychosocial services related to HIV/AIDS, and highlighted the importance of meeting the needs of persons with severe mental disorders outside the public mental health system in nursing homes and the child welfare system. Severely depressed mothers, for example, may often be identified through the child welfare system. Additionally, plans to strengthen collaborations among service systems, academia, and NIMH should not overlook the fact that social workers are major mental health providers and that an increasing number of schools of social work are involved in mental health research.

Dr. Sherry Marts from the Society for Women's Health Research commented, with respect to the concept for a cooperative drug development group, that it is feasible, safe, and ethical to include women in early phases of clinical trials. She continued that it is becoming increasingly evident that the search for gender-related differences should begin in the early phases of research, especially with respect to determining safe and effective dosages as well as a drug's pharmacokinetic and pharmacodynamic properties.

Dr. Darrel Regier, Director of Research at the American Psychiatric Association and Director of the American Psychiatric Institute for Research and Education, applauded NIMH's priority setting and review efforts and its major contributions to treating mental illness. The breakthroughs in understanding mental illness recognized by *Science* magazine provide a good opportunity for the APA's academic consortium, in conjunction with the advocacy and research communities, to make a case before Congress for increasing appropriations to NIMH this year. The APA also is initiating a cooperative agreement with NIMH, NIDA, and NIAAA to examine the mental health field's readiness to identify biological markers for specific disorders. Since no one is satisfied with the diagnostic knowledge reflected in the current DSM, the APA is undertaking a systematic, broad-based review of the scientific basis for DSM revisions in conjunction with the World Health Organization's World Psychiatric Association and a large number of other multi-disciplinary experts.

Ms. Laura Lee Hall, Director of Research at the National Alliance for the Mentally Ill (NAMI), requested NIMH's scientific leadership on determining the efficacy, side effects, and risk benefits of prescribing typical or atypical SSRIs for depressed or suicidal children whose parents are desperate for reliable information. While clinical trials are urgently needed to test differences in these drugs, NAMI does not believe that industry should fund such research if the findings are to be perceived as credible. Ms. Hall also commended the science-to-service grants for States, stressing that they often provide the only funding a State receives for initiating an evidence-based practice (EBP). In the aging arena, she hoped NIMH would spearhead efforts to improve the identification and treatment of depression in primary care settings and provide resources to service providers and policymakers for operationalizing EBPs. In these tight fiscal times, NAMI expects to join with other advocacy organizations in supporting increased funding for NIMH.

ADJOURNMENT

After reminding members that Council would reconvene on May 13-14, 2004, Dr. Insel adjourned the 205th meeting of the NAMHC at 1:00 p.m. on February 6, 2004.

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