Department of Health and Human Services

PUBLIC HEALTH SERVICE

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE OF MENTAL HEALTH

National Advisory Mental Health Council

Minutes of the 207th Meeting

September 20-21, 2004

Minutes of the 207th Meeting of the National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 207th meeting in closed session for the purpose of reviewing grant applications at 10:30 a.m. on September 20, 2004, in Conference Room C/D/E of the Neuroscience Center, Rockville, Maryland, and adjourned at approximately 3:30 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened in open session at the same location from 4:00 p.m. until 5:20 p.m., and continued the open session on the following day, September 21, 2004, in Wilson Hall, Building I, National Institutes of Health, Bethesda, Maryland, from 8:30 a.m. until adjournment at 12:30 p.m. In accordance with Public Law 92-463, the open policy meeting was open to the public. Thomas R. Insel, M.D., Director, National Institute of Mental Health (NIMH), chaired the policy meeting.

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

Sergio A. 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 Open Sessions

Elspeth Cameron Ritchie, M.D., Department of Defense
Robert Freedman, M.D., Department of Veterans Affairs

Liaison Representative

A. Kathryn Power, M.Ed., Director, Center for Mental Health Services, SAMHSA

Others Present at Open Policy Session

Merry Bullock, American Psychological Association
Christine deVries, American Association for Geriatric Psychiatry
Mary Ann Dulton, Georgetown University
Saiza Elayda, Society for Neuroscience
Cynthia Folcarelli, National Mental Health Association
E. Aracelis Francis, Council on Social Work Education
Sarah Gaia, Lewis-Burke Associates LLC
Stephen Heinig, Association of American Medical Colleges
Jamileh Jemison, Center for Scientific Review
Alan Kraut, American Psychological Society
Janice Krupnick, Georgetown University
Anand Kumar, American Association for Geriatric Psychiatry
Anne Mathews-Younes, Center for Mental Health Services/SAMHSA
Mary Ann McCabe, Society for Research in Child Development
Anne Michaels, National Foundation for Mental Health
Pam Moore, *LRP Publications*
Bob Nichols, Association for the Advancement of Psychology
Bill Northey, American Association for Marriage and Family Therapy
Delores Parron, Office of the Director, NIH
Tim Perrin, American Association for Geriatric Psychiatry
Chris Petr, University of Kansas School of Social Welfare
Darrel Regier, American Psychiatric Association Research Institute
Mercedes Rubio, American Sociological Association
Angela Sharpe, Consortium of Social Science Associations
Viviana Simon, Society for Women's Health Research
Paul Sirovatka, American Psychiatric Association
Mickey Smith, National Association of Social Workers
Susan Solomon, Office of Behavioral and Social Sciences Research, NIH
Lynne Marie Stout, Alliance for Aging Research
Karen Studwell, American Psychological Association
Shiang-Jong Tzeng, National Institute of Allergy and Infectious Diseases
Karen White, Children and Adults with Attention Deficit Disorder
Barbara Wanchisen, Federation of Behavioral, Psychological, and Cognitive Sciences
R. Yanes, Clinical Social Work Federation
Jeffrey Young, *The Blue Sheet*
Nancy Moy Yuen, SRI International
Joan Levy Zlotnik, Institute for the Advancement of Social Work Research

OPEN POLICY SESSION: Call to Order

Thomas R. Insel, M.D., Director, NIMH, and Chairman, NAMHC, convened the open policy session of the 207th Council meeting at 4:00 p.m. on September 20, 2004, in Conference Room C/D/E of the Neuroscience Center in Rockville, Maryland, by noting that the time for discussion of agenda items was being expanded beyond the usual half-day session to cover such Council business as concept clearances and feedback about priority setting and other grant review issues.

CONCEPT CLEARANCES

Dr. Insel announced that Council-approved concepts are posted on the NIMH Web site (see http://www.nimh.nih.gov/council/conceptindex.cfm) following the Council meetings in order to alert potential applicants to prospective research activities. However, the issuance of new initiatives is dependant on the availability of sufficient funds to support them.

Comorbidities in Persons Living with HIV/AIDS: Behavioral and Clinical Research

Dr. David Stoff, Chief of the HIV/AIDS Neuropsychiatry Program in the Center for Mental Health Research on AIDS (CMHRA), Division of Mental Disorders, Behavioral Research and AIDS (DMDBA), presented a concept on non-HIV-related comorbidities in HIV-infected persons–a priority in the strategic plan of the Office of AIDS Research (OAR).

The concept stems from important trends in the HIV/AIDS epidemic over the last decade when clinical care for HIV has improved dramatically. Advances in pharmacotherapy that stabilize the deteriorating immune system have allowed HIV infection to evolve from a progressive, ultimately fatal disease to a chronic condition that often can be managed over a long period of time. Concomitant with these changes in the course of HIV are alterations in the comorbidities affecting patients. While such associated illnesses such as Kaposi's sarcoma and pneumocytstis carinii pneumonia have been decreasing, new ones have emerged. Increasingly common comorbid medical conditions such as hepatitis C, hypertension, and diabetes as well as substance abuse and other neuropsychiatric disorders are major complications that impact the progression and treatment of the disease and must be addressed in their own right and in terms of how they interact with HIV.

The specific aims of the proposed research are to reduce the high prevalence rates and lower the incidence rates of these co-occurring disorders that now plague HIV-infected persons; to examine how these multiple co-occurring conditions relate to and either additively or synergistically interact with one another with respect to posing additional risks or consequences; and to ascertain whether targeted treatments of individual comorbidities facilitate the effectiveness of HIV treatments. For example, there are indications that antidepressant medications improve patients' adherence to HIV treatment, but little is known about how psychotropic drugs interact with HIV therapies.

Another issue to be addressed by the proposed research is how to develop a comprehensive, integrated, and interdisciplinary care system for HIV-related comorbidities. The current system

that encompasses a variety of funding streams and parallel–but separate–treatments often is expensive, fragmented, and ineffective. Since the majority of HIV-infected patients with comorbid medical and psychological problems enter treatment through a general medical setting, access to better mental health and substance abuse services is critical. However, it is unclear how such services should be integrated as well as what additional services should be available at what point in an individual's treatment trajectory to match treatment readiness.

Discussion

Ms. Henry commented that the proposed concept reflected findings from a June conference on the complexities of co-occurring disorders that focused on patients' overlapping physical health problems, HIV/AIDS, substance abuse, and serious mental illness. She asked whether a partnership with the National Institute on Drug Abuse (NIDA) was proposed since these intractable comorbidities appear in a majority of clients who are enrolled in inner-city public substance abuse and mental health clinics and compel more research on the interactions between medications for HIV infection and such drugs as buprenorphine and methadone that are used to treat substance abuse.

Dr. Stoff responded that NIMH has partnered with NIDA and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) on related studies and agreed that the concept grew out of extensive literature on dually diagnosed persons with both mental disorders and substance abuse problems to which the dimension of HIV infection is now being added. He concurred that effective substance abuse treatment can be essential to helping HIV treatments work better.

HIV and Psychiatric Comorbidity Basic Research Project

Dr. Kathy Kopnisky, Chief of the Neuropathogenesis Program in CMRHA, DMDBA, introduced the proposed concept by addressing biological and genetic factors underlying the high comorbidity between HIV infection and psychiatric disorders. Epidemiological data indicate that a majority of HIV-infected individuals will suffer from a psychiatric illness–ranging from a depressive episode to clinical depression, anxiety, or psychosis–during the course of their disease. The mechanisms by which neurotropic viral infections cause emotional and cognitive changes are largely unknown, although viral infections are known to affect gene expression, synaptic activity, and neuronal network systems. Since the systems affected by HIV may contain some of the same anatomic, cellular, and molecular substrates of the disease as psychiatric illnesses, the reasons for co-occurring HIV and psychiatric disease progression potentially pertain to involvement of the same brain structures, neurocircuitry, receptor, and transmitter systems. Also, gene variances and polymorphisms in viral and emotional stress-responsive systems may contribute to a comorbid physiological path. A viral or environmental insult to a genetically or otherwise vulnerable brain may precipitate or accentuate an existing psychiatric disorder.

The research objectives of this concept include: (1) ascertaining the genetic and biological determinants of comorbid HIV-infection and psychiatric illnesses; (2) determining the mechanisms by which psychiatric illness or HIV infection contribute to individual variability in disease progression; (3) identifying the vulnerable brain structures, neurocircuitry systems, or

other substrates involved in comorbid psychiatric and HIV disease progression; (4) investigating the effect of HIV on the developing or mature brain as this pertains to elucidating vulnerable gene by environment or other interactions and immune profiles most likely to influence psychiatric conditions; and (5) developing pharmacological agents that not only decrease the ability of HIV to infect cells or replicate but also alleviate symptoms of depression, anxiety, or other psychiatric disorders.

Discussion

To a question from Ms. Hellander regarding whether funding for this concept would include preventive interventions for teenagers with a psychiatric disorder who are at higher risk for HIV infection by virtue of their behavior, Dr. Kopnisky replied that the concept is expected to focus more on clinical and behavioral problems. Dr. Stoff added that the behavioral component will include psychiatric comorbidities across the life span. The CMRHA already funds a project derived from the Pediatric AIDS Clinical Trials Group to examine psychiatric comorbidities in perinatally HIV-infected children. Comorbidities among HIV-infected persons are a major problem not only among children, teenagers, and adults but also among the elderly who are even more vulnerable to co-occurring disorders.

After Dr. Nestler noted that Dr. Kopnisky's presentation described HIV infection as potentially involving some of the same pathophysiological mechanisms as psychiatric illnesses–even though very little is known about the pathophysiology of psychiatric illness–he recommended slight but important changes in the wording of the proposed concept. Definitions of psychiatric illnesses can be misleading since their distinguishing characteristics are salient behavioral abnormalities for which the causes are unknown. While HIV infection may be a precipitating factor for mental illness, it is probably one of tens–even hundreds–of such factors. Dr. Stoff agreed that the wording in the concept should reflect this subtlety.

