



Minutes of the 199th NAMHC Meeting

January 25, 2002

The National Advisory Mental Health Council (NAMHC) convened its 199th meeting in closed session for the purpose of reviewing grant applications at 11:00 a.m. on January 24, 2002, in Conference Room C/D/E of the Neuroscience Center in Rockville, Maryland, and adjourned at approximately 5:30 p.m. (see Appendix A: Review of Applications). The NAMHC reconvened in open session at 8:00 a.m. on January 25, 2002, in Conference Room 6C10, Building 31, on the campus of the National Institutes of Health in Bethesda, Maryland. In accordance with Public Law 92-463, the policy meeting was open to the public until its adjournment at 1:50 p.m. Richard K. Nakamura, Ph.D., Acting Director, National Institute of Mental Health (NIMH), chaired the meeting.

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

Mary L. Durham, Ph.D.	<u>Chairperson</u>
Javier I. Escobar, M.D.	
Susan Folkman, Ph.D.	Richard K. Nakamura, M.D.
Henry A. Lester, Ph.D.	
Jeffrey A. Lieberman, M.D.	<u>Executive Secretary</u>
James L. McClelland, Ph.D.	
James P. McNulty	Jane A. Steinberg, Ph.D.
Charles B. Nemeroff, M.D., Ph.D.	
Elaine Sander-Bush, Ph.D.	
Edward Scolnick, M.D.	
Larry R. Squire, Ph.D.	
Ming T. Tsuang, M.D., Ph.D.	
Roy C. Wilson, M.D.	

Ex-Officio Council Members Present at Closed and/or Open Session:

Bernard Arons, M.D. (for Michael English, J.D.)
 Robert Freedman, M.D.
 E. Cameron Ritchie, M.D.

Special Consultants in Attendance:

Megan R. Gunnar, Ph.D.
 Norwood W. Knight-Richardson, M.D.
 Eric Nestler, M.D.

Guest Speakers at Policy Session:

Ruth L. Kirchstein, M.D., Acting Director, NIH
 Steven E. Hyman, M.D., Former NIMH Director, Provost Harvard University
 David Kupfer, M.D., University of Pittsburgh

Others Present at Open Policy Session:

Christine Acebo, Sleep Research Society
 Nancy Bateman, National Association of Social Workers
 Doreen Bell, National Depressive and Manic-Depressive Association
 Carol Bush, International Society of Psychiatric-Mental Health Nurses (ISPN)
 G. P. Daus, Asian and Pacific Islander American Health Forum
 Kenneth Davis, Mt. Sinai School of Medicine

Ranen Forzigen, J & J

Marilyn Goldstein, Treatment and Research Advancements Association for Personality Disorders (TARA)

Lee Grossman, Autism Society of America

Denyse Hicks, African American Women's Health Authority

Perry Hoffman, National Education Alliance for Borderline Personality Disorder (NEA-BPD)

Dottie Jeffries, American Psychoanalytic Association

Beth Kaplanek, Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD)

Alan Kraut, American Psychological Society

Monica Latham, American Public Health Association

Octavio Martinez, Harvard Medical School

Kathleen McCann, National Association of Psychiatric Health Systems

Kathy Michels, Fogarty International Center

Robert Nichols, Association for the Advancement of Psychology

William Northey, American Association for Marriage & Family Therapy

Dixianne Penney, National Education Alliance for Borderline Personality Disorder (NEA-BPD)

Valerie Porr, Treatment and Research Advancements Association for Personality Disorders (TARA)

Gordon Raley, National Mental Health Association

Stephanie Reed, American Association for Geriatric Psychiatry

Darrel Regier, American Psychiatric Association

Dawn Roscoe, National Mental Health Awareness Campaign

Fatema Salam, Academy for Educational Development (AED)

Angela Sharpe, Consortium of Society Science Associations

Nora Shehz, The Blue Sheet

Barbara Solt, Institute for the Advancement of Social Work Research

Karen Studwell, American Psychological Association

Laura Swanson, Council on Social Work Education

Barb Wanchisen, Federation of Behavioral, Psychological and Cognitive Sciences

Susan Weiss, National Mental Health Association

Jerry Weyrauch, Suicide Prevention Advocacy Network, USA

Ronita Wisniewski, Autism Society of America

Richard Yanes, Clinical Social Work Federation

OPEN POLICY SESSION: Call to Order/Opening Remarks

Richard K. Nakamura, Ph.D., Acting Director, NIMH, and Chairman, NAMHC, convened the open policy session of the 199th Council meeting at 8:00 a.m. on January 25, 2002, in Building 31, Conference Room 6C10, on the campus of the National Institutes of Health (NIH) in Bethesda, Maryland. Dr. Nakamura, after introducing himself and welcoming those present, remarked on the many changes since the previous NAMHC meeting in May 2001. The most significant events were the September terrorist attacks that temporarily halted all air flights and resulted in the cancellation of the fall Council session and the resignation in December of Dr. Steven Hyman as NIMH Director.

NIMH ACTING DIRECTOR'S REPORT

Dr. Nakamura began his formal report of NIMH activities by introducing three new Council members. Dr. Megan Gunnar, Professor of Child Development and Adjunct Professor of Adolescent Psychiatry at the Institute of Child Development at the University of Minnesota, is internationally recognized for her work in developmental physiology, infant and child development, parent and child relationships, and the psychobiology of stress. She is a leader in several organizations, including Zero To Three and the International Society for Infant Studies, has published extensively, and has received grant support from NIH, the National Science Foundation, and the MacArthur Foundation, as well as numerous awards.

Dr. Norwood Knight-Richardson, Medical Director of the CareMark Behavioral Health Services, was one of five private citizens invited by the White House to serve as part of the U.S. delegation to the World Health Organization's (WHO) annual World Health Assembly in Switzerland last May. He has served as Commissioner and Vice-Chair of the Texas Commission on Alcohol and Substance Abuse and is currently Adjunct Professor, Oregon Health Sciences University, and Clinical Associate Professor, Baylor College of Medicine in Houston, Texas.

Dr. Eric Nestler, Lou and Ellen McGinley Distinguished Professor and Chairman, Department of Psychiatry, University of Texas Southwestern Medical Center, is the author of several books and numerous articles on neurobiology and neuropharmacology and a member of many professional societies. Dr. Nestler also serves on the editorial boards for several

scientific journals. He was elected to the Institute of Medicine, National Academy of Sciences, in 1998 and has received extensive grant support from the NIH and elsewhere to study molecular neurobiology, pharmacology, and brain reactions.

Dr. Nakamura also thanked Dr. Bernard Arons, Director of the Center for Mental Health Services (CMHS), Substance Abuse and Mental Health Services Administration (SAMHSA), for attending the Council meeting as a substitute for Mr. Michael English, who recently had bypass surgery.

Elaborating on national reactions to the terrorist attacks on September 11, Dr. Nakamura noted that these events not only shocked citizens but also stimulated the country to reach out to the victims. Encouragingly, the public and elected officials recognized that the aftermath of such a disaster among policemen, emergency workers, and firemen might include symptoms of major mental illnesses, which were not shameful and would not diminish their roles as heroes. This response seems to reflect a real change in public understanding that mental disorders are health conditions requiring treatment and services, as is typical for other medical conditions.

Regarding Dr. Hyman's resignation as Director of NIMH after 5 1/2 years, Dr. Nakamura praised his accomplishments. He recalled Dr. Hyman not only as an exceptional scientist and clinician but also as a gifted spokesperson who brought greater recognition and respect to NIMH by interacting with the President, members of Congress, and constituency groups in very constructive ways. It will be difficult to find a replacement for Dr. Hyman; however, the Institute has strong leaders in both the extramural and intramural programs who will continue to direct a strong program of research. The Institute also maintains a solid infrastructure for long-term budgetary stability. Dr. Nakamura noted that a number of highly qualified individuals have expressed interest in the NIMH directorship and that he would not be a candidate.

Dr. Nakamura noted the upcoming resignation in February of Surgeon General Dr. David Satcher—a friend of the Institute with a primary interest in the mental health of the Nation. Dr. Satcher will become Director of the National Center for Primary Care at Morehouse School of Medicine, and Dr. Kenneth Moritsugu, Deputy Surgeon General, will serve as Acting Surgeon General until the President appoints a replacement.

Dr. Nakamura referenced Dr. Satcher's recent report "Mental Health: Culture, Race, and Ethnicity, A Supplement to Mental Health: A Report of the Surgeon General" (see <http://www.surgeongeneral.gov/library/mentalhealth/cre/>). Staff of NIMH worked with the Surgeon General and CMHS to prepare the report, which probes the mental health disparities affecting racial and ethnic minorities. The report stresses that mental illnesses are real and affect all of humanity, that effective treatments are available and should be used, and that persons with symptoms should seek help. The report also describes how American minorities often lack access to effective mental health services in their own communities. This disparity results, at least in part, from the stigma associated with mental illness—both among clinicians and others who treat mental illnesses and within the minority groups, especially among Asian Americans, African Americans, Hispanics, and American Indians. The report notes that "...mental health care disparities may also stem from minorities' historical and present day struggles with racism and discrimination, which affect their mental health and contribute to their lower economic, social, and political status. The cumulative weight and interplay of all barriers to care, not any single one alone, is likely responsible for mental health disparities." Finally, the report emphasizes that effective new treatments have been developed and should be available for *all* population groups.

Interesting lessons from investigations of mental illness among minority groups are also included in the report. For example, a study by Dr. William Vega found that Mexicans who immigrated to the United States within the last 10 years have had steadily increasing rates of mental illnesses across several categories. The prevalence of these disorders has now reached the same levels as those of non-Hispanic Caucasian Americans—at about twice the rate seen among Mexicans. Thus, members of an ethnic group may develop greater levels of mental illness after they come to this country. The environmental elements that affect rates of mental illness are not yet understood.

Dr. Nakamura continued his report of notable NIMH activities since the last Council meeting by recalling the joint celebration with the National Institute of Neurological Disorders and Stroke (NINDS) of 50 years of brain research and the fruitful collaboration between these institutes in recent years. The symposium featured sessions on "The Communicating Brain," "The Changing Brain," "The Vulnerable Brain," and "The Thinking, Feeling Brain," and Council members Drs. Edward Scolnick and Larry Squire were among the presenters. In addition, the meeting included a session "My View" where patients and advocates discussed how they had benefited from advances in brain research. The meeting also featured a panel of Nobel Laureates—Drs. Paul Greengard, The Rockefeller University; Eric Kandel, Columbia University College of Physicians and Surgeons; Stanley Prusiner, University of California, San Francisco; and Torsten Wiesel, The Rockefeller University. The panel was moderated by Leslie Stahl of CBS's "60 Minutes."

Dr. Nakamura commented on the availability of a new NIH educational loan repayment initiative for researchers who agree to

conduct clinical research (see <http://grants.nih.gov/grants/guide/2002/02.01.11/index.html>). The purpose of the program is the recruitment and retention of highly qualified health professionals as clinical investigators. This initiative may aid in attracting more clinicians in areas including health disparities, child health, and geriatric psychiatry. The program provides for the repayment of up to \$35,000 of the principal and interest of the educational loans of extramural grantees or awardees for each year of obligated service. Also, NIH covers the Federal taxes on the loan repayments, which are considered taxable income to program participants. About 25 NIMH loan repayment awards are planned for funding this year, and 50 are planned for funding next year. Further announcements will be available on the NIH Web site.

Dr. Nakamura reported that the first meeting of a new Interagency Autism Coordinating Committee (IACC) (see <http://www.nimh.nih.gov/events/interagencyautism.cfm>) demonstrated the successful collaboration of several institutes and agencies in an effort to conquer a devastating childhood illness. The Children's Health Act of 2000 (P.L. 106-310), Title I, Section 104, mandated the establishment of an IACC to coordinate autism research and other efforts within the Department of Health and Human Services (DHHS).

Dr. Nakamura also announced that NIMH has initiated an intramural research program with Howard University wherein scientists from both institutions will interact to stimulate and facilitate more research at Howard to ensure diversity in clinical trial opportunities. Dr. William Larson, Chairman of the Department of Psychiatry at Howard University, has been the primary contact person, and Dr. Dennis Charney of NIMH was responsible for establishing the contract.

With respect to staffing changes, Dr. Nakamura announced that Dr. Wayne Fenton will serve as NIMH Acting Deputy Director. Dr. Ernest Marquez, a training leader at the National Institute of General Medical Sciences (NIGMS)—the premiere training organization within NIH—has been recruited to fill the position of Director, Office for Special Populations (OSP). Dr. Carolyn Strete, formerly with the OSP, has joined the National Cancer Institute's training program. Dr. Kimberly Hoagwood, former Chair of the NIMH Child Consortium and Associate Director for Child and Adolescent Research, departed NIMH to direct New York State's children's programs and has been appointed as a Professor at Columbia University. A search to replace her is underway. Dr. Mark Chavez is now the Associate Director for Research Training in the Division for Mental Disorders, Behavior Research and AIDS (DMDBA). In the Division of Neuroscience and Basic Behavioral Science (DNBBS), Dr. Kathleen Anderson has been appointed leader of the Cognitive Neuroscience Program, and Dr. Margaret Grabb was recently hired to serve as the Chief of the Small Business Innovation Program. In the Division of Services and Intervention Research (DSIR), Dr. David Chambers is heading the Research Dissemination Program.

Several staff and Council members have recently received prestigious awards. Dr. Jeffrey Lieberman, a Council member, was elected to the Institute of Medicine, as was Dr. Leslie Ungerleider of NIMH. Council member Mr. James McNulty was elected President of the Board of Directors for the National Alliance for the Mentally Ill. Dr. Karen Babich from the NIMH Office of Science Policy and Program Planning was named Nurse of the Year for 2001 by the American Psychiatric Nurses Association. Dr. Ellen Stover was presented with the 2001 Presidential Rank Award for leadership within the Senior Executive Service.

Additionally, the NIMH Web site has received several acknowledgements for the high quality mental health information it provides. A study by the Rand Corporation that was published in the *Journal of the American Medical Association* gave the site highest marks for information accuracy and completeness, and the Tufts University Child and Family WebGuide awarded a five-star rating to the site for its child and adolescent mental health information. Dr. Nakamura acknowledged the significant contribution of NIMH staff members Misses Clarissa Wittenberg and Joan Abell in directing the successful Web site.

Finally, a search committee for a new NIMH Director has been formed and met once under the co-chairmanship of Drs. Claude L'Enfant and Francis Collins. The position will be advertised for an adequate time to ensure applicants that the search is fully open. Discussions with prominent members of the field suggest that several very strong candidates are interested.

Discussion

Dr. Bernard Arons commented that the Surgeon General's report on race, culture, and ethnicity is being used as a textbook for courses at many universities and medical centers to focus on an area that has not heretofore received sufficient attention. The actual production of the report required almost 2 years—to find the best available and relevant science and to make certain that the report's messages reflected Dr. Satcher's thinking.

NIH ACTING DIRECTOR'S REPORT

Dr. Ruth Kirschstein, NIH Acting Director, thanked the Council members for their services and remarked on the importance of their activities to ensure that NIMH's work is both scientifically accurate and reflects the public pulse. Since Congress specifies

the composition of each institute's advisory council, members represent a range of scientific expertise as well as leadership in the fields of public policy, law, health policy, economics, and management. Dr. Kirschstein expressed her confidence in Dr. Nakamura's leadership abilities to serve as Acting Director of NIMH.

Turning to newsworthy activities at NIH, Dr. Kirschstein recalled that Congress passed an appropriations bill for DHHS in December that provided NIH with a budget of \$23.5 billion. This action marked the fourth consecutive year of increases in the NIH research budget—a reflection of the commitment of the Congress, the Administration, and the American public to double the budget of NIH in 5 years (by FY 2003). NIMH was allocated \$1.2 billion.

Dr. Kirschstein reported that the events of September 11 have increased the NIH-wide focus to the potential physical and emotional toll of bioterrorism. This emphasis could significantly impact NIMH and the National Institute of Allergies and Infectious Diseases (NIAID). Certainly, the Health and Human Services (HHS) Secretary has and will continue to rely on NIMH to help with the fallout of emotional stress related to terrorism.

Other obvious changes resulting from September 11 relate to campus security. Since NIH is a premier biomedical research institution with a specialty in infectious diseases, it is also an attractive terrorist target. The heightened security at NIH emphasizes the protection of three priority groups: the very ill patients who often come from homes far from the NIH and bring their family members; the dedicated NIH employees who work on campus or elsewhere; and the research that must continue without interference.

NIH is a crucial part of DHHS, which became a center point for much of the post-September 11 activities. The Medical Emergency Service, which always has been called upon to help with such natural disasters as hurricanes or tornadoes, was sent to New York City. The U.S. Navy ship *Comfort* was mobilized and turned over to the Coast Guard and the Public Health Service to travel up New York Harbor and provide mental health and other services on board. The NIH Warren Grant Magnuson Clinical Center, which has remarkable microbiological services, performed much of the testing when the anthrax spores were first discovered.

Another important NIH activity has been the search for qualified persons to fill current vacancies in five important positions: the directorships of the NINDS, NIMH, National Institute on Alcohol Abuse and Alcoholism, National Institute on Drug Abuse, and the Office of Technology Transfer. Although not an institute, this latter office is very important for turning the various products of NIH-conducted or NIH-sponsored activities into materials that can benefit both the American public and the world. Dr. Kirschstein reported that the selection process is proceeding smoothly and that carefully selected search committees are already working to find highly qualified persons for all five positions. The NIH has a stable and dedicated workforce. Moreover, the turnover pattern of institute directors has remained the same since 1992. When Dr. Varmus directed NIH, he anticipated that superb institute directors would require about 5 years to accomplish their goals, although some would stay longer. Dr. Kirschstein noted that she held the position of NIGMS Director for 14 years.

Related to the appointment of a new NIH Director is the congressional requirement in the FY 2001 appropriations bill that the National Academy of Sciences (NAS) review NIH's organizational structure, which then consisted of 25 Institutes. Since the study was mandated after Dr. Varmus announced his intention to depart NIH, Dr. Kirschstein has argued that it would be a disservice to NIH and the next director to adhere to any restructuring recommended by the NAS prior to allowing the future NIH director the opportunity to review those recommendations. Hence, Congress has agreed that the Reorganization Report will not be due until 1 year after a new director has at least been nominated. Thus, the NAS has delayed initiation of the requested study, although Dr. Harold Shapiro, the former President of Princeton University and Chairman of the former National Bioethics Advisory Committee, has been asked to chair the upcoming review. While no one can predict whether or not this NAS study will lead to organizational changes, recommendations of previous studies have been taken seriously, and many have been implemented.

The other congressional activity of great importance to NIH—the controversial hearings on human embryonic stem cells—ended when the President agreed in his speech on August 9, 2001, to allow the use of Federal funds for important basic research on human embryonic stem cells. Since then, NIH has developed a series of implementation documents that are available on the Web site (see <http://www.nih.gov/news/stemcell/index.htm>). The first research awards in this area, which were supplementary awards to ongoing grants, were made in mid-January. Additional applications have been received and will soon be reviewed. While there is great hope that this promising technique will be viable, an enormous amount of basic biology must be learned about the individual cell lines. The sooner this information is gained, the more likely that next steps can be made toward the development of targeted therapies.

Dr. Andrew von Eschenbach was recently appointed Director of the National Cancer Institute (NCI). He came to NCI from the University of Texas M.D. Anderson Cancer Center in Houston, where he directed the Genitourinary Cancer Center and was

director of the Prostate Cancer Research Program. Also, HHS Secretary Tommy Thompson toured NIH in late August and plans to interact with all the agency heads on a regular basis. As already announced, Surgeon General Dr. Davidatcher will leave DHHS in mid-February. Dr. Kirschstein concluded by noting that all of NIH will miss the strong NIMH leadership provided by Dr. Hyman. He was a vital part of the NIH family and made many contributions to NIMH.

Discussion

To a question from Dr. Larry Squire about the process for selecting a new NIH Director, Dr. Kirschstein responded that although everyone looks forward to the appointment of a new director, a presidential appointment that requires Senate confirmation, the NIH continues to support a strong program of research.

FAREWELL TO NIMH

Before Dr. Hyman made his farewell remarks to Council, Dr. Henry Lester, NAMHC member, presented him with a plaque inscribed with a picture of the NIMH Advisory Council and a citation reading, "The National Advisory Mental Health Council is deeply appreciative of the wisdom, talent, and leadership that you have provided in advancing a robust and innovative program in mental health research and bringing mental health to the forefront of our national awareness." Dr. Lester added that, in the 2 years he has worked with him, Dr. Hyman was a role model for using intelligence and wit to accomplish worthwhile and lasting goals. First, he re-energized the NIMH staff and promoted an unmistakable rigor and sense of service to the research community. He functioned as a consummate scientist who could comfortably converse with clinicians about DSM-IV, talk with students about research, teach neuroscience, and exchange knowledge with scientists about the latest molecule that excites them. Additionally, Dr. Hyman, in collaboration with Dr. Gerald Fishbach and others, spearheaded the vision, planning, and building of the Porter Neuroscience Building on the NIH campus—an embodiment of the idea that mental health research is part of the unbreakable continuum of neuroscience.

To this accolade, Council member Mr. James McNulty added his appreciation for Dr. Hyman's ability to interact with the advocacy community at a very fundamental level. He cited the constituency outreach and education programs as examples of that commitment as well as the valuable meetings that Dr. Hyman held in various parts of the country. Dr. Nakamura then praised Dr. Hyman's emphasis on research ethics, noting that when some research projects came under attack, his reaction was not simply to defend them but to seriously question whether there were problems that needed to be addressed. Other important improvements were adding public members to scientific review committees and providing the opportunities for Council to be a more active advisory body to the Institute.

After expressing his appreciation for the compliments and plaque and pointing out that Dr. Nakamura was always a more efficient administrator than he had been, Dr. Hyman noted his appreciation for being invited back to address Council and his enormous warmth for the NIH and Dr. Kirschstein, whom he credited with convincing him to come to NIMH almost 6 years ago. Dr. Hyman recalled that when he had mentioned his plans to go to Harvard, his friend pointed out that "the road from peaks does not go up." The experience at NIMH, according to Dr. Hyman, had been an absolute peak. After more than 5 1/2 years, however, it was time to take stock of other aspects of his life, including his three young children who repeatedly asked why he was never home. The Provost position at Harvard is a wonderful job with very little associated travel.

While Dr. Hyman agreed with Dr. Kirschstein's observation that 5 years is about right, he noted that he did not feel he was moving on because he had accomplished what he had intended. In any vital organization, he said, an enormous amount of work always remains to be done. The real question is whether someone else should have the opportunity to infuse new ideas and energy with a more objective eye.

The most remarkable aspect of his tenure at NIMH, said Dr. Hyman, was that it coincided with a golden age for science and its support. Working with incredibly talented and dedicated colleagues at NIMH was another joy. While he appreciated the comments that he helped energize staff, Dr. Hyman felt that having reasonable expectations could unleash enormous potential. NIMH staff met many such demands and continued to improve the Institute's reputation and strengthen relationships with constituencies. The other significant accomplishment of staff and Council was to ensure that science—not politics—remained the center of NIMH daily activities. Council members have contributed greatly to this process. Additionally, the basic science portfolio at NIMH is remarkably strong compared to 5 or 6 years ago, and the Institute finds itself in a position of supporting robust basic science research applications that other Institutes are unable to fund.

Dr. Hyman stressed that much remains to be done. Although a comprehensive and up-to-date genetics program has been started, the science is difficult. The elusive genes that create risk for mental disorder still need to be discovered even though a strategy is in place for undertaking this complex task. Much also remains to be done in the translation of both neuroscience and behavioral science. This unfinished business will be around for a long time because the human brain is a very complex

structure, operating through a combination of bottom-up forces from genes and top-down forces related to development. NIMH faces a real challenge to integrate and move what is learned in basic science—from genomics, molecular and cellular science, human development, psychology, and other social sciences—into treatment and preventive programs that impact patients' lives. Moreover, because of the complexity of the brain and behavior, this field does not have simple diagnostic laboratory tests. Even recