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NATIONAL INSTITUTE OF MENTAL HEALTH

National Advisory Mental Health Council

Minutes of the 208th Meeting

February 3-4, 2005

Minutes of the 208th Meeting of the National Advisory Mental Health Council

The National Advisory Mental Health Council (NAMHC) convened its 208th meeting in closed session for the purpose of reviewing grant applications at 10:00 a.m. on February 3, 2005, at the Neuroscience Center in Rockville, Maryland, and adjourned at approximately 3:30 p.m. *(see Appendix A: Review of Applications)*. The NAMHC (the Council) reconvened in open session at the same location from 4:05 p.m. to 5:15 p.m. and continued the open session on the following day, February 4, 2005, in Building 31, National Institutes of Health, Bethesda, Maryland, from 8:35 a.m. until adjournment at 12:35 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 meeting.

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

Sergio A. Aguilar-Gaxiola, M.D., Ph.D.
Jonathan D. Cohen, M.D., Ph.D.
Susan M. Essock, Ph.D.
Faye A. Gary, Ed.D., R.N.
Megan R. Gunnar, Ph.D.
Raquel E. Gur, M.D., Ph.D.
Martha E. Hellander, J.D.
Renata J. Henry
Peter J. Hollenbeck, Ph.D.
Ned H. Kalin, M.D.
Jeffrey A. Kelly, Ph.D.
Helena C. Kraemer, Ph.D.
Eric J. Nestler, M.D., Ph.D.
Charles F. Reynolds, III, M.D.
Peter Salovey, 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 Member Present at Closed and Open Policy Sessions:
Robert Freedman, M.D., Department of Veterans Affairs

Others Present at Open Policy Session:
Bernard Arons, National Development and Research Institutes, Inc.
William Benzing, Center for Scientific Review
Dan Blazer, American Association for Geriatric Psychiatry
Steven Breckler, American Psychological Association
Jane Browning, Learning Disabilities of America
Rosemary Chalk, The National Academies Board on Children, Youth, and Families
Francis S. Collins, M.D., Ph.D., National Human Genome Research Institute
Heather Cowley, Tourette Syndrome Association
Chris deVries, American Association for Geriatric Psychiatry
Chamberlain Diala, ABT Associates, Inc.

E. Aracelis Francis, Council on Social Work Education
Alan Friedman, Friedman and Associates
Hikmah Gardiner, Older Adult Consumer Mental Health Alliance
Irene Goldstein, Science Writer
Lee Grossman, Autism Society of America
Allan Kaplan, Academy for Eating Disorders
Alan Kraut, American Psychological Society
Dawn Leeks, Children and Adults with Attention-Deficit/Hyperactivity Disorder
Sue Levi-Pearl, Tourette Syndrome Association
Anne Michaels, National Foundation for Mental Health
Robert Nichols, Association for the Advancement of Psychology
Andrei Perlloni, Food and Drug Administration
Frances Randolph, D.P.H., Center for Mental Health Services, SAMHSA
Stephanie Reed, American Association for Geriatric Psychiatry
Darrel Regier, American Psychiatric Association
Michelle Rodriques, SRI, International
Mercedes Rubio, American Sociological Association
Marian Scheinholtz, American Occupational Therapy Association
Angela Sharpe, Consortium of Social Science Associations
Viviana Simon, Society for Women's Health Research
Barbara Solt, Institute for the Advancement of Social Work Research
Audrey Spolarich, Prader-Willi Syndrome Association USA
Karen Studwell, American Psychological Association
Audrey Anne Sukacz, Constella Group
Jane Tilly, The Alzheimer's Association
Marjorie Vanderbilt, American Association for Geriatric Psychiatry
Barbara Wanchisen, Federation of Behavioral, Psychological, and Cognitive Sciences
Richard Yanes, Clinical Social Work Federation
Joan Levy Zlotnik, Institute for the Advancement of Social Work Research

OPEN POLICY SESSION: CALL TO ORDER AND OPENING REMARKS

Thomas R. Insel, M.D., Director, NIMH, called the open session to order at 4:05 p.m.

NIH Public Access Policy

Dr. Insel announced the release of a new NIH public access policy (see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-022.html) that will make publications resulting from NIH-funded research available to the public in a way that provides ready, equal access to all at no cost. Within the 12-month period following acceptance for publication, NIH-funded investigators will be expected to submit a manuscript, resulting from NIH-funded studies, in its original form to PubMed Central, an electronic database maintained by the National Library of Medicine. The policy is intended to: (1) create a stable archive of peer-reviewed research publications resulting from NIH-funded research to ensure the permanent preservation of these vital published research findings; (2) secure a searchable compendium of these peer-reviewed research publications that NIH and its awardees can use to manage more efficiently and

understand better their research portfolios, monitor scientific productivity, and, ultimately, help set research priorities; and (3) make published results of NIH-funded research more readily accessible to the public, health care providers, educators, and scientists.

Discussion

Dr. Warren asked how compliance with the policy would be monitored. Dr. Insel responded that NIH staff will monitor journals and annual reports for papers submitted for publication. Dr. Warren commented that he had proposed that journals release their content electronically to all public libraries in the United States, with access closed for a period of time. Dr. Nestler questioned how the submission date would be determined, and Dr. Insel responded that the new policy will provide such details.

NIMH'S STRATEGIC PRIORITIES: COUNCIL DISCUSSION

Dr. Insel began by noting that despite a decelerating research budget, NIMH funds more grants than at any time in its history [i.e., more than 3,000 research project grants in fiscal year (FY) 2004]. It remains imperative, he said, that NIMH fund applications that have the greatest potential for impacting the prevention and treatment of mental and behavioral disorders. Typically, applications scoring up to the 10-12th percentiles will be funded, and those scoring up to the 20th percentile will be funded by priority (relevance to the mission of the Institute, traction for rapid research progress, and innovation). He cautioned that the budgets for each funded competing application will be closely evaluated with the goal of redirecting funds to support a wide array of studies.

Dr. Salovey urged that the priority-setting documents approved by the Council serve as the basis for determining funding priorities. He noted skepticism in the field about whether the priorities described in the documents reflect current NIMH priorities. Dr. Insel suggested that potential applicants consult NIMH staff and visit the NIMH Web site for statements about strategic research priority areas. Dr. Salovey stated that despite his reassurances to the contrary, many researchers believe that NIMH no longer funds basic behavioral science research that does not involve a clinical population or a neuroscience component and that fewer applications of that type are being submitted. He suggested communicating a clear, positive message to the scientific community and perhaps posting a statement on the Web site that NIMH continues to fund basic behavioral science research that does not involve patient populations or a neuroscience component. (*Note: Following the Council session, a statement was posted on the NIMH Web describing the Institute's commitment to supporting behavioral research. See* http://www.nimh.nih.gov/about/dirupdate_behavioralresearch.cfm.)

Several Council members commented on the need for a diversified research portfolio and for flexibility in funding decisions to enable support for truly innovative applications. Dr. Gary cautioned that restricted budgets may impact funding for new investigators and, in particular, investigators who may be new to the field of mental health and at institutions that have not been recipients of NIMH support in the past. Dr. Gunnar questioned the value of modular budgets in an environment where budget negotiations are routine for funding competing applications. She stressed the importance of adequate funding to provide the opportunity for any project to meet its

goals and avoid early submission of a competing renewal application. Dr. Wagner urged attention to perceptions in the field about a declining payline that might have a chilling effect on researchers entering the mental health field. She urged proactive efforts to encourage new investigators to pursue research in areas with critical need, including research on children.
Dr. Insel noted that many Institutes are struggling with these same issues and that in addition to setting strategic priorities, it is important to implement some best practices to promote, for example, new investigators in targeted research areas and to encourage researchers to continue to submit applications.

On the issue of priorities, Ms. Hellander urged more research on questions that relate to children with serious mental illnesses, especially those illnesses that begin in early childhood, so that children suffering with mental illnesses can realize their potential.

Dr. Reynolds asked if budget reductions for non-competing continuation applications had been considered, noting that about 80 percent of the Institute's research budget supports non-competing continuations. Dr. Insel replied that the Institute follows NIH policy and plans to maintain its initial commitment to non-competing continuation applications. Dr. Essock expressed support for targeted rather than across-the-board budget reductions, and she encouraged program staff to work with investigators to develop plans that do not result in underpowered studies.
Dr. Aguilar-Gaxiola concurred with the need for staff flexibility in negotiating budgets, in particular with new investigators, to avoid reductions that would significantly impact proposed work.

Regarding the possibility of limiting the number of awarded grants supporting any one principal investigator, Dr. Nestler commented that awards should be based on the quality and productivity of the science. Dr. Gur suggested reviewing the success of various training programs in developing researchers and considering a consolidation of training programs at institutions with multiple training programs and overlapping faculty. She observed the need for a critical number of trainees to maintain a viable training grant and that any reductions in training budgets must be made on a case-by-case basis. Dr. Kalin also supported the need for a critical mass of researchers at all levels and the need for continued support for those programs that are successful in developing trainees to become independent researchers.

Dr. Gary commented on the importance of access to research results by persons who have serious mental illnesses and their family members who typically do not read academic manuscripts and journals. She suggested funding a manuscript-abstracting project using a user-friendly format that would advance health literacy. Dr. Insel responded that some journals (e.g., *Annals of Internal Medicine*) publish abstracts written for the lay public on the Internet, although this is not a current practice of journals in the mental health field. Ms. Henry underscored the need for NIMH to engage in user-friendly communications with its stakeholders. In that regard, Dr. Freedman cited evidence of the success of NIMH's *Real Men Real Depression* public awareness program, and Dr. Insel announced plans for a user-friendly Web site that will be similar to *Alzheimer Research Forum* (see http://www.alzforum.org/home.asp) that will post information for researchers and families on schizophrenia and that will offer a forum for interactions between and among families and scientists.

CONCEPT CLEARANCE

Dr. Thomas Lehner, Chief, Genetic Basis of Mental Disorders Program, Office of Human Genetics and Genomic Resources, Division of Neuroscience and Basic Behavioral Science, NIMH, introduced a concept for clearance, "Deep Sequencing and Haplotype Profiling of Mental Disorders." Dr. Lehner explained that researchers have begun to desegregate the phenotypes and genetic components of mental disorders that have been studied over the last 15 years but that replications and functional models have been lacking due to limitations in the availability of large datasets and well-designed studies. New opportunities will arise from the completion of the Human Genome Project and from dramatically lower sequencing and genotyping costs. The nearly completed HapMap Project will provide data reduction tools to analyze complex genetic traits. However, large-scale studies remain expensive, and it is essential to control costs and maximize quality in these studies. Researchers in the proposed initiative will draw on the NIMH Human Genetics Data and Sample Repository, in which nine mental disorders are represented. The resource includes data, cell lines, and phenotypic information.

The research aims of this initiative are to identify disease and susceptibility genes in mental disorders using whole genome association designs and deep sequencing of large regions across the genome. These studies will apply innovative and novel sequencing and genotyping technologies together with novel analytical methods and bioinformatics tools. In order to minimize costs and maximize quality, a once-a-year receipt date for applications will be established. Diseases studied will include schizophrenia, depression, bipolar disorder, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, autism, and anorexia nervosa.

Discussion

Dr. Insel stated that new tools and resources soon will emerge that will change the field and permit rapid progress. Dr. Warren commended the concept, noting that for schizophrenia, candidate regions that have replicated multiple populations need to be resequenced. To Dr. Kalin's question regarding the quality of the diagnostic data, Dr. Steven Moldin responded that the data have been collected by NIMH-funded projects in recent years. The phenotyping aspects have been peer reviewed, and diagnoses have been made by leaders in the field of psychiatric genetics. To Ms. Hellander's question regarding how other genetics applications would fit this initiative, Dr. Stephen Foote explained that other large genetics applications fall outside the scope of this initiative and that NIMH is considering a once-a-year submission date for them also to enable comparisons in the review process.

Approval of the Concept

The Council voted unanimously to approve the concept.

SESSION RECESS

Dr. Insel recessed the initial session of the 208th meeting at 5:15 p.m. The Council reconvened the following morning on the main NIH campus in Bethesda, Maryland.

CALL TO ORDER/OPENING REMARKS

Dr. Insel called the open policy session to order at 8:35 a.m. Following Council members self-introductions, Dr. Insel introduced two new NIMH staff members, Dr. Andrea Beckel-Michener, Chief, Functional Neurogenomics Program, Division of Neuroscience and Basic Behavioral Science (DNBBS), and Dr. Jing Bao, Scientific Program Analyst, Adult Health and Behavioral Research Program, Division of Adult Translational Research and Treatment Development (DATR).

Approval of the Minutes for the Previous Council Meeting

The minutes of the September 20-21, 2004, Council meeting were adopted unanimously as amended.

DIRECTOR'S REPORT

In his Director's Report, Dr. Insel updated the Council on important recent issues and activities (see http://www.nimh.nih.gov/council/dirreportFeb05.pdf).

NIMH Reorganization

NIMH's reorganization (see http://www.nimh.nih.gov/researchfunding/reorganization.cfm) became effective on October 1, 2004, and was designed to create an environment that would exploit scientific breakthroughs, increase cross-disciplinary collaboration, and facilitate translation of basic science discoveries into new interventions. The Institute will maintain its Division of Neuroscience and Basic Behavioral Science (DNBBS) and Division of Services and Intervention Research (DSIR) and will add three new divisions—the Division of Adult Translational Research and Treatment Development (DATR), the Division of Pediatric Translational Research and Treatment Development (DPTR), and the Division of AIDS and Health and Behavior Research (DAHBR). The locus of several programs has shifted; for example, NIMH's basic behavioral research program now resides in programs across DNBBS, DATR, DPTR, and DAHBR. The Clinical Neuroscience Branch has moved to DATR in an effort to align research on elucidating the pathophysiology of mental disease more closely with translating these findings to clinical diagnosis, treatment, and prevention strategies. Dr. Insel expressed his appreciation for the effort of NIMH program staff in the reorganization, and he referenced the funding priority statements for each division that are now available on the NIMH Web site (see http://www.nimh.nih.gov/dnbbs/dnbbs.cfm for DNBBS; http://www.nimh.nih.gov/datr/datr.cfm for DATR; http://www.nimh.nih.gov/dptr/dptr.cfm for DPTR; http://www.nimh.nih.gov/dahbr/dahbr.cfm for DAHBR; and http://www.nimh.nih.gov/dsir/dsir.cfm for DSIR).

NIH-wide Issues

Dr. Insel explained that in recent years, NIH leadership has emphasized coordination and consistency among its 27 Institutes and Centers to identify major opportunities and gaps in biomedical research that no one Institute could undertake alone but rather could be addressed by

the NIH as a whole. Under the NIH Roadmap (see http://nihroadmap.nih.gov/index.asp), the most compelling research opportunities fall in three main areas: new pathways to discovery, research teams of the future, and re-engineering the clinical research enterprise. In terms of funding, NIMH allocates less than 1 percent of its research budget to the Roadmap but far more in terms of time and its accomplishments.

Turning to the Neuroscience Blueprint (see http://neuroscienceblueprint.nih.gov/), Dr. Insel described the initiative as an effort to accelerate the pace of neuroscience research across 15 NIH Institutes and Centers. In discussions spanning a year, NIMH, its partners, and extramural and intramural advisors have compiled a series of collaborative projects to develop new scientific resources and tools that would benefit all neuroscience research. Examples of FY2005 projects include building a neurobiology of disease course as a supplement to T32 grants in basic neuroscience and creating a more thorough inventory of databases and other resources available for studies of the nervous system.

Regarding new conflict-of-interest regulations, Dr. Insel noted that NIH is concerned about perceived and real conflicts of interest involving NIH employees and that the Department of Health and Human Services (DHHS) recently issued supplemental guidelines for the ethical conduct and financial disclosure requirements for its staff. That policy, published in the *Federal Register* with a request for comment by April 4, 2005 (see http://a257.g.akamaitech.net/7/257/2422/01jan20051800/edocket.access.gpo.gov/2005/pdf/05-2029.pdf), specifies additional procedural and substantive requirements related to outside activities, financial holdings, and awards for NIH employees and makes several changes to the Standards of Ethical Conduct for all DHHS employees. Dr. Zerhouni has stressed that NIH is working to balance its public health, mission-related need for public-private cooperation with the equally vital need of ensuring the public's trust in both the integrity and objectivity of findings and decisions coming out of the NIH.

Recent NIMH Public Outreach Activities

As a part of its public outreach effort, NIMH held a second Alliance for Research Progress meeting in January that convened patient advocates (see http://www.nimh.nih.gov/outreach/AllianceReport24Jan05.pdf). The meeting was structured to provide research updates and to continue the dialogue with patient and family advocacy groups on pressing needs in the mental health field.

The NIMH Outreach Partners Program (see http://www.nimh.nih.gov/outreach/partners/partners.cfm) is a nationwide initiative that enlists national and State organizations to help bridge the gap between research and clinical practice. These partners have an active role in disseminating the latest scientific findings, informing the public about mental disorders, alcoholism, and drug addiction, and reducing the stigma and discrimination associated with these illnesses. The National Institute on Drug Abuse (NIDA) and the Substance Abuse and Mental Health Services Administration's Center for Mental Health Services also have joined this program, which will host the annual meeting of representatives from 50 States and the District of Columbia on March 31to April 3, 2005, in Omaha, Nebraska.

In a continuing effort to educate the public about depression, NIMH is working with Caterpillar Inc. to raise awareness of depression among its employees and their family members. The company began the program in January 2005 using *Real Men Real Depression* posters, brochures, and fact sheets, and materials, which will be distributed to each of the company's business units in the United States, reaching more than 50,000 employees.

Recent NIMH Research Findings

Turning to recent research findings, Dr. Insel reported that it is clear that the synthesis of serotonin depends largely on the enzyme tryptophan hydroxylase. For decades, scientists have studied the enzyme and its gene in the peripheral system to find a link to the pathophysiology of depression. About 18 months ago, scientists discovered a brain-specific gene, TPH-2, which led to questions about whether the gene relates uniquely to depression. When a single nucleotide polymorphism is put into cells, the cells make serotonin at a rate less than the rate of a normal cell. The normal form of the enzyme makes serotonin, which is taken up normally in the synapse. Selective serotonin reuptake inhibitor (SSRI) drugs block the uptake, providing for more serotonin in the synapse. The variation prompts less serotonin to be released in the synapse, which may explain some individual variation in response to SSRIs. Dr. Marc Caron and colleagues at Duke found that of 87 elderly subjects with major depressive disorder, 9 had the variation; in a control group of 219, only 3 had the variation—and 2 of those had a family history of depression (see Zhang, X., Gainetdinov, R.R., Beaulieu, J.M., Sotnikova, T.D., Burch, L.H., Williams, R.B., Schwartz, D.A., Krishnan, K.R., and Caron, M.G. "Loss-of-Function Mutation in Tryptophan Hydroxylase-2 Identified in Unipolar Major Depression." *Neuron* 45(1):11-16, 2005). An intriguing aspect of that study was that patients with the polymorphism were either entirely resistant to SSRIs or required high doses and also that the variation was not found in a separate cohort of subjects with bipolar disorder. Although the study has not been replicated to date, the findings offer the possibility of a pathophysiological marker that might predict which patients will not respond to SSRIs when they experience depression.

Dr. Insel reported that investigators participating in a Conte Center collaboration (William E. Bunney, Principal Investigator) used DNA microarray technology to look at transcripts in postmortem human brain tissue of people with depression. The collaborators—University of Michigan, University of California, Davis, University of California, Irvine, and Stanford University—used samples from the Davis Gene Bank and conducted a broad sampling of the genome to find out which genes may be over- or under-expressed in specific brain areas. The investigators used gene ontology analysis, followed by real-time polymerase chain reaction (PCR), to do quantitative measures of each candidate gene. An important finding centered on the fibroblast growth factor (FGF); namely, there were two ligands and two receptors within this family that consistently were decreased in the cohort of patients with depressive disorder. Replication of the study with a different cohort found the same results, and validation was achieved using an independent method. The investigators also determined that FGF changes in expression were not secondary to SSRI treatment. These findings introduce a new, complex system for consideration in mental health research. The system, found in limbic structures, is decreased in major depressive disorder but thus far appears not to be decreased in bipolar disorder. Dr. Insel noted that the lack of relationship to medication suggests the critical importance of further investigation in this area. He commented on the developmental

implications, querying whether early stress or experience might prime this system over the life span.

NIMH Budget

Dr. Insel stated that in FY2005, NIMH will invest more than $1.4 billion in research, including $183 million in AIDS research, representing a 2.4 percent increase over the FY2004 budget. Since 1997, NIMH has funded substantially increasing numbers of grants–1,450 in 1997 to about 2,250 currently, an approximate 50 percent increase; however, the majority of funding supports non-competing continuation grants that extend 4 to 5 years. Although NIMH funds more grants than ever, the number of awards for new grants has decreased from 630 in FY2004 to 560 in FY2005. Dr. Insel commented that he anticipates the number of awards for both new and competing renewal grants to increase in FY2006.

While the overall budget has increased, the cost of grants has risen by approximately 30 percent since FY1998 as the number of grant applications has continued to increase. NIMH staff members have continued to negotiate budgets for each grant in an effort to fund a diverse research portfolio, preserve innovative grants, foster the success of new principal investigators, and set priorities according to the principles of relevance, traction, and innovation.

In Memoriam: Julius Axelrod

Dr. Insel remembered Dr. Julius Axelrod, a Nobel Laureate and NIMH researcher since 1955, who died in December 2004. Dr. Axelrod is well known for his work on brain chemistry in the early 1960s that led to modern-day treatments for depression and anxiety disorders. In 1970, Dr. Axelrod was awarded the Nobel Prize in Physiology or Medicine for his discoveries about how brain cells communicate with each other. He explained how neurotransmitters operate in the brain, forever altering the way modern antidepressant drugs are designed and laid the groundwork for the treatment of anxiety and depression. He also mentored and trained more than 70 scientists, many of whom went on to become leaders in brain research. He was a true leader in the field and will be greatly missed.

THE REPRESENTATION OF RACIAL AND ETHNIC MINORITIES IN NIMH RESEARCH: PARTICIPANTS, INVESTIGATORS, STAFF

Dr. Catherine Roca, Chief of Women's Programs, Office for Special Populations, NIMH, described NIH's biennial report to Congress to verify compliance with the policy of inclusion of women and minorities as subjects in clinical research. Dr. Roca stated that the Advisory Councils for all NIH Institutes are asked to review data collected over the prior 2 years and to vote whether the Institutes are in compliance with Federal policy.

NIH's definition of clinical research, Dr. Roca said, includes traditional clinical research, epidemiological and behavioral studies, and outcomes and services research. Dr. Roca also noted that the aggregate data are reported in two formats that reflect OMB 1977 and revised 1997 categories. When comparing FY 2003 and FY 2004 data on the old form, fewer protocols were reported and few changes were recorded, other than a decreased percentage of "unknowns"

for race and ethnicity resulting from improved efforts to obtain the data. For aggregate data on the new form, again, no significant substantive changes were evident across the 2-year reporting period, other than an increase in the number of protocols.

Turning to NIH's Phase III trials that involve experimental pharmacological and behavioral interventions for the prevention and treatment of disease, aggregate data using the old form show a slight rise in enrollment of African Americans, and new-form data show a large increase in African Americans, due to more African-American enrollment and also to inclusion of a contract study through the NIMH Intramural Research Program with Howard University that had not been tracked previously.

Council members unanimously voted their approval that NIMH clinical studies are in compliance with the inclusion policy.

Report on Clinical Trials Recruitment

Dr. Richard Nakamura, Deputy Director, NIMH, referring to the recent report of the Council Workgroup on Clinical Trials (see http://www.nimh.nih.gov/council/interventions_research.cfm), reported on a small planning meeting in January with Council members Ms. Henry and Drs. Aguilar-Gaxiola, Essock, Gary, Gunnar, and Reynolds to discuss potential strategies for future action in the areas of clinical research, training, and staffing.

Dr. Nakamura presented several options for a proactive approach in improving patient recruitment. Steps include empowering a new ethnic minority recruitment committee, under the direction of the NIMH Office for Special Populations, to evaluate the acceptability of any modifications to recruitment plans in those applications flagged for minority recruitment issues during peer review. Dr. Nakamura stressed that the recruitment of ethnic minority participants must be evaluated in the context of overall recruitment and that steps would be needed to address overall recruitment as well. Strategies would include a grant-by-grant review of initial recruitment plans and progress and a proactive approach to community engagement by institutions that engage in clinical research.

At the referenced January meeting, Drs. Ernest Marquez and Robert Mays of the NIMH Office for Special Populations presented information on the current status and progress on many of the recommendations contained in the 2001 Council document "Report on Racial/Ethnic Diversity in Research Training and Health Disparities Research" (see http://www.nimh.nih.gov/publicat/nimhdiversity.pdf). NIMH has one of the largest investments in research training overall and in training for minorities among NIH's 27 Institutes. Dr. Della Hann is leading an evaluation effort to produce detailed data on outcomes of specific training mechanisms. The number of R01 awards to minority scientists from FY 2002 to FY 2004 has shown significant growth among African American (26 percent) and Hispanic (39 percent) scientists, particularly compared to NIH overall (13 percent). Dr. Nakamura asserted that NIMH's efforts are making a difference. Other specific activities discussed at the meeting included progress of an NIMH-supported Hispanic scientist mentoring program initiated in 1998, an African-American mentoring program initiated last year that will have its first

mentoring meeting in March under the leadership of Drs. Anthony Strickland and Gail Wyatt, and progress towards a partnership among NIMH, the Morehouse School of Medicine, and the Carter Center to encourage mental health research training. Former Surgeon General Dr. David Satcher, the President of the Morehouse School of Medicine, will have a prominent role in the latter project.

Regarding staffing patterns at NIMH, Dr. Nakamura reported that over the past decade, the data show increasing percentages of minority personnel in both managerial and non-managerial positions, despite a reduction in the overall number of personnel. However, Dr. Nakamura commented that staffing at both the intramural and extramural programs is not satisfactorily diverse.

Dr. Nakamura concluded his comments by noting that the Institute is committed to effective inclusion of minority populations in its training program and that the evaluation effort to evaluate the effectiveness of these mechanisms will serve as a basis for discussion of future directions in this area.

Discussant Ms. Renata Henry, Director, Division of Substance Abuse and Mental Health, State of Delaware**,** stated that she fully endorsed the Council's approach to racial/ethnic minority recruitment and diversity. She noted that the overarching goal is to increase the participation of racial and ethnic minorities in clinical research.

Ms. Henry introduced the following recommendations on minority recruitment and diverity: (1) Develop data on NIMH's investments and outcomes in research and training for underrepresented racial and ethnic groups for presentation to the Council; (2) Council should consider sending a letter to NIH to encourage multi-Institute strategies that strengthen university-community relationships and shared resources; (3) Endorse the recommendations in the Council report "An Investment in America's Future: Racial/Ethnic Diversity in Mental Health Research Careers"; (4) Increase collaborations across and outside NIH concerning ways to increase racial and ethnic diversity in research; (5) Endorse the adoption of a human participant recruitment and retention policy designed to improve outcomes for all racial and ethnic group members, and encourage community engagement on clinical research as an NIH-wide effort, with the community engagement initiatives of NIMH as a model, and encourage changes in policy to monitor overall and minority recruitment/retention so that poorly performing projects receive early attention; (6) Develop definitions of what is meant by having "appropriate and on schedule" recruitment and retention outcomes, with the goal to promote broad representation of racial and ethnic groups and, on Phase III trials, to determine how to analyze ethnic/racial/gender differences; (7) Support regular review of the composition of institutional review boards (IRBs) and initial review groups (IRGs) to encourage diverse representation or experience in those processes; (8) Encourage support for mentoring efforts and clarification of the goals for mentoring activities; (9) Recognize NIMH's leadership in training, compared to other NIH Institutes; (10) Recommend that NIMH identify and be thoughtful about intended outcomes and what is measured; (11) Recognize that NIMH and NIH still have far to go and must use resources effectively to achieve change; (12) Coordinate efforts between NIMH's Office of Special Populations and NIH's Office of Equal Opportunity and Diversity Management, in addition to other collaborative possibilities that result in greater synergy; (13) Publicize

executive leader, scientific, and other employment opportunities at NIH and NIMH at the NIMH Web site; (14) Define the goals for staff recruitment; (15) Encourage partnerships between strong academic research organizations with heavy NIMH/NIH funding and institutions historically serving minority populations; and (16) Identify and involve key individuals (i.e., opinion leaders) who can influence others to become involved and help remove barriers, impediments, and obstacles to increased participation of underrepresented racial and ethnic group members in mental health research.

Discussion

Dr. Nestler noted that evaluation of overall and minority recruitment at the annual review for non-competing grants is a critical intervention. Dr. Hann stated that NIMH is reviewing a variety of options in a redesign of NIMH recruitment policies. A survey of best practices among other Institutes found, for example, that the National Institute of Heart, Lung, and Blood staff works with the investigator for any study that involves more than 150 study participants to identify realistic recruitment goals that then become part of the notice of award. Expectations are explicitly understood, and quarterly reports are required on recruitment milestones. If recruitment falls below 80 percent on any milestone, a process is invoked to help the investigator improve recruiting. If NIMH were to adopt this type of practice, program staff would closely monitor grants for recruitment and, if needed, work with investigators to put new recruitment strategies into place.

Dr. Aguilar-Gaxiola identified the need for an action plan that identified the NIMH components responsible for carrying out specific recruitment practices. He urged publishing and distributing the recommendations. He also urged NIMH to maintain momentum in moving the Council recommendations forward. Dr. Cohen emphasized that in addition to investigators accountability to NIMH, it will be important for NIMH to provide to investigators the tools they need to meet recruitment goals. A critical strategy would be to partner with institutions and provide resources locally to help investigators engage in outreach efforts. Dr. Kraemer pointed out that even with studies that include women and minorities, analytical methods assume no diversity among groups in terms of ethnicity or gender. She suggested asking research groups with minority and women representation to focus on diversity in order to understand interactions. Dr. Gunnar concurred that community relationships are essential to diversity in recruitment and that NIH can be instrumental in helping to forge them. She also noted that reporting to NIMH at non-competing renewal time on activities to promote minority recruitment will help to develop best practices. Dr. Kelly stated that other Institutes deal with these same issues. In order to meet or exceed minority recruitment goals in the AIDS area, for example, it has been critical to involve community stakeholders—the end users of the research—in project planning.

Dr. Salovey noted the encouraging increases in numbers of NIMH minority scientists and trainees. He suggested looking into programs such as the Robert Wood Johnson Foundation's Clinical Scholars, which trains physician researchers to conduct participatory, community-based, collaborative research and provides tools that foster more productive collaborations with community groups. Dr. Gur identified the need for universities to instruct on the specific skills involved in working with minority participants early on in an individual's training/career path.

She suggested that program directors in university settings convene to discuss effective strategies and skills needed in reaching minority study participants.

Ms. Henry urged Council members to encourage NIH to support multi-Institute strategies to increase diversity, and Dr. Insel recommended adding the Neuroscience Blueprint as a mechanism for focusing on diversity issues. Dr. Insel noted that this issue would be revisited at the May Council session.

GENOMICS AND MENTAL HEALTH

Dr. Francis Collins, Director, National Human Genome Research Institute (NHGRI)**,** detailed progress of the International HapMap Project (see http://www.hapmap.org/), which he described as having major implications for research into behavior and mental illnesses over the next few years. The Project, which is led by the NHGRI on behalf of 19 NIH Institutes, Centers, and Offices that contribute funding, will provide a powerful tool to identify the way in which the genome influences the risk of disease, including, for example, schizophrenia, bipolar disorder, diabetes, heart disease, cancer, and other conditions.

As background to the development of the HapMap Project, Dr. Collins noted that the Human Genome Project (HGP) (see http://www.genome.gov/10001772), which began in 1990, was officially completed in 2003 with the publication of the full sequence of the human genome. Data from the HGP is freely and publicly available. To coincide with the completion of the HGP, more than 600 scientists worldwide and from NIH were invited to provide input on a vision for the future of genomics. The resulting document (Collins, F.S., Green, E.D., Guttmacher, A.E., and Guyer, S.M. "A Vision for the Future of Genomics Research." *Nature* 422:835-847, 2003) has three major focus areas: the application of genomics to biology, to health, and to society. These themes are highlighted through a series of 15 "grand challenges."

Dr. Collins noted that real progress has been made in finding the genes involved in a number of (typically rare) single-gene Mendelian diseases. However, finding genes that contribute to complex illnesses, such as Alzheimer's disease, schizophrenia, manic depression, autism, diabetes, stroke, and others, will be more difficult to accomplish using the methods that have worked well for single-gene disorders. He noted that there has been frustratingly slow progress in this area, as documented in a report by Glazier and colleagues (see Glazier, A.M., Nadeau, J.H., and Aitman, T.J. "Finding Genes that Underlie Complex Traits." *Science* 298(5602):2345-2349, 2002) that summarized the data for genes identified for Mendelian or non-Mendelian traits. Despite the fact that more than 1,600 human Mendelian traits were identified at the deoxyribonucleic acid (DNA) level in 2002 (today more than 2,000 have been identified), just 7 genes underlying human complex traits were identified (today there are possibly 20). However, in 2002, the repertoire of research tools with sufficient power and resources were not in place to identify candidate genes effectively.

Today, research sits on the brink of a systematic way to survey the whole genome for specific variants associated with a disease, such as schizophrenia. Dr. Collins described a potential direct, but expensive, strategy to approach that goal, assuming that more than half of the genetic variation that contributes to common diseases arises from common variants. That is, it would be

possible to test all the single nucleotide polymorphisms (SNPs) to look for overrepresented SNPs in both affected and unaffected individuals, but the cost to produce 20 billion genotypes at a rate of $0.01 per genotype would be $200 million for each disease. Theoretically the process is a clean, straightforward–but cost-prohibitive–way to determine whether a common variant or set of common variants in the genome are associated with the disease. An alternative and more cost-effective approach would be to survey the entire genome, looking for specific variants (SNPs) that are associated with a disorder. In schizophrenia, a strong case could be made that at least a significant portion of the genetic variability that accounts for the illness would arise from common SNPs. By looking at SNP combinations and permutations in a stretch of DNA, assuming that the polymorphisms were independent, three SNP positions would produce eight specific chromosomal sequence patterns, or haplotypes. These specific SNPs would represent "tag SNPs". In a test of 100 people, two haplotypes will account for 96 percent of all the chromosome patterns present. Therefore, it would be necessary to test variation at only one of the three tag SNPs to determine whether a gene for schizophrenia is likely to be present. The utility of this approach depends on the extensiveness of the linkage disequilibrium: the average linkage disequilibrium in European and Asian samples is about 20 kilobases and in African samples it is about 13 or 14 kilobases. Approximately 60 common SNPs would be within 20 kilobases, which would break down into four or five common haplotypes to be analyzed. This represents a savings in time, effort, and cost. To construct information experimentally across the whole genome, one must test many chromosomes to identify the SNPs, assemble the observed patterns into haplotypes, and then choose carefully which tag SNPs to test.

The goal of the HapMap Project is to compare the genetic sequences of individuals around the world in order to enable the wise selection of tag SNPs and to capture information cost-effectively about whole genome variation for use in association studies. The HapMap Project aims to develop a map by October 2005 that covers 80-90 percent of the genome and is usable in all populations. The total budget is $135 million, of which several NIH Institutes are contributing $40 million. International partners include Japan, the United Kingdom, China, Nigeria, and Canada. NIH is managing the effort, which is ahead of schedule and under budget for the production of the original goals. All of the data generated by the project are being released into the public domain. In terms of the ethics-related considerations, an extensive community consultation process was conducted, and no clinical information has been collected for the anonymous samples. Two-hundred seventy samples from people of African, Asian, and European descent were collected and genotyped for the project. These samples are available as DNA or cell lines from the Coriell Cell Repository. Studies in additional populations are in the pilot phase.

In order to obtain a deep representation of variation across the genome, more SNPs were required than were available at the start of the HapMap Project in 2002. The sequencing centers derived more SNPs using various approaches, and the private sector donated or sold variant collections as well, resulting in a deep and rich catalogue of genetic variation. The total number of SNPs has risen to 9.5 million, many of which are common, easily validated, and usable. The experimental strategy for building the map involved participating centers dividing up the genome according to the capacity of each center. Each center uses a different genotyping platform, and quality control exercises using random data subjected to regenotyping with different platforms have resulted in error rates of less than 0.1 percent.

Phase I of the HapMap involved obtaining genotypes from a working SNP at 5 kilobase intervals across the genome; Phase II involves increasing the SNP density to one SNP every kilobase. The European samples in Phase I have been completed; Phase I for the African, Japanese, and Chinese samples will be finished in February 2005, and by spring/summer 2005, another several million SNPs will be added for all samples. In fall 2005, the HapMap will be complete with an identified SNP about every 600 base pairs. Dr. Collins stated that the identification of tag SNPs will improve as the depth of coverage of the HapMap samples increases; he anticipates being able to represent 80-90 percent of common variation with 250,000 SNPs in European or Asian samples and 400,000 SNPs in African samples.

Dr. Collins stated that the HapMap will accelerate a better understanding of the genetic variation underlying a variety of diseases, including mental illnesses. As an example, Dr. Collins referenced the work of Sefansson and colleagues who examined the role of the neuregulin (NRGI) gene in schizophrenia and found that defects in NRGI signaling may be implicated in schizophrenia (see Sefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., et al. "Neuregulin 1 and Susceptibility to Schizophrenia." *American Journal of Human Genetics* 71:877-892, 2002).

Another NIH-supported resource that is available to the scientific community is the Center for Inherited Disease Research (CIDR) (see http://www.cidr.jhmi.edu/), which provides genotyping and statistical genetics services to applicants through a competitive peer review process. Dr. Collins reported that NIMH investigators are frequent users of CIDR services.

A challenging aspect of the HapMap Project, according to Dr. Collins, is whole genome association analysis, which provides greater power than that associated with linkage studies. An example of this approach is work on myocardial infarction by Ozaki and colleagues, who, with 1,133 cases and 1,878 controls, tested almost 100,000 SNPs and found variants in the lymphotoxin-alpha gene with an odds ratio of 1.78 for myocardial infarction (see Ozaki, K., Ohnishi, Y., Iida, A., Sekine, A., Ramada, R., Rsunoda, T., Sato, H., Sato, H., Hori, M., Nakamura, Y., and Tanara, R. "Functional SNPs in the Lymphotoxin-α Gene That Are Associated with Susceptibility to Myocardial Infarction." *Nature Genetics* 32(4):650-654, 2002). Another example is work on Crohn's disease by Raelson et. al, which was presented at the November 2004 meeting of the American Society for Human Genetics. This work described findings on French Canadians who were affected with Crohn's, but whose parents were not. They tested 248,000 SNPs across the genome and found the two known associated genes plus 10 more loci with *p* values better than 10^{-6}. Some of these loci were deemed "drugable" targets. Dr. Collins asserted that this type of work could be critical for understanding schizophrenia, bipolar disorder, and other conditions, although caveats to this approach include: the need for very large, well-phenotyped clinical cohorts, improvement in statistical analysis methods, possible failure of association studies if multiple individually rare alleles underlie the disease rather than a major common variant, and sample stratification leading to false positives; and, although genetic analysis can narrow the susceptibility variant to a small interval, functional studies still will be needed.

Other projects that offer genomic opportunities include the ENCODE Project (Encyclopedia of DNA Elements), which is an effort to define the functional elements within the genome, and efforts to create the Human Genome Translation Toolbox, which will include databases, a Transcriptome Reference Set, and small molecules (see http://www.genome.gov/).

Dr. Collins concluded his presentation by noting that we live in exciting times when, over the next few years, scientists may uncover the hereditary factors involved in many common diseases. This understanding will lead to improved diagnoses and new approaches to treatments, as well as to possible changes in our health care delivery systems.

Discussion

Dr. Cohen stated that the HGP has been a source of inspiration for the neuroimaging community to work as a team, to share data, and to establish databases. He acknowledged the neuroimaging community's painful experience with false positives and the efforts to avoid the same problem in genetics, as well as the challenges of interpreting structural findings in functional terms. Dr. Collins replied that there is a need to increase contacts between disciplines, noting that overlaps exist with other nongenetic statistical dilemmas that will be useful to examine. Dr. Cohen suggested that sharing expertise and combining resources could benefit both fields.

Ms. Hellander noted her excitement about the potential payoffs of this work. Dr. Collins commented on the value of studying early onset cases, particularly those in which access to parents is possible to allow for a more in-depth analysis.

Dr. Warren questioned whether endophenotypes might be a better way to approach the work. He also asked about the widespread insertions and deletions in the human genome and the potential for impact on the HapMap. Dr. Collins urged collecting every kind of phenotype information possible about one's cases, including endophenotypes, and doing analyses of correlations. He stated that some interesting endophenotypes are associated with various mental illnesses. He expressed concern that geneticists may not collect adequate environmental exposure data, and he urged undertaking sophisticated environmental exposure studies in genetics work . Regarding work on large variants–for example, copy number polymorphisms–Dr. Collins indicated that it would be surprising if such a variation did not have some phenotypic consequences. He indicated an interest in seeing what degree of variation identified in the 270 HapMaps run through ROMA or a similar approach, correlates with SNP variation. He suggested that a more cost-effective approach is needed to look at copy number polymorphisms.

ACCELERATING THE DEVELOPMENT OF PET AND SPECT RADIOTRACERS FOR BRAIN IMAGING

Dr. Linda Brady, Chief, Molecular, Cellular, and Genomic Neuroscience Research Branch, DNBBS, NIMH, discussed NIMH's efforts to accelerate development of PET and SPECT radiotracers, which permit imaging of disease-related proteins, receptors, enzymes, and other signaling molecules within the human brain in order to accelerate basic research discoveries and speed translation into clinical research. Impediments have included a time-intensive and

laborious development process, difficulty in predicting *in vivo* properties in humans based on preclinical animal studies, uncertainty that the first radiotracer introduced in human studies will be adequate, and paucity of small molecule research tools. Roadblocks include the fact that while genomics and proteomics have led to increasing numbers of targets related to disease and disease processes, the targets are poorly characterized, there are delays in using radiotracers in humans, and there have been inconsistent regulations worldwide that have led to increased research abroad.

The Food and Drug Administration (FDA), in an effort to expedite the development of molecules for drugs and research tools, has issued the report "Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products." Dr. Brady noted that imaging agents are useful at each stage of the research process but that the number of imaging probes entering the pipeline and available for use at various stages is not keeping pace with the need to use them.

A Consortium for Safety Assessment of Radiotracers for Use in Research and Drug Discovery was convened with participants from NIH, academia, industry, and professional organizations. The consortium's long-term objectives are to enhance human subject safety in medical research and clinical trials; fill the clinical research toolbox with novel, useful radiotracers; accelerate discovery and validate PET and SPECT radiotracers by optimizing resource use; and advance both drug and device development through investigational imaging, while simultaneously managing risks to patients. Specific objectives of a January 2005 consortium meeting were to provide consolidated advice to assist in overcoming regulatory roadblocks; to optimize the use of resources required for radiation dosimetry, safety pharmacology, and chemical toxicology; and to provide imaging tools that will facilitate and accelerate the introduction of improved and novel treatment to serve unmet medical needs, with a focus on brain imaging and brain disorders.

Dr. Brady explained that the FDA and the European Agency for the Evaluation of Medicinal Products (EMEA/CPMP) have developed guidance documents regarding the development and safety of a wide range of imaging probes, but the guidance was designed for molecules intended to be developed into commercial products, rather than imaging ligands to be used as research tools. Participants at the consortium meeting explored potential alternatives to the current guidance documents that would be helpful in research settings and protect human subject safety, including the need to explore low dose studies and the safety assessment of low doses that are administered for a short period of time; a stratified approach that would be based on what is known about the compound class, the target site that it is being directed towards, and the safety margin on that particular ligand; and a proposal from the Pharmaceutical Research and Manufacturing Association for an exploratory Investigational New Drug (or IND) to accelerate the speed at which novel chemical entities go into first in human studies. Expertise at the consortium meeting covered the areas of clinical pharmacology, toxicology, and safety assessment.

Participants generally agreed that the safety risk for tracers is low but not negligible; the critical path for radiotracer development is not limited to first in human studies but extends to proof of concept and research uses of a radiotracer. There should be worldwide consistency in preclinical safety testing of tracers prior to first in human studies; pre-IND discussions with the FDA on the

safety package should be encouraged; and exploratory IND safety testing should be sufficient to identify real risks for low-mass radiotracer exposures in planned studies, not theoretical or extrapolated risks. A strategy for safety assessment for the chemical component of radiotracers should be that studies to support the safety profile of radiotracers should be phase appropriate and focused specifically on mechanistically related, medically meaningful risks. In addition, safety and regulatory needs should be balanced by doing the best science; the number of animals in investigations should be reduced; and science should be conducted to the highest standards and, to the degree possible, consistent with the overall views and scope of the guidance documents. Participants also agreed on the need for developing a flexible clinical design to allow identification of critical data that would permit investigators to make early go/no-go decisions useful in clinical research and in drug development. Regarding the safety assessment of the radioisotopic component, participants concluded that clinical safety and efficacy studies should be conducted prior to the human radiation dosimetry, which contradicts current guidelines. Only a single animal species would be needed; if no problems were identified, early assessment of clinical safety and efficacy would be followed by quantification of organ dosimetry in typical populations, with quantification in special populations only if indicated.

Outcomes of the meeting included a constructive set of recommendations aimed to accelerate radiotracer development in pathophysiological studies across a wide spectrum of diseases and disorders, as well as in the drug development process. Dr. Brady stated that NIMH's support for the consortium's recommendations, along with that of other Institutes and Centers, would be important and should be communicated to the FDA. The FDA is in the process of developing guidelines for an exploratory IND that covers radiotracers and new drugs. The consortium recommends that the FDA consider its recommendations in developing guidelines specifically for high-specificity/low-mass tracers. Dr. Brady noted that a spectrum of possible actions has been developed, including a letter to be developed by Council to the FDA, general endorsement of the consortium's recommendations, and publication of the consortium's proceedings in the journal of the Society of Non-Invasive Imaging in Drug Development, *Molecular Imaging and Biology*.

Discussion

Dr. Insel commented that the goal of Dr. Brady's and the consortium's efforts is to remove specific impediments to progress while protecting the safety of study participants. To Dr. Kalin's question about the timing of the publication of the recommendations, Dr. Brady responded that following an initial endorsement by NIMH, publication would take place in 4 to 6 weeks. Dr. Gunnar suggested the need for a developmental approach in the animal model, and Dr. Brady responded that the FDA currently is considering guidance for pediatric imaging and the safe use of tracers in pediatric populations. The consortium also recommends that the NIH Institutes invest effort to create probes with mass doses below the toxicological threshold. If radiation risks are very low, the probes might be more amenable for use in pediatric populations. There have been no developments regarding toxicology in young animals.

Council members concurred on the importance of the consortium's efforts and on the need to draft a letter to the FDA strongly supporting the consortium's recommendations.

SILVIO O. CONTE CENTERS FOR NEUROSCIENCE RESEARCH

Dr. Steven Zalcman, Chief, Clinical Neuroscience Research Branch, DNBBS, NIMH**,** stated that the clinical Silvio O. Conte Centers for the Neuroscience of Mental Disorders (see http://grants.nih.gov/grants/guide/pa-files/PAR-02-122.html) serve as a powerful catalyst in the productive, bidirectional movement of information in translating research from bench to bedside. Conceptualized in 1988, the primary goal of the centers is to support the integration and translation of basic and clinical neuroscience research on the etiology, pathophysiology, and pathogenesis of the major mental disorders, ultimately leading to improvements in the diagnosis, treatment, and prevention of mental disorders.

The centers' highly focused research programs usually build on a single mechanistic hypothesis using the latest in technological approaches. The programs facilitate the formation of collaborations between eminent basic and clinical scientists. Dr. Zalcman observed that the programs are geographically distributed and that the 15 centers' total cost exceeds $31 million a year, with each center capped at $1.5 million in direct costs. On average, each center has six projects and three cores. Nine centers focus on schizophrenia, five on mood/anxiety disorders, and one on suicide. The specific question being asked by each of these centers is largely non-overlapping, although complementary with the focus of other centers. The centers, with their 90-plus projects and 50-plus cores, provide an invaluable research infrastructure that is cost-effective (when compared the to the costs of individually funded projects), sets the standard for clinical neuroscience at NIMH, provides a mechanism to recruit new talent for team science regarding mental disorders, promotes improved treatment for patients based on the centers' preliminary work that allows discoveries of novel therapeutic candidates; and provides the potential for critical cross-center networking.

Dr. Laurie Nadler, Chief, Basic Neuroscience Centers Program, DNBBS, NIMH**,** explained that the main goal of the basic neuroscience centers is to support innovative, multidisciplinary, collaborative neuroscience research relevant to NIMH's mission to reduce the burden of mental illnesses. At the same time, the centers seek to attract leading researchers from various neuroscience disciplines in hopes that the centers' discoveries will have potential for translation to clinical applications. Both the basic and clinical centers bring together different research approaches, enjoy a high level of integration and synergy, offer opportunities for innovative, high-risk, and high-impact research with potential for fundamental scientific advances, and involve world-class scientists who are leaders of their fields.

The basic centers have two current program announcements, the Silvio O. Conte Centers for Neuroscience Research (see http://grants.nih.gov/grants/guide/pa-files/PAR-02-121.html) and Silvio O. Conte Centers to Develop Collaborative Neuroscience Research (see http://grants.nih.gov/grants/guide/pa-files/PAR-02-123.html). Seven basic neuroscience centers are funded at a total cost of $7 million, with a range of $600,000 to $1.7 million per center. The number of projects per center ranges from three to six, and the number of cores from zero to four. Dr. Nadler noted that the cost per project typically is less than that for an R01 of similar scope. The centers' research spans the breadth of neuroscience covered in DNBBS.

Value added by investment in the basic neuroscience centers is achieved by bringing together the best scientists to work as a team on problems unable to be addressed by individual research projects. Dr. Nadler identified several unique outcomes, including the discovery of a new role for the locus coeruleus in the modulation of cognitive control and study of the molecular mechanisms of synapse modification during learning.

Discussion

Dr. Kelly observed that in the AIDS area, centers do well with a relatively narrow thematic focus informed by many different perspectives and that the centers are good mechanisms for high-risk research projects.

PUBLIC COMMENT

Ms. Audrey Spolarich, Prader-Willi Syndrome Association, suggested that training in neuroimaging via telemedicine or collaborating with other Institutes might reduce NIMH's training costs, monies that might be redirected to support research on Prader-Willi Syndrome. Ms. Spolarich stated that she agreed with Ms. Hellander's comment about losing a generation of children, adding that they may be lost as a possible source of investigators. To avoid doing so, Ms. Spolarich suggested establishing a center for talented youth at the Conte centers, which would help with retention and recruitment and could motivate some children to become mental health scientists.

Ms. Hikmah Gardiner, Consumer Advocate and Advisory Board Member, American Association of Geriatric Psychiatry, urged Council members to support more research on elderly persons, especially on such topics as pharmacological interactions and Alzheimer's disease and to work toward making medicines affordable. In response, Dr. Reynolds thanked Ms. Gardiner for underscoring the critical public health need for research on older Americans who live with mental illnesses. He stated that NIMH is committed to supporting the necessary science to lead to more effective care of elderly people with depression and other illnesses.

Dr. Darrel Regier, American Psychiatric Association, stated that the recent controversy about SSRIs and a "black box" warning has drawn attention from a range of medical, consumer, and patient groups, which together have sponsored the Web site http://www.parentsmedguide.org . The Web site posts parents' and physicians' guides on the risks and benefits of using SSRIs in children and adolescents. He suggested conducting research to understand the difference between adverse event reports on suicidal ideation and attempts, in comparison with systematic reports that are obtained in clinical trials on those same issues. Dr. Regier asserted that the findings go in opposite directions, a fact that was not revealed in FDA's hearings; while adverse event self-reports show increased risk of suicidal ideation and attempts, the systematic reports show no difference. The real issue, he stated, is determining the signal that health professionals should be looking for when determining the risks of medications. He noted that parentsmedguide.org would be updated as new research information becomes available.

Ms. Sue Levi-Pearl, Tourette Syndrome Association, told Council members that the Association is conducting a minority outreach initiative to promote more involvement by minorities in the

organization. She added that the organization has funded neuroimaging and genetic initiatives for many years, having brought together two consortia of genetics and neuroimaging. The Association has developed a protocol and submitted it to the National Institute of Neurological Disorders and Stroke, which she expects to capitalize on the well-characterized phenotypical information in genetic studies and newer technologies.

Ms. Hellander stated that her perspective on the SSRI controversy is different from that of the advocacy organizations that have joined the APA. Many parents of children with bipolar disorder believe that clinical trials have been designed to exclude those children who may have genetic vulnerability to develop bipolar disorder and suicidal ideation and that the trials are not designed to separate out which subgroups of children are susceptible to suicide. Dr. Insel acknowledged the difficulties in distinguishing whether an adult or child who initially presents with depression is experiencing major depression or the beginnings of a bipolar disorder. He noted that that search for genes discussed by Dr. Collins and the imaging work presented by Dr. Brady will provide a valid way to distinguish between major depression and bipolar disorder.

ADJOURNMENT

Dr. Insel adjourned the 208th meeting of the NAMHC at 12:35 p.m. on February 4, 2005.

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

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Thomas R. Insel, M.D., Chairperson