Dr. Folkman, expressing enthusiasm for this concept that reflects both a hierarchical progression from basic biological analysis to service delivery and a horizontal, multidisciplinary approach, remarked that this is an important model for studying an illness like HIV that affects multiple systems and requires inclusive approaches from prevention to treatment. Dr. Insel added that any forthcoming RFAs pertaining to this concept would be circulated to other Institutes and thus foster cross-disciplinary collaborations.

To a question from Dr. Tsuang regarding whether any research has examined the impact of intrauterine HIV infection on the development of severe mental disorders, Dr. Kopnisky replied that many of the substrates involved in emotional regulation (e.g., noradrenergic, serotonergic, MU opioid systems and their agonists) have been shown to facilitate HIV infection into cells and to elicit a feed-forward cycle in HIV-infected persons. Hence, there are reasons to believe that emotional and HIV circuitry and treatments directed towards these systems may facilitate both conditions. It appears that drugs of abuse can facilitate HIV infection in human and cell models. For example, human studies have shown an increased mother-to-child transmission of HIV infection among women who abuse ethanol or opioid substances. It is unclear whether the responsible physiological mechanism is a change in the natural killer cell responses of the

maternal immune system or a change in the chemokine receptors (co-receptors for viral infections) in the developing fetus. With regard to whether prenatal exposure to HIV has consequences for the developing brain and nervous system, epidemiological and longitudinal human studies in international settings that do not yet have anti-retrovirals may provide data, as may other viral models of human neuroinfection.

Dr. Tsuang continued his comments by noting that NIH's valuable cache of stored blood from 15,000 babies and their mothers who participated in a national corroborative study might be analyzed for antibodies. While the proposed concept probably does not include research on the effects of prenatal HIV exposure, future studies may be able to examine what kinds of viruses affect different parts of the brain and how this contributes to developing psychopathology.

Dr. Pim Brouwers, a new NIMH staff member with expertise on HIV-infected children and adolescents, explained that CMRHA is working closely with both the Pediatric AIDS Clinical Trial Group and the Women and Infant Transmission Study Group to follow cohorts of children who were exposed in utero–but not infected with–HIV as well as children born to mothers who took a variety of antiretroviral agents. These studies are trying to determine whether the exposed children have mitochondrial abnormalities–a major concern–or other more subtle anomalies as they mature. Although these issues are not part of the proposed concept, Dr. Insel concluded that the may be appropriate for future research.

Anorexia Nervosa

Dr. Grayson Norquist, Director of the Division of Services and Intervention Research (DSIR), reported on a concept to evaluate interventions for treating anorexia nervosa that stemmed from workshop recommendations by practitioners in this field who examined obstacles to such research (*note: in October 2005, Dr. Norquist departed NIMH to become Chair of the Department of Psychiatry at University of Mississippi School of Medicine, and Dr. Junius Gonzales was appointed Acting Director, DSIR*). They concluded that a constellation of larger studies by a collaborative network of investigators would be required to overcome the inherent difficulties of recruiting a sufficient number of research participants to obtain definitive results.

While anorexia nervosa is a relatively rare disease, it poses a large public health problem. Nonetheless, there remains a paucity of research in the area. In designing the concept, a decision was made to bring together as many collaborative study sites as possible, not only to facilitate the enrollment of a sufficient number participants but also to help build capacity in the field. The proposed RFA would be a reissuance of an earlier RFA (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-04-002.html) and would be structured to replicate the mechanism used in the successful Research Units in Pediatric Psychopharmacology (RUPPs) to promote a network of anoxia specialists who could conduct further studies and become a resource for future ancillary efforts.

Discussion

After Dr. Folkman asked why the Institute is moving to a multi-site trial rather than soliciting more initial research at the R01 level to stimulate the development of appropriate interventions that might be ready for further testing in a collaborative effort within 3 to 5 years, Drs. Norquist and Linda Street replied that prior individual studies in this area have had problems in the recruitment and retention of study participants at a single site, resulting in the collection of more limited data upon which to draw meaningful conclusions.

Dr. Folkman commented that the most promising results from pilot studies in the area should be identified, and NIMH could then spearhead a collaborative effort–modeled on a cooperative agreement–to ensure that the best ideas and most effective methodologies are incorporated. Additionally, since the most pressing issue is not the capacity of the researchers but participant recruitment problems, she suggested that NIMH be more directly involved to increase the likely participation of the small number of available participants.

Dr. Freedman noted that specialty centers, similar to those used to organize the initial Alzheimer's Disease and Mental Health Centers, can serve two purposes–the peer review of good ideas and the provision of the needed infrastructure to study an illness (e.g., diagnostics, interventions, patient enrollment, and retention).

Dr. Kalin commented that the proposed RFA should be revised in light of the small number of investigators studying anorexia nervosa and the paucity of existing research. The NIMH might consider "seeding" investigators and encouraging them to bring new ideas and skills to this difficult population by supporting career development awards that broaden current researchers' focus from affective and anxiety disorders or related illnesses into this arena.

Ms. Hellander suggested that NIMH work with advocacy groups to identify and enlist study participants. She continued that the Internet might be an effective tool in building networks of sites and patients in more than one location. She said that many children with diagnosed bipolar disorder refuse to eat and develop what appear to be feeding problems. Since they begin to eat normally when treated with an antipsychotic medication for their other symptoms, this might be an area for further investigation in the treatment of anorexia nervosa.

Dr. Tsuang agreed that NIMH should take the lead in a cooperative agreement design with a controlled study methodology and an explicit plan for securing participants. Since not all clinicians who treat anorexia nervosa are experts in research design, it may be necessary to secure the participation of more experienced methodologists in conceiving a feasible approach in collaboration with clinicians. After clarifying that the RFA would limit participants to those with diagnosed anorexia nervosa and not bulimia, Dr. Tsuang recommended that the announcement require the inclusion of experts who specialize in locating and tracing research participants.

Dr. Lieberman remarked that, while only a small number of good researchers have eating disorders programs in their institutions and can apply sophisticated research methodology, anorexia nervosa is a relatively easy disorder to study, although a difficult one to treat. Research

on anorexia nervosa has very clear and objective outcome parameters—life or death, gaining or losing weight, and remaining cachectic versus normal weight. Since anorexia nervosa is an urgent public health problem, NIMH might consider issuing a contract- or cooperative agreement-driven mechanism to ensure collaboration among experienced investigators in the conduct of a well designed study.

Dr. Essock agreed that a multi-site study is critical for recruiting a sufficient number of participants but observed that the status of research on anorexia nervosa (i.e., a paucity of investigators, a pressing public health need, and too few interventions with proven effectiveness) was reminiscent of the start-up for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trials. The investigators who ran those studies had strong advisory committees that could fine tune the designs and offer other good ideas. The same opportunity exists in the field of eating disorders. Last year's applicants should benefit from the previous review and feedback.

To conclude the discussion, Dr. Insel noted that even though neuroscience is currently focusing on issues pertaining to feeding, eating, weight gain, and metabolism, the new findings about hypothalamic factors, for example, do not seem to have impacted the field of anorexia nervosa. This unrealized opportunity may be stimulated once a trial is organized by more attention to career development and translational research. He thanked Council members for their thoughtful comments that would be considered in future decisions about how best to go forward with the proposed research.

OTHER COUNCIL ISSUES

Observations of a Retiring Council Member

Mr. James McNulty, commenting that his 4 years as an Advisory Council member were about to end, spoke about his experiences on behalf of the "Graduating Class of 2004." After praising NIMH's leadership and its emphasis on serious mental illness, especially bipolar disorder and the interests of children and minority groups, he lamented the gathering storm clouds that seem likely to impinge on Council and Institute activities. Although recent congressional hearings included positive testimony from NIMH about the pharmacology for children given findings from the Treatment for Adolescents with Depression Study (TADS) (see https://trialweb.dcri.duke.edu/tads/) that for adolescents with major depression, a combination of fluoxetine and psychotherapy is the most effective treatment; nevertheless, the FDA recently asked the manufacturers of all antidepressant drugs to include in their labeling a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality in children and adolescents treated with the medications. Mr. McNulty went on to say that while NIMH has too little funding–the lowest of any illness group per disability-adjusted-life-year–it is the only credible institution that can reassure the public that psychopharmacology benefits many people.

Mr. McNulty continued by noting that NIMH faces an enormous public relations challenge. Many persons still believe that mental illnesses are not real brain disorders, and negative attitudes

toward their treatment have not improved during the time that so many positive changes have occurred within the Institute. A recent article in an Illinois newspaper reflected this viewpoint by expressing shock that the President's New Freedom Commission would recommend screening children for mental illness. The status of pharmacotherapy is not encouraging, and the treatments provided to those who seek care often are not often the optimal treatments. The NIMH, which is charged with studying mental illness and its treatment, must address these issues more aggressively.

After commending the many NIMH staff members and fellow Council members for their efforts during his tenure on Council, Mr. McNulty promised to make certain that the practitioners, politicians, and citizens he encounters in the future become educated about NIMH's mission and do their part to help achieve it.

Council Discussion

At Dr. Insel's request, several Council members commented on priority setting at the Institute.

When Ms. Hellander commented on the difficulties often inherent in determining the public health importance of proposed research when considering grant applications, Dr. Insel explained that to the extent possible, NIMH will commit funding to intersecting areas that reflect the biggest public health problems and the greatest scientific opportunities.

Dr. Folkman expressed concern about the message that investigators receive when a strong grant application is not funded, given the limited availability of research funds. Despite the importance of encouraging new investigators, it remains paramount for the Institute to inform investigators as early as possible about the need for applications–especially for new R01s–to address Institute priorities.

Dr. Insel encouraged potential applicants to contact NIMH program staff and to visit the NIMH Web to learn more about research priorities (see http://www.nimh.nih.gov/strategic/strategicplanmenu.cfm).

Dr. Wagner cautioned that the recent FDA hearings would be a major setback for future research on psychopharmacology, children's treatment, participant recruitment for drug studies, and any further fiscal support from pharmaceutical industry. While these are "unintended consequences," it is critical that NIMH monitor reactions and encourage future psychopharmacology studies for children. The high interest and enthusiasm for studying antidepressants in children is lessened, and every antidepressant, even in the absence of data, will undoubtedly carry a black box warning label in the future. Dr. Insel also expressed concern about the lack of a positive response to findings from the TADS trial and the future treatment for children with depression.

Dr. Salovey said that he supports the concept for selecting the best scoring grant applications for immediate funding before moving on to the next ranked set and applying the criteria of relevance to NIMH's public health mission, with some areas clearly becoming more relevant than others. A problem, however, relates to the message that NIMH conveys–whether inadvertently or not–to

new investigators and potential applicants. Dr. Salovey expressed concern about the numerous communications that he receives often claiming that the Institute no longer funds "X." In reality, most priority-setting statements specify a way to conduct research on "X" that increases its relevance to the NIMH mission. Potential applicants need to hear that it is not correct that NIMH no longer supports "X" but rather that there are ways to study "X" that would advance NIMH's public health priorities and thus should be considered in shaping a research application.

Dr. Nestler commented that, although the Institute's budget is twice as large as it was 6 to 8 years ago, the number of funded grants has only increased by 40 percent. Program officers and the Institute's Web site should convey the message that NIMH has a relatively strong funding baseline and that this is an opportune time for mental health research.

Dr. Gary expressed concern that review criteria do not adequately reflect NIMH's mission to advance the Nation's public health and reduce the painful burdens of mental illness disproportionately borne by socio-economically disadvantaged and under-represented ethnic minority groups. She suggested that summary statements for fundable applications might include information about how the proposed research relates to resolving health disparities for a specified target population. She stressed that the goal of encouraging new researchers should be broadened to encompass investigators from institutions that have never received NIMH funding and who need more explicit encouragement to join the NIMH family. The cultivation of new researchers might be facilitated through inducements for forming more partnerships similar to those discussed for anorexia nervosa research. Finally, she pleaded that members of Council and NIMH staff assist consumers, parents, and advocacy groups, as well as clinicians, in interpreting the confusing FDA findings and warnings about antidepressant medications for children. She suggested that perhaps a brochure with objective information about these drugs could allay misunderstandings. As a clinician with extensive experience treating disadvantaged children, Dr. Gary said she was familiar with the reluctance that members of ethnic minority groups express about medicating children with behavioral problems–especially their sons.

SESSION RECESS

After thanking Council members for their contributions to the preceding discussion, Dr. Insel recessed the initial session of the 207th meeting at 5:20 p.m. with a comment that the session would reconvene at 8:30 a.m. the following morning on the NIH campus.

CALL TO ORDER/ Opening Remarks

Dr. Insel reconvened the open policy session by welcoming members of the public and the press as well as Council. He first recognized the contributions of the retiring Council members Drs. Susan Folkman, Jeffrey Lieberman, Larry Squire and Ming Tsuang, Mr. James McNulty, and the ex-officio representative from the Department of Defense, Dr. E. Cameron Ritchie. After thanking each member for his/her unique contributions to the Council deliberations, Dr. Insel reported that a slate of new Council members had been approved by the Department of Health and Human Services and that the Council meeting in February 2005 would mark the first Council meeting for the new members.

Approval of the Minutes for the Previous Council Meeting

After Dr. Insel requested and received no comments on the minutes of the May Council meeting, a motion to approve them without changes was duly made, seconded, and unanimously endorsed.

NIMH DIRECTOR'S REPORT

Turning to his Directors Report (see http://www.nimh.nih.gov/council/dirreportSept04.pdf), Dr. Insel noted that he would be addressing several important activities at NIMH: the NIMH reorganization, updates on NIH-wide issues, recent scientific findings, staff departures, and the NIH Blueprint for Neuroscience Research.

The NIMH Reorganization

Recalling plans discussed at the May Council meeting for reorganizing the extramural divisions at NIMH to enhance translational research, Dr. Insel summarized the movement from "discovery to recovery" as encompassing two facets: (1) the development of biomarkers, diagnostic tests, and new treatments that help move science from the bench to the bedside and (2) the application of approaches (e.g., clinical trial networks, practical trials, and services research) that move findings and proven interventions from the bedside to practice–to improve public health.

Currently, NIMH has three major extramural research divisions: the Division of Neuroscience and Basic Behavioral Science (DNBBS), the Division of Mental Disorders, Behavioral Research and AIDS (DMDBA), and the Division of Services and Intervention Research (DSIR). In an effort to facilitate translational research and generate research that will transform the prevention of and recovery from mental disorders, a new organizational structure will be in place on October 1, 2004 (see http://www.nimh.nih.gov/researchfunding/reorganization.cfm). The reorganized NIMH will include a division of basic science at the bench level headed by Dr. Steve Foote, a division of services research at the practice level headed by Dr. Grayson Norquist, and three divisions focused on translational science: one for adult translational research directed by Dr. Wayne Fenton, another on pediatric translational research led by Dr. Susan Swedo, and a division on health and behavior, including AIDS, led by Dr. Ellen Stover.

The new structure is designed to ensure a reciprocal, translational flow through between the basic science and trials/services divisions. A strong investment will be maintained in both basic science and the trials/services research arenas as the solid pillars that support translational efforts. Priorities will be set by public health needs so that funded basic science informs the other divisions and facilitates more rapid movement into practice.

The three overarching goals of the reorganization are to: (1) focus efforts on understanding, diagnosing, and treating mental illness; (2) increase collaboration so that resources are allocated strategically to implement priorities; and (3) identify and adopt best practices, standards for operation, and assessment strategies for improving Institute performance.

Many of these concepts were discussed at the July 2004 meeting of The Alliance for Research Progress (see http://www.nimh.nih.gov/Outreach/roundtablemenu.cfm) that was attended by representatives from 34 different advocacy groups, NIMH staff, and the Directors of NIH, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Nursing Research (NINR). The agenda for that meeting encompassed the Institute's reorganization, issues around public trust and cross-Institute and Center initiatives, and presented an opportunity for NIMH staff to hear directly from stakeholders about NIMH priorities.

As the reorganization effort continues, Dr. Insel noted that several new and key positions are being actively recruited. The new divisions will require additional efforts to develop inter-disciplinary, inter-divisional teams that support the translational research focus. Ultimately, more extensive priority statements will be available so that applicants can be better informed about NIMH's funding intentions to support a diversified program of research.

NIH-Wide Issues

Dr. Insel reported that as the NIH Roadmap reaches its first anniversary, there have been many significant accomplishments stemming from the initial Roadmap initiatives. Dr. Insel reminded the audience that Dr. Mayada Akil serves as NIMH liaison to the NIH Roadmap. The Roadmap lays out the most compelling research opportunities in three areas: New Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise. During its first year, the Roadmap accomplishments have been many, including the Molecular Libraries Initiative, which NIMH co-leads, that has developed the PubChem project and indexed a million chemical compounds, which are available on the National Library of Medicine Web site (see http://pubchem.ncbi.nlm.nih.gov/). The goal of this initiative is to provide organic chemical compounds, known as small molecules, for scientists to use in modulating gene function to improve our understanding of biological pathways in health and disease. Progress to date includes the recent award to Discovery Partners International of a multi-year contract to set up and maintain a Small Molecule Repository, to manage the Repository, and to provide up to a million chemical compounds to multiple NIH screening centers. In addition, the NIH National Chemical Genomics Center (NCGN), the first of the screening centers, has been launched in the intramural program. Up to nine more centers will be funded at academic institutions and other locations to build a network providing a broad range of small molecules with promising properties for biological research. In the first year of operation, the NCGN plans to screen more than 100,000 small molecules in high throughput assays, opening up the use of small molecules as biological probes to public sector biologists for the first time.

Another continuing NIH-wide issue pertains to NIH conflict-of-interest regulations that have received much attention over the past 6 months. As reported at the May Council meeting, NIH instituted a new policy in response to a Blue Ribbon Panel's recommendations regarding potential conflicts of interest. These initial policies have recently been amended–to make them more rigorous and restrictive–and submitted to the Office of Government Ethics for approval before NIH-wide implementation. The proposed requirements were crafted to balance the importance of having NIH investigators interact–and partner–with industry and, at the same time, to avoid the appearance of any kind of bias or conflict of interest. The new rules should help to avoid any

ambiguity with respect to researchers' relationships with industry and other outside organizations, including the receipt of honoraria for giving grand rounds lectures at universities that house grantees. To make certain that everyone abides by the same rules, the new restraints also apply to investigators in the NIMH Intramural Research Program (IRP).

Other NIH-wide news pertains to the building program that is coming to fruition. The new 152,000 net square foot Mark O. Hatfield Clinical Research Center will open on September 22, 2004, with a 242-bed hospital and multiple clinics. In addition, the first wing of the John E. Porter Neuroscience Center opened in June for 50 investigators from eight different Institutes. This 560,000-square foot research facility houses conference rooms, offices, imaging equipment, animal holding space, and other laboratories. Rather than assigning space by Institute, the Center encourages collaborations among scientists who are working on common research goals. Currently, nine investigators are working together on aspects of neural degeneration, plasticity, neurophysiology, and related topics. Construction of the second wing is scheduled to begin in the next 9 months, after Building 36 is demolished.

Recent NIMH Research Findings

Turning to recent research, Dr. Insel highlighted findings from the NIMH-funded clinical trial, the Treatment of Adolescent Depression Study (TADS), a study of 439 adolescents with major depressive disorder across 13 sites (see http://www.nimh.nih.gov/healthinformation/tads.cfm). The project, which is relevant to recent FDA reviews of antidepressant drug use in children, is comparing four groups: participants who receive fluoxetine, placebo, cognitive-behavior therapy (CBT), or a combination of fluoxetine and CBT. As measured by several outcomes, initial 12-week results show that fluoxetine is more effective than either placebo or CBT, and the combination of fluoxetine and CBT is better than placebo, CBT, or medication alone. More specifically, 60.6 percent of participants receiving fluoxetine were much or very much improved, compared to similar improvements for only 43.2 percent of those on CBT and 34.8 percent of participants assigned to the placebo group. Over 70 percent of the participants receiving the combination of fluoxetine and CBT showed this level of improvement. Key data for 6- and 12-month outcomes are still pending–and expected to provide critical information about the longer-term effectiveness.

These important findings are the best evidence available from a controlled randomized trial that medication is associated with significant improvements in adolescents with major depressive disorder. As in other trials, however, a total of 24 negative, suicide-related events occurred. Fifteen (7 percent) of these befell individuals on fluoxetine alone or in combination with CBT, while the other 9 (4 percent) were experienced by participants who did not receive medication. Although this was not a significant difference, the study showed that fluoxetine still has risks for children, especially those who are not monitored closely.

Since the failure to treat depression can also have severe adverse outcomes, the risks of antidepressant treatment need to be weighed against the risks of no treatment. While substantial epidemiological data are not available, the Methods for the Epidemiology of Child and Adolescent Mental Disorders study (MECA) found that 17 percent of children with major

depressive disorder–from a community sample of about 1,300 untreated children with mental illness–either attempted or completed suicide. None of the more than 4,500 children with depression who have been studied in a variety of publicly and privately funded randomized controlled trials has completed suicide, and the rate of suicidal behavior in the combined studies is about 0.7 percent, compared to 17 percent for the untreated cohort. Even if suicidal ideation is added to suicidal behavior, the rate only increases to 1.7 percent. Further, the larger number of adverse events experienced by TADS participants in the medication-only group in relation to the placebo group might be attributed to activation of hypomania or mania among those with bipolar disorder.

A remaining question with respect to these studies of antidepressant medications for children is whether sufficient data are available to make policy decisions or adequately evaluate the risks of adverse events. The TADS, for example, was not designed to study suicide or other negative reactions. Since such events occur in less than 1 percent of children with major depressive disorder, a very large study would be necessary to identify who is at risk and for what severity of reactions. Despite this lack of definitive evidence, the FDA is about to require a black box label on all the antidepressant drugs that recommends very careful monitoring when prescribed for children. Although rigorous monitoring is a good idea, the presence of a black box warning may substantially decrease the prescription of antidepressant medication for children and adolescents with depression.

While it might be appropriate to recommend that children with depression receive CBT instead of medication–since the two interventions are about equally effective in adults–it is not clear that CBT is available for most children in the United States, and findings from TADS suggest that it is no better than placebo.

The other critical issue is whether careful monitoring–or its lack–is the key to reducing adverse events. If the problem is really the type of care children receive, not the medication, then reducing the availability and acceptability of the medication could put children at greater–not lesser–risk. The greatest concern is that, even in the best studies like TADS, at least 40 percent of the children do not respond to the medication. While the reasons for this lack of responsiveness are not yet evident, those youngsters still need some form of treatment. Since this is an area where NIMH needs to assume leadership, a group of experts is being formed to study the feasibility of conducting a large-scale examination of the risk/benefit ratio of medications, how to identify children at greatest risk for adverse events, and what can be done for children who do not respond to the selective serotonin reuptake inhibitors (SSRIs) or other forms of depression treatment.

Staff and Other Departures from NIMH

In reporting changes at NIMH, Dr. Insel noted that both recruitment efforts and retirements have increased as a result of the ongoing reorganization. Among valued staff who are leaving NIMH are:

- Dr. Robert Desimone, Scientific Director of the IRP, will become Director of the McGovern Institute at the Massachusetts Institute of Technology next year. Until a replacement is found, Dr. Insel will serve as the Acting Scientific Director of the IRP.
- Dr. Dennis Charney, Chief of the Mood and Anxieties Disorders Program, who built a renowned research program in this area during a 3-year tenure, left NIMH in July to become the Dean of Research at Mount Sinai Medical School.
- Dr. Grayson Norquist, Director of the Division of Services and Intervention Research and champion of the practical clinical trials network, is moving to the University of Mississippi to chair the Department of Psychiatry. Dr. Junius Golzales will serve as Acting Director of DSIR.

Dr. Insel continued by reporting that the *Schizophrenia Bulletin*, which has been part of the Institute for over 4 decades, is moving to the Oxford University Press with Dr. William Carpenter, Jr., of the Maryland Psychiatric Research Center, as Editor-in-Chief. However, NIMH will continue disseminating important schizophrenia research through a Web-based public-accessible site, *Schiz Forum*, that will be similar in format to *Alz Forum* (see http://www.alzforum.org/home.asp) for the Alzheimer's disease community and includes recent papers and discussions by experts in the field, information for families, caregivers, and patients, and slide presentations and videos from recent meetings. The transition from the archival *Schizophrenia Bulletin*, which has had an 18-month lead-time from manuscript acceptance to publication, to an up-to-date Web site reflects NIMH's focus on providing current research findings.

The NIH Blueprint for Neuroscience Research

Dr. Insel concluded his report with details about the NIH Blueprint for Neuroscience Research (see http://www.nih.gov/news/pr/oct2004/ninds-24.htm). Through this Blueprint, 14 Institutes and Centers at NIH with mutual interests in neuroscience research will leverage funds to conduct large-scale initiatives pertaining to three unifying themes–neural development, degeneration, and plasticity–that are relevant at a basic science level to such illnesses as Parkinson's disease, schizophrenia, addiction, and macular degeneration. Collaborations among the involved Institutes are expected to provide neuroscientists with a tool kit for the 21st Century–whether they are working within the retina or the cortex. One example is a planned, publicly accessible repository of knockout mice with targeted deletions of the approximately 16,000 genes expressed in the brain. Since the functioning of only about 1 percent of these genes is known, the repository will facilitate resource sharing among scientists studying gene functioning and curb support for 500 or more different R01s that each develop a particular but un-disseminated mouse strain. Similar tools are being developed to improve stem cell research with the hope that investigations of dopamine and serotonin cells may yield regenerative interventions. Clearly, there are many tools

and resources that are needed across multiple disciplines. Several meetings have been held with external advisors and Council members as well as with representatives from the various Institutes that are collaborating on the Blueprint, and there is real excitement about the Blueprint plans that will be detailed at the next meeting of the Society for Neuroscience.

Discussion

Dr. Gunnar noted that both parents and pediatricians may need help in defining what close monitoring of antidepressant use by children entails. She suggested that NIMH bring together the best experts in pediatric depression to create a tracking sheet that helps parents know what symptoms and behaviors to observe and when to bring concerns to the attention of the prescribing physician. Dr. Insel noted that a major concern for practitioners is the required time for close monitoring and that the best evidence-based approach to effective monitoring is a collaborative care model in which a network of helpers–families, social workers, nurses, and masters-level technicians–provide a backup safety net for the physician. Unfortunately, the approach is not well known, is not reimbursed, and is not available in most service settings.

Dr. Essock stressed the importance of studying barriers that hinder the general application of proven treatments as well as ways to overcome this resistance. The NIMH reorganization, which will foster a portfolio of useful, practical research, is critical to this effort. Any recommendations for close monitoring must be persuasively explained with examples of what is at stake if such supervision is not available.

Dr. Tsuang asked whether NIMH has concrete plans for responding to the TADS findings and the FDA hearings and remarked on the discrepancies between public and scientific perspectives about the adequacy of evidence. From a theoretical, epidemiological point of view, the longitudinal course of suicide is unknown. Moreover, the definition of suicide–with respect to inclusion of suicidal ideation, frequency of suicide attempts, and successful completions–varies among studies. Some of the long-term studies have yielded only soft data. It will be necessary to conduct long-term, carefully designed catchment area research involving many investigators to resolve questions about suicide risk and interactions with medication because of the many different variables that affect clinicians, families, and patients. Currently, it is unclear whether medication or the worsening of depressive symptoms leads to suicidal behavior. Nonetheless, recent progress in neuroscience, particularly research on interactions between gene expression and the environment as well as a focus on translational research and the development of biomarkers, puts NIMH in a position to conduct relevant research on gene expression patterns that might predict the onset of suicidal ideation.

Dr. Insel agreed that the relationship between suicide and depression is a complex issue and that adolescence further complicates the issue because suicide may be more related to impulsiveness than to fluctuating moods. Dr. Insel continued that the FDA and congressional hearings are rapidly changing the situation. Unfortunately, the TADS data have been cited as evidence that medications are not helpful and can be dangerous, without considering the implications–and unintended consequences–of not providing treatment. Although NIMH is concerned that black box warnings may decrease the number of children with depression who receive antidepressant

medications, the Institute fully endorses FDA recommendations for close monitoring. The challenge is how to counter uninformed negative publicity with accurate information and evidence that informs policy.

Mr. McNulty remarked that there is often a sense among the public that mental illnesses are minor and relatively benign. Because of his personal experience with the devastating impact of untreated mental illness, Mr. McNulty beseeched NIMH to publicize vigorously the tragic consequences of not providing effective treatments and to challenge those who oppose the use of antidepressant medications in children and adolescents to offer alternatives.

Ms. Hellander reflected that from her perspective as the parent of a child with bipolar disorder who has been suicidal on antidepressants and from reports by other families with similar experience, a poorly understood fact is that depression in children, especially among pre-pubertal youngsters, often leads to bipolar disorder. The TADS study, which excluded children with bipolar disorder, did not speak to which subgroups of depressed children might become more impulsive and suicidal. Since childhood depression is likely to be a chronic, recurring, lifelong illness, clinicians need to be educated about how to recognize and treat early onset and emerging bipolar disorder in children.

Dr. Insel reiterated the importance of developing better ways to detect childhood depression and the likely trajectory for the illness, which has different manifestations with different implications for treatment.

Dr. Aguilar-Gaxiola, reporting that he had closely followed the controversy about antidepressants for children, concluded that by heightening public awareness, the debate offered NIMH an opportunity to present correct information that stresses the importance of evidence-based science. Proactive efforts by NIMH that encourage researchers to couch their findings in terms of public health burdens and implications could advance NIMH's objectives for improving public relations and better publicizing study outcomes for consumers, families, and policymakers.

Dr. Essock, in concluding the discussion, pointed out that the TADS trial will yield important 12-month outcome data regarding how well initial results hold up over time and whether the effectiveness of CBT is different at that point. The TADS also will be able to characterize how well children and their parents adhere to these different interventions–a question of great practical significance. One challenge is to make certain that NIMH attracts and retains researchers who ask questions that are relevant to practical and important public health issues.

CLINICAL TRIALS WORKGROUP: FINAL REPORT

Dr. Insel reminded Council members that the final report from the Clinical Trials Workgroup, which was presented at the May meeting, generated much discussion about participant recruitment and that a decision was made to postpone voting on its acceptance until relevant data could be re-examined and the findings refined accordingly. This has been accomplished over the past few months by the Workgroup leader, Dr. Jeffrey Lieberman, in conjunction with his Council colleagues–Drs. Susan Essock, Karen Wagner, and Sergio Aguilar-Gaxiola, Ms. Renata Henry,

and Mr. James McNulty, former Council members Drs. Javier Escobar and Norwood Knight-Richardson, and other expert advisors. Although many NIMH staff members assisted with the revisions, Dr. Insel acknowledged the substantial time and effort provided by Dr. Grayson Norquist to the Workgroup.

Dr. Lieberman reported that these efforts resulted in several Workgroup-approved refinements to the report: (1) a re-examination of the data on participant recruitment; (2) editorial modifications to more closely align the text with the data; and (3) an expanded discussion of historically under-represented populations to highlight the complexity of this issue. These revisions did not substantially change the earlier conclusions or recommendations.

The Clinical Trials Workgroup, Dr. Lieberman went on to say, was charged with reviewing DSIR's fiscal year (FY) 2003 clinical trials portfolio to assess its balance and relevance to public mental health and the burden of mental illness in the United States and to identify any critical gaps in knowledge or scientific opportunities that were not being adequately addressed. In addition, the Workgroup was asked to assess the progress being achieved by DSIR-supported clinical treatment trials and to recommend changes that would maximize the yield and enhance the productivity and success of funded treatment research.

Overall, 16 percent ($121.4 million) of NIMH's $784.1 million FY 2003 budget for non-AIDS-related extramural research was devoted to clinical treatment trials research. While the majority (49 percent) of clinical treatment trials research was targeted at adults, child-oriented trials comprised nearly 38 percent of the portfolio. Geriatric research accounted for 13 percent of the portfolio and was judged to be under-represented relative to the demographics of the aging population.

With respect to resource allocation, the largest proportion of funding and the greatest number of studies pertaining to adults were directed at depression, followed by anxiety disorders, schizophrenia, and bipolar disorder. For children and adolescents, depression also was the major area of support, followed by anxiety disorders, attention deficit hyperactivity disorder (ADHD), and bipolar disorder–a historically under-represented area that recently has seen increased activity. For geriatric populations, depression studies received the greatest resources, followed by dementia and schizophrenia.

Another measure of resource allocation is career development awards. While NIMH invests a relatively large proportion of its budget in this area, only 16.2 percent of the FY2003 career awards were for investigators pursuing non-AIDS-related clinical treatment research. The percentage of support for predoctoral and postdoctoral training positions and fellowship awards was smaller, with 6.8 percent of awards supporting clinical treatment research trainees. The Workgroup was concerned that funding in this area suggests a capacity-building problem in terms of developing an adequate supply of experienced investigators who are committed to conducting clinical treatment research.

An issue of special concern to the Workgroup was the success of funded clinical treatment trials in meeting recruitment goals. Using a threshold criterion of recruiting at least 80 percent of the

projected number of participants for a given study–a critical factor in achieving adequate statistical power to test a primary hypothesis–about half of the funded adult and geriatric clinical treatment trials met this goal. More than 70 percent of funded pediatric clinical treatment trials did not meet stated recruitment goals for these populations.

In terms of the inclusion of historically under-represented racial and ethnic minority study participants in clinical trials, over 60 percent of the geriatric-oriented projects and 70 percent of the pediatric clinical treatment trials did not achieve the minimal threshold (applying the 80 percent criterion) for racial and ethnic minority representation. It is important to note that recruitment of racial and ethnic minorities could be affected by the poor success in general recruitment.

A closer examination of the recruitment data from individual grants revealed that the magnitude of the problem varies by study and site. Interestingly, recruitment problems are more likely to exist in small, investigator-initiated single-site studies than in the larger cooperative agreements or contract-driven clinical treatment trials that are more likely to meet participant enrollment goals, including optimal targets for representation of different genders and demographic population groups.

In general, the Workgroup's review of the clinical treatment trials portfolio determined that the projects were scientifically meritorious and reflected a reasonable balance and proportional diversity in the range of mental disorders, age-relevant populations, and treatment modalities represented. While some areas were well covered, more research was thought to be warranted in several areas–most notably, polypharmacy, treatment adherence, bipolar disorder, and anorexia nervosa. In addition, too few studies are likely to have an immediate impact on clinical practice; rather, the larger clinical treatment trials, conducted through contracts and cooperative agreements, have a greater potential to influence clinical practice and impact public health.

There were a number of more general issues that surfaced during the Workgroup's portfolio review, including:

- There is a lack of incentives for researchers from the private sector and the pharmaceutical industry to address major public health concerns and clinical issues.
- Members of review committees may not be adequately informed about NIH priorities or the larger scientific and public mental health context of treatment needs.
- No formal mechanism exists for many stakeholders and other constituencies in the field of mental health to systematically inform the research enterprise
- Only a limited number of novel compounds are in the pipeline for pharmaceutical development.
- The larger scale, greater costs, and complexity of clinical treatment research studies make them inherently different from most other areas of NIMH-supported research.
- NIMH must determine the priorities for various types of treatment development and effectiveness research to ensure that more innovative therapies become available.

The forthcoming NIMH reorganization, Dr. Lieberman continued, will provide an organizational structure that is crafted to support basic science discoveries, translate these discoveries into new interventions, and ensure that new approaches can be used for diverse populations and in diverse settings. He stressed the importance of studies like the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (see http://www.matrics.ucla.edu/) and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) (see http://www.nimh.nih.gov/press/prturns.cfm) programs to support the development of innovative therapies as well as the continuation of clinical trial networks for evaluating the comparative effectiveness of marketed treatments.

The Workgroup formulated 17 recommendations that fell into three categories: (1) creating the optimal treatment and research portfolio; (2) building clinical trials capacity and expertise; and (3) improving the operation, efficiency, and productivity of clinical trials to ensure that funded studies deliver what they promise and have the greatest impact on public health (see Workgroup report, soon to be available at http://www.nimh.nih.gov/council/advis.cfm for a description of the recommendations).

Discussion

Dr. Reynolds commented that the Institute's investment of 16 percent of its funding in clinical treatment research seems insufficient to meet the nation's public health needs, particularly in the areas of child and geriatric psychiatry, which are disproportionately neglected. He stressed that more investigators who are members of under-represented minority groups are needed before substantial progress can be made in recruiting these subpopulations as participants.

In response to Ms. Henry's remarks that under-representation of minority populations is a long-term and continuing concern in need of further investigation, Dr. Lieberman remained optimistic that some of the report's recommendations would prove helpful. Dr. Insel suggested that, although the report offers useful data for an evidence base, the importance of adequate representation minority participation in NIMH research warrants that a workshop be convened in the near future to develop an action plan.

Dr. Kalin, noting that the large clinical trial research contracts that NIMH has funded are beginning to pay off, expressed support for an even larger NIMH investment in infrastructure support and more proactive monitoring of contracts and other funding mechanisms. When he asked for more details about the recruitment of under-represented minorities in the contracted studies, Dr. Lieberman responded that 18 percent of the 1,493 participants in the CATIE studies were African American, 12 percent Hispanic, and 3 percent Asian American. Gender distribution, however, was an area in which representation fell short and where special efforts are needed.

Dr. Salovey, recalling previous Council discussions about the desirability of encouraging the larger clinical trials to identify mechanisms of action for positive outcomes, expressed disappointment that reported results still do not clearly define many aspects of successful treatment or specify whether some variables might need modifications in practical applications of

the findings. He asked whether mediating and moderating variables were still seen as desirable endpoints in clinical trials and remarked that it seemed important to emphasize these more subtle outcomes for purposes of generalizability.

Dr. Lieberman replied that, although the large clinical trial contracts primarily were designed to evaluate treatment effectiveness in broad populations and provide widely generalizable results, some opportunities exist to examine associated questions. For example, a component to collect blood and bank DNA samples has been added to allow for the study of genetic mechanisms. Further, investigators are encouraged to conduct ancillary studies addressing specific questions in the context of the larger trial. Finally, the databases accrued in the clinical trials are made public with appropriate technical assistance to facilitate the examination of questions, such as mechanisms of action as well as mediating or moderating variables.

Noting that the clinical trials have marked a key change in measuring treatment effectiveness–from simple improvements on the rating scales to improved functioning over time–Dr. Insel predicted that future studies will determine which intervention is most suitable for a particular individual. Over the next 5 years, the mental health field should begin focusing more on genetics, biomarkers, diagnoses, and predictors of treatment response–domains already being explored by cancer research. Since the mediators and modulators of treatment effectiveness will be crucial to this exploration, plans to examine these should routinely be one criterion for application reviews, particularly for clinical trials. This does not require a large investment but a new way of thinking.

Ms. Hellander expressed disappointment that the report gives little attention to child-oriented research. The word "child" does not appear, for example, in "Recommendation 5: The NIMH should expand its efforts to include historically under-represented populations, including women, ethnic and racial populations." Since mental illnesses often begin in childhood and adolescence, child-oriented research should be the rule, not the exception. Additionally, she noted, more emphasis should be given to early detection and intervention. Finally, she noted that the NIH definition of a child (individuals under the age of 21 years) should to be amended to limit the age range to younger children.

After Dr. Lieberman highlighted advances in DSIR's child portfolio over the past decade as well as the new attention children will receive under the plans to create a pediatric research division at NIMH, Dr. Insel remarked that some of the problems in recruiting children into clinical trials reflect the regulations governing pediatric studies.

Dr. Ritchie, speculating that participant recruitment for studies of mental illness is hampered by individuals' reluctance to reveal their psychiatric disorders, asked how NIMH compares to other Institutes in terms of clinical recruitment and enrollment efforts. If the Institute is less successful in recruitment efforts, then perhaps more attention should be given to the impact of privacy issues and the stigma of mental illness.

Dr. Lieberman replied that the Workgroup did not compare NIMH's recruitment rates with those of other Institutes, although that would be an interesting exercise. Dr. Norquist added that research participation varies by disease. For example, although cancer treatment is often

delivered in sites where researchers conduct their studies, the participants in cancer research represent only about 4 percent of persons with diagnosed cancer.

Mr. McNulty stressed the importance of building mechanisms to encourage collaborations among stakeholders, grant applicants, and consumers. The NIMH Alliance for Research Progress has made some progress in this direction, but more work is needed. One model for soliciting this type of cooperation is the Cancer Institute's involvement of advocacy organizations and patient support groups in research trials. He suggested that it might be possible to recruit more participants from public mental health systems rather than from academic medical centers.

Dr. Gary expressed appreciation for the excellent studies conducted by the Clinical Trials Workgroup that provided important baseline information and suggested that mechanisms should be in place to assist researchers who do not meet projected recruitment targets. She asked whether NIMH tracks the annual reports from grantees to ascertain how they are performing each year rather than waiting until a grant ends. With respect to providing information to review committees concerning pressing public health issues, it is crucial that committee members be informed about public health needs and the NIMH mission. Another way to stimulate the movement of science to service might be by showcasing NIMH findings in public service announcements on TV and radio. At another level, researchers need to build partnerships with communities and stakeholders to convince them of the relevance of the science before projects are funded and then enlist their assistance in recruitment and other operational activities. Finally, Dr. Gary asked what percentage of the child samples in the clinical trials are American Indians and Alaska Natives.

Dr. Lieberman replied that American Indians and Alaska Natives comprise less than one percent of the child samples. This is probably due to the sites' locations, although appropriate geographic distribution for recruiting representative samples was a consideration for site selection. With respect to monitoring enrollment targets over the course of funded studies, progress reports from non-competing continuation grantees are regularly submitted. If Workgroup recommendations are adopted, these will be acted on immediately, rather than waiting until a grant is completed to see if target participant enrollment goals were met.

Dr. Insel added that generic participant recruitment issues have become a policy issue for NIMH consideration. Dr. Della Hann in the Office of Science Policy and Program Planning has formed a staff working group to examine this problem and recommend courses of action for a grantee's failure to meet projected recruitment goals. This group's findings will be a topic for discussion at the next meeting. In rejoinder to the observations about the relative insulation of review committees, Dr. Insel reported that these groups, particularly the ones that review the clinical trials contracts, have members from the public sector as well as academia who stringently apply criteria for recommending awards that include the NIMH mission and the burdens of mental illness. To garner more constituency advice, Dr. Insel asked members for their interest in forming a workgroup to consider the next generation of practical clinical trials, given the near completion of the TADS and CATIE studies and that STAR*D and STEP are well underway, and several members expressed an interest in participating in such a workgroup.

Dr. Freedman, noting that the TADS trial will cost $17 million for less than 500 enrollees–or almost $40,000 a child–asked whether this was a reasonable funding level in light of all the other NIMH priorities. Dr. Insel replied that while costly, the TADS trial has been worth the outlays to date and that the results for CATIE, STAR*D, and STEP studies will be available next year.

Approval of the Clinical Trials Workgroup Report

After Dr. Insel called for a Council vote on accepting the final report of the Clinical Trials Workgroup with the a few amendments to reflect the day's discussion, a motion to that effect was made, seconded, and approved without dissent.

Report on the Extramural Loan Repayment Program

Dr. Insel gave a brief report on the status of the Extramural Loan Repayment Program (LRP) that provides for the repayment of educational loan debt of qualified health professionals who agree to conduct clinical or pediatric research for 2 years. This year, the Institute will fund 128 applications at a total cost of $5.1 million. Of these, 25 are in the pediatric LRP (see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-005.html), and the remaining are served by the more general clinical LRP (see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-004.html). Of 37 selected M.D.s, eight are part of the pediatric LRP, and 29 are in the clinical LRP.

BRAIN IMAGING IN DEPRESSION RESEARCH

Dr. Wayne Drevets, Chief of the Section on Neuroimaging in Mood and Anxiety Disorders in the NIMH Intramural Research Program (IRP), explained that his presentation would address the range of existing brain imaging technologies, the applications underway in the Mood and Anxiety Disorders Program, and the results of some completed studies as well as preliminary findings that are still being refined.

In general, positron emission tomography (PET) imaging is used to measure receptor binding in the brain across a range of neuroreceptors as well as glucose metabolism and cerebral blood flow (CBF). Magnetic resonance imaging (MRI) can measure cerebral volumes to learn more about the structure of the brain and dynamic changes in the hemodynamic response that serve as markers for local neuronal activity during a variety of neurocognitive and emotional tasks. Magnetic resonance spectroscopy is used to examine the brain chemistry of various species.

Brain imaging, Dr. Drevets went on to say, offers psychiatric nosology an opportunity to advance from the current practice of generating diagnostic labels–syndromes–from combinations of clinical signs and symptoms to understanding the pathophysiology involved in the conditions that NIMH studies. Because mood and anxiety disorders tend to cluster in families–and other evidence, largely from twin studies, indicates that these are usually heritable conditions–combining genetic and phenotypic definitions with imaging likely will yield fruitful results with respect to diagnoses.

The current thrust is to define biological patterns or phenotypes by combining the physiological measures generated by PET and functional magnetic resonance imaging (fMRI) for receptor pharmacology, cerebral volumes, and cerebral chemistry. These procedures are used to investigate where and how treatments work in the brain and to understand normal as well as pathological emotional processing. Imaging also is increasingly used to guide genetic studies, although genetic studies guide imaging as well. To date, imaging does not have the needed sensitivity and specificity for such clinical applications as establishing diagnoses or predicting treatment outcome.

A major obstacle to clinical applications of imaging is the small effect size of abnormalities. That is, the spatial resolution of the current tools is low in comparison to the signal size of the biological processes being measured. Anatomical variability additionally complicates imaging measurements, especially the biological variability within individuals who have the same DSM-defined syndromes. Further, the diagnostic specificity of findings has not been well established, and a variety of other non-specific factors (e.g., medication effects and a stressed environment) can impact measurements.

Investigators in the IRP and elsewhere are attempting to increase imaging sensitivity. Higher field strength MRIs will increase the resolution of some volumetric measures. In addition, an MRI-based technique involving arterial spin labeling is being used to measure quantitatively cerebral blood flow at high resolution. NIMH has purchased one of the new generation PET cameras that doubles spatial resolution and quadruples volumetric resolution. In addition, multivariate statistical models are being applied to increase the sensitivity for detecting pattern differences. This approach has great promise for improving diagnostic specificity and sensitivity.

To further expand capabilities, a new radiochemistry laboratory was built within the NIMH to generate novel PET radioligands (radioactively labeled molecules that can be used to measure specific chemical receptors in the brain) that can be widely disseminated and show promise with respect to encouraging new discoveries and helping characterize existing abnormalities in psychiatric disorders. One example of novel radioligand developed at NIH by Dr. William Eckelman's laboratory is [18F]TZTP–a marker for the muscarinic type II cholinergic receptors (one of several receptor types that bind to the chemical transmitter, acetylcholine)–which led to the discovery that the binding to these receptors was abnormally reduced during the depressed phase of bipolar disorder. This reduction was specifically located in the anterior cingulate cortex, a region known to play a major role in modulating emotional behavior. Notably, a mutation in the gene for the muscarinic M2 receptor was recently associated with increased risk for developing depression. Investigators at the IRP are now measuring this mutation in all participants studied with [18F]TZTP imaging in order to learn more about how this mutation relates to these images. The M2 antagonist, procainamide, can produce dysphoria, anxiety, and euphoria in healthy humans. It additionally activates metabolism in the same area of the cingulate where abnormal TZTP binding is found among persons with bipolar disorder.

Studies of patients with mood disorders are also underway at the NIMH to assess the relationships between abnormal serotonin 1A receptor binding and other neuroreceptor or neuroendocrine abnormalities associated with depression . Studies with experimental animals have already found

that this receptor system interacts with both the serotonin transporter system and the benzodiazepine receptor system, so PET studies in which both the serotonin 5-HT1A receptor and the benzodiazepine receptor are measured have been initiated. Moreover, although antidepressant drugs do not normalize the abnormal 5-HT1A receptor binding in depression, lithium, in preclinical models, seems to normalize binding, so bipolar patients are undergoing PET-serotonin 1A receptor imaging both before and after lithium treatment to see whether this effect also extends to humans. A range of other IRP studies is examining the influence of hormones known to influence the serotonin 1A receptor system in experimental animals, such as cortisol and the gonadal steroids, estrogen and progesterone.

Dr. Drevets summarized the results of imaging studies of brain metabolism and structure, which have illuminated where abnormalities exist in the brain circuits that are known from other types of evidence to modulate emotional behavior. In a very complex relationship, increased metabolic activity and CBF are found in some structures, such as the amygdala, the orbital cortex, and the medial thalamus, but activity appears reduced in other structures, such as the area of the ventral anterior cingulate located beneath the genu of the corpus callosum. The abnormal glucose utilization in these regions is particularly noteworthy because about 80 percent of the PET signal for glucose metabolism is thought to be accounted for by transmission of the excitatory amino acid transmitter, glutamate. Studies in experimental animals have found that repeated stress over several weeks sustains tonic activation of glutamatergic systems and this effect interacts with the elevation of glucocorticoid hormone secretion induced by stress to "reshape" the regions that are modulating emotional expression. This reshaping process is seen as a shrinkage or atrophy of the dendritic tree of pyramidal neurons. This debranching of the dendritic tree could potentially explain the reduction in gray matter seen in anatomical MRI and postmortem human studies of depressed participants with cellular changes compatible with dendritic reshaping (e.g., loss of synapses). Thus, the elevation of glutamatergic activity in the presence of too much cortisol that is evident in depression may be related to the development of the reductions in tissue volume seen in depression.

The Neuroimaging Section also is actively involved in applying another, more dynamic imaging technique–fMRI–to study the modulation of emotional processing. These studies are specifically assessing the reciprocal interactions between the amygdala and prefrontal cortex systems, which modulate or inhibit many aspects of emotional behavior. These interactions appear highly relevant to the development of major depression, as the more active the amygdala becomes during a depressive episode, the more depressive symptoms the patient displays. Studies of experimental animals also illustrate how amygdala activity organizes emotional behavior. The amygdala receives input from all sensory systems and is involved in assigning emotional significance to these sensory or social stimuli. It also organizes the emotional response by driving the endocrine, autonomic, and behavioral responses to behaviorally salient stimuli. For example, one function of the amygdala is to mediate the stressed component of cortisol release by stimulating corticotrophin-releasing hormone. This hormone not only acts on the pituitary gland as part of the axis that ultimately affects cortisol release but also exerts neurotransmitter-like effects in the brain that cause feelings of anxiety, insomnia, decreased feeding, and decreased sexual activity. Notably, older studies performed in humans during neurosurgical operations had shown that electrical stimulation of the amygdala produces the experiences of anxiety, fear, or dysphoria, all

of which are commonly seen in patients with major depression. In addition, the amygdala stimulates autonomic and "fight, fright, or flight" behavioral responses through its projections to the lateral hypothalamus and the dorsolateral columns of the pariaqueductal gray region. Finally, the social withdrawal and isolation that are commonly features of depression can be imitated in experimental animals by stimulating the amygdala's projection to the ventrolateral column of the periaqueductal gray region.

Dr. Drevets noted that a variety of different symptoms in the depressive syndrome are potentially accounted for by an overactive amygdala that drives emotional behavior. The prefrontal regions described above (orbital cortex, ventrolateral prefrontal cortex) that are affected by reductions in tissue volume are known to modulate emotional expression via the anatomical projections they send to the amygdala, hypothalamus, and periaqueductal grey. Consistent with these roles, the orbital cortex and ventrolateral prefrontal cortex are activated in depression, and the extent of their activity shows an inverse relationship to depression severity. However, the findings that these regions show losses in tissue, cells, and synapses in postmortem and MRI studies of depression suggest that the function of these emotion-regulating systems is disturbed in patients with major depression. Consistent with this hypothesis, the MRI studies of Dr. Ranga Krishnan and his colleagues at Duke University have shown that patients who develop cerebrovascular disease involving the orbital cortex are at particularly high risk for developing depression.

The Neuroimaging Section at NIMH has built its fMRI program around a number of well-characterized cognitive tasks that have been studied in neuropsychological studies of depressed patients. These neurocognitive tasks are now being presented as participants undergo fMRI scanning to assess anatomical correlates–particularly in prefrontal cortical-limbic interactions–of such brain processing among participants with depression. These studies specifically address how alterations in brain processing underlie the attentional biases toward sad stimuli, impaired responses to monetary incentives, catastrophic responses to perceived failure, and impaired habituation to sad stimuli. Such knowledge is expected to provide understanding of brain processes that account for common depressive symptoms such as persistent negative and self-depreciating thoughts, loss of motivation, and inability to enjoy pleasurable activities. The effects of antidepressants, cortisol, cholinergic manipulations, and monoamine manipulation on performance of these tasks also are being examined to understand how the deficits in neurotransmitter function that have previously been found in depression may relate to depressive thought and emotion and how antidepressant drugs, which compensate for these deficits, are able to partly normalize such processes.

Finally, the Neuroimaging Section is beginning to study the clinical impact of some of these structural changes in mood disorders on the longitudinal course and outcome of depression and whether better treatments can be found to modulate identified abnormalities. Among the noteworthy finding are:

- Volumetric changes are not essential for developing major depression but are specific to some mood disorder subtypes.
- Volumetric abnormalities are not a sufficient explanation for the presence of the major depressive symptoms because these may persist in remission.

- Volumetric changes can be reversed with such mood stabilizers as lithium and divalproex.
- Among affected cortical areas that modulate emotional expression and experience are the orbital/ventrolateral PFC, the left ventral anterior cingulated, the dorsal anterolateral/ dorsomedial PFC, the ventral striatum, and the amygdala.

To address the observation that the severity of recurrent depressive illness worsens over time and this may be related to as yet unproven inherited, but correctable, vulnerabilities, Dr. Husseini Manji and his colleagues at NIMH have been studying the molecular effects of mood stabilizers and antidepressant drugs. It appears that the risk factors for depression that are related to excessively active glutamatergic and glucocorticoid circuits, as well as reductions in the brain-derived neurotropic factor (BDNF) that may endanger neurons, might be corrected by such available treatments as lithium and divalproex as well as such compounds used for neurodegenerative disorders as pramipexole. A recent longitudinal study involving a collaboration between NIMH scientists and researchers at Wayne State University demonstrated, for example, that lithium increases gray matter in the prefrontal cortex to an extent that is associated with clinical improvement.

In summary, recurrent, familial mood disorders appear to be associated with over-activity of the limbic structures that drive emotional expression and experience. The over-activity in these structures may partially result from disinhibition caused by dysfunction of the prefrontal cortical structures and neurotransmitter systems that normally modulate emotional behavior. Imaging provides important tools for characterizing these abnormalities and their consequences on brain function. It appears that clinically effective pharmacological treatments for depression may exert beneficial effects in depressed patients both by quieting limbic functioning (e.g., as seen by their ability to reduce amygdala activity) and by protecting or –and perhaps also in some cases by restoring–the function of some of the braking systems that normally modulate emotional behavior. Imaging also provides a way to relate a pattern of abnormalities to a person's genetic vulnerabilities and may ultimately be able to identify individuals who would benefit from early interventions to compensate for–or possibly correct–some of these abnormal processes.

Discussion

Dr. Gunnar, noting that children are not good at emotional regulation, asked why youngsters who are frequently subjected to stressors do not necessarily develop depression. When Dr. Drevets explained that the brain has built-in protective systems, Dr. Gunner opined that the same protective systems that save a young child from becoming depressed should not be overlooked in ascertaining why some adults show this same response pattern but are depressed.

BRIDGING AND TRANSFORMING SCIENCE, SERVICE, AND MORE

As background for presentations on the science-to-service cycle, Dr. Grayson Norquist recalled the 1999 Council workgroup report, "Bridging Science and Service," described a series of recommendations for increasing the relevance, speeding the development, and facilitating the utilization of research-based treatment and service interventions into both routine clinical practice and policies guiding local and national mental health service systems. To ensure that research

findings from more recent clinical trials are rapidly assimilated into practice, a stronger collaborative relationship has developed between NIMH–as well as NIDA and NIAAA–and the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Center for Mental Health Services (CMHS), which is charged with moving new knowledge about the effectiveness of treatment/prevention efforts into community-based service delivery systems.

Dr. Junius Gonzales, Chief of the Services Research and Clinical Epidemiology Branch, DSIR, elaborated on the emphasis that report placed on making mental health research useful and practical for all stakeholders and its recommendations that NIMH foster the integration and synthesis of the disparate research domains of efficacy, effectiveness, practices, and service systems into one coherent whole. He noted that recent years have witnessed tremendous growth and innovative changes in services research. Since 1999, NIMH has implemented 45 of the 49 recommendations from the Bridging report, including not only the large-scale clinical trials but also the development of new or enhanced mechanisms to encourage implementation of research findings in the real world. For example, an approved procedure now allows investigators who work with community-based partners on such efforts as State health policies to request expedited grant reviews and funding that meet real world timelines. Similarly, the Interventions and Practice Research Infrastructure Support Program (IP-RISP), which encourages partnerships between researchers and community-based users, has linked mental health care with criminal justice systems to improve inmate treatment and has also encouraged social service agencies to create a collaborative field research organization for traumatized children. The revamped and innovative centers that NIMH supports have yielded practical results, including a Georgia site that focuses on prevention programs for rural African American families and a center in Los Angeles that sets the research agenda through a participatory process with such community-based entities that serve minority populations as fire stations, schools, social service agencies, and supermarkets.

The NIMH has been partnering with CMHS/SAMHSA as shown by the release of two jointly issued RFAs that entailed collaborations with the National Association of State Mental Health Program Directors and helped nine grant-recipient States implement evidence-based practices (EBPs). These initial grantees have leveraged additional monies to continue this work, formed strong partnerships with researchers that were not previously in place, and are planning to collaborate on cross-State research projects. The DSIR has also participated in a larger, SAMHSA-led science-to-service initiative.

Transforming clinical research results into service delivery system practices is an NIMH priority. Among the potentially interacting impediments to implementation of even the most effective EBPs are problems with patient access and engagement, provider behavior and knowledge, the structure and climate of the organizations that deliver services, and such external factors as stigma and available financing. Additional barriers to providing the highest quality care to persons with mental disorders include a lack of input from policymakers, stakeholders, and consumers about relevant research needs as well as the lag time between release of research results and their practical implementation.

Ms. A. Kathryn Power, Director, CMHS, explained that the concept of mental health systems transformation–a broad-based approach to improving services that all SAMHSA components have adopted-stems from the President's New Freedom Commission on Mental Health. The Commission report, "Achieving the Promise: Transforming Mental Health Care in America," available at http://www.mentalhealthcommission.gov/reports/FinalReport/toc.html, envisions a future in which "everyone with a mental illness can recover, all mental illnesses can be prevented or cured, mental disorders are detected early, and anyone with a mental illness at any life stage has access to effective treatment and supports for living, working, learning, and participating fully in community life." CMHS, which is responsible for a service continuum that ranges from promoting mental health to preventing and treating mental disorders, is committed to realizing this vision by transforming the way mental health services are perceived, accessed, delivered, and financed. A transformed American mental health system will, according to the Commission report, focus on recovery, use evidence-based practices, implement comprehensive State mental health plans, and design and follow appropriate, individualized plans of care.

Several innovative strategies are involved in transforming any organization or system. Initially, small steps are needed to change core missions and make incremental improvements at a daily level. These must be followed by a series of exploratory, medium-level changes, such as the decision Ms. Power made as the Director of the Rhode Island Mental Health System that day treatment should be replaced by supported employment. This medium-level change pushed the boundaries of core competencies and created a new entity within the existing system. Larger jumps entail significant changes with new rules that leverage new ideas. One example of such a paradigm shift would be if CMHS decided to support only consumer-run services.

An initial investment in transformation begins with a broad inventory to establish a baseline understanding of what needs transformation. CMHS has inventoried its entire portfolio and matched the results against its six goals to ascertain whether transformation targets are being achieved. Essentially, the broad inventory was followed by a strategic assessment to evaluate how well proposed work aligns with the detailed vision that is guiding change. The three components required to transform the system–the golden triangle of systems change–are research, policies, and funding.

The science-to-services initiative is viewed as an integral part of the transformation and essential to rapid progress in moving science to services as well as in obtaining feedback from services to science. Significant opportunities exist for integrating a national mental health research agenda into mental health transformation efforts. The six goals that drive this transformation and directly impact CMHS activities are:

- All Americans understand that mental health is essential to overall health.
- Mental health care is consumer and family driven.
- Disparities in mental health services are eliminated.
- Early mental health screening, assessment, and referral to services are common practices.
- Excellent mental health care is delivered and research is accelerated.
- Technology is used to access mental health care and information.

Although CMHS focuses on service delivery and NIMH is primarily interested in research, the collaboration must be seamless, with each agency keeping the other informed about progress toward common goals. An effective science-to-service partnership requires that: (1) business be conducted in a different way; (2) all involved parties benefit from the activities that are undertaken jointly; (3) each member brings new ideas and resources to the table; (4) the process includes cooperation, collaboration, and prioritization; and (5) States play a key role in developing, improving, and maintaining the infrastructures for mental health service delivery systems as States are the transformation centers where publicly funded mental health systems assume responsibility for taking caring of people with serious mental illnesses.

SAMHSA has also undertaken several science-to-service transformation activities, including the allocation of $44 million in Mental Health Transformation Grants that will be initiated in FY 2005 if the President's proposed budget is approved. These grants will help States develop and implement comprehensive, target population-sensitive State Mental Health Plans that demonstrate how research findings can impact delivery systems. Another innovative FY 2005 SAMHSA initiative is the Strategic Prevention Framework (SPF) that empowers communities to identify and implement carefully targeted and effective substance abuse and mental health promotion activities as well as to undertake projects that prevent mental disorders and substance abuse. The selected States that will soon be awarded SPF grants are challenged to foster local collaborations of stakeholders and practitioners in a science-to-services cycle that transforms not only the mental health system but also all behavioral health.

In addition, CMHS has re-engineered the discretionary grant program so that all awards are made through four standard funding mechanisms that reflect the science-to-services initiative: infrastructure grants, best practices planning and implementation grants, service grants, and science-to-service grants. CMHS also is implementing the National Registry of Effective Programs and Practices (NREPP) that evaluates all submitted practices as either promising, effective, or models through a rigorous review of their research reliability, credibility, and outcomes. In addition, a panel of mental health experts (including providers, researchers, administrators, consumers, and families) identified a set of six evidence-based practices that should be embedded in comprehensive systems of care with the greatest promise of recovery. CMHS has developed corresponding toolkits to help States implement these critical EBPs that address: illness management and recovery, medication management approaches in psychiatry, Assertive Community Treatment (ACT), family psychoeducation, supported employment, and integrated treatment of co-occurring disorders. Implementation of the six EBPs is being evaluated through a contract with the Dartmouth Psychiatric Research and Training Center.

Recovery is another focus of the New Freedom Commission's report and CMHS's transformation activities. Again, the Commission envisions a future in which "... recovery will be the common, recognized outcome of mental health services, the stigma that surrounds mental illnesses will be reduced, and this, in turn, will reinforce the hope of recovery for every individual with a mental illness." In this context, recovery is seen as: (1) the process by which people are able to live, work, and participate fully in their communities; (2) the ability to live a full and productive life, despite a disability; (3) a reduction, and in some cases, a complete remission of symptoms; and (4) the ability of an individual to make important decisions affecting his/her own life.

To refine the definition of recovery and build a recovery research agenda, CMHS is convening a National Consensus Conference composed of researchers, policymakers, consumers, family members, other stakeholders, representatives of the Department of Education's Interagency Council on Disability Research, and NIMH staff members. One major item on the agenda will be deciding how to measure recovery–once it is defined. To assess how much a prevention and treatment system impacts and improves the lives of the individuals served, CMHS is developing a prototype report card with recovery measures that embody consumer values. NIMH has also expressed an interest in documenting how research and practices help improve people's lives.

Ms. Power concluded by noting that CMHS and NIMH are now collaborating on the science-to-services agenda that was initiated in 1999 and continued in the President's New Freedom Commission on Mental Health report. The high level of urgency given to the transformation process is exemplified in these two institutions' common focus on conducting appropriate, mental health-related research that is rapidly applied as evidence-based practices in community-based service delivery systems.

Discussion

Dr. Essock underscored the utility of the CMHS-produced tool kits that are based on NIMH-supported research and have been widely disseminated to enthusiastic recipients at the State level. The renewed CMHS/NIMH partnership is likely to have many powerful and positive impacts on the mental health service delivery system and individuals' lives.

To questions from Dr. Aguilar-Gaxiola about whether CMHS's efforts to emphasize the importance of recovery incorporate consumers' perspectives, Ms. Power responded that the majority of participants in the forthcoming series of consensus dialogues on recovery will be consumers and family members. These discussions will address concerns that the term "recovery" does not resonate the same way for children in the mental health system as for adults. Hence, part of the dialogue will pertain to agreements on appropriate and consistent language and will focus on recovery, resiliency, and healing. The discussions, which will also incorporate vigorous debates about the definition of recovery, are taking place throughout SAMHSA between representatives from the substance abuse and mental health fields.

PUBLIC COMMENT

Dr. Merry Bullock, Assistant Executive Director for Science at the American Psychological Association (APA), opened the public commentary by lauding the meeting presentations and thanking Dr. Insel for involving the APA and other scientific organizations in the recent NIMH reorganization process. Nonetheless, the APA has great concern about some of the means being adopted to accomplish the expressed intent to "harvest basic research for its applications to mental disorders." The APA, fearing that the reorganization could hinder scientists' abilities to conduct basic behavioral research, has two paramount concerns: a number of NIMH positions in basic behavioral research are vacant, and some have been shifted to other branches within the Institute. Also, there is a potential imbalance between the emphasis given to translational

research and the support for basic science research that ultimately, but not immediately, contributes to prevention, diagnosis, and treatment of mental disorders. Hence, the APA urges that all basic behavioral positions be filled as rapidly as possible and that funding for basic behavioral research remain a high priority even though APA is aware of the small anticipated increases in appropriations that can make such choices difficult. Continued fostering of this kind of research is especially important, especially in the face of recent activities, including an amendment adopted on the Floor of the U.S. House of Representatives that called for no more funding for two NIMH behavioral research grants.

Dr. Joan Zlotnik, Executive Director of the Institute for the Advancement of Social Work Research (IASWR), after praising the Institute's focus on translating research into real world settings, enhancing partnerships with CMHS and SAMHSA, and involving communities and individuals in developing the research agenda, remarked that a variety of professional groups as well as consumers need to be involved in these efforts. Unfortunately, no Council members are social work researchers even though this group has a critical interest in some of the envisioned workgroups, particularly those pertaining to clinical trials. Dr. Zlotnik also announced that IASWR is holding a December conference on psychosocial care in nursing homes. Given NIMH's growing attention to aging issues, she hoped that some Institute staff would participate and that the conference would generate relevant recommendations for future research in this area.

Dr. Anand Kumar, President of the American Association of Geriatric Psychiatry (AAGP), thanked Dr. Insel for initiating a research group on aging within the adult branch and broadening its focus from interventions to translational research. He concurred, nonetheless, with the observations made by the two Council workgroups chaired by Drs. Reynolds and Lieberman that NIMH support for aging research still lags behind the projected demographic need. The AAGP hopes that NIMH will continue to increase support for geriatric research to ensure that an aging population receives the programmatic support it deserves.

Dr. Darrel Regier, Director of Research at the American Psychiatric Association, commended NIMH's recent portfolio reviews at a time of limited resources, the focus on translating science into services, and the model NIH efforts to advance neuroscience at the Porter Research Center through collaborations among researchers from multiple Institutes. In fact, behavioral science might benefit from a similar cross-Institute approach coordinated by NIH's basic behavioral science directorate to encourage research on behavioral components of cardiovascular disease, cancer, and a range of other illnesses. With respect to public perceptions of mental illness and treatment risks, Dr. Regier noted that the recent FDA hearings reflected difficulties encountered in translating research findings into public policy, particularly when some groups still question the reality of mental disorders as well as the effectiveness of any treatment. Disseminating research data without careful attention to the dynamics of the public debate can be a dangerous and naive undertaking. To implement the transformations described by Ms. Power will require carefully focused efforts to communicate scientific findings to the Congress and the public. The APA has been trying to assist such efforts with press releases about study findings and analyses of such important projects as TADS. Finally, Dr. Regier volunteered the assistance of the APA's new Director of Minority National Affairs, Dr. Nell Primm, for any NIMH or Council workgroup that addresses the important issue of ethnic minority participant recruitment for the clinical trials.

ADJOURNMENT

After thanking each member of the public who spoke, the observers who attended, and Council members' wisdom, patience, and support for the Institute, Dr. Insel adjourned the 207th meeting of the NAMHC at 12:35 p.m. on September 21, 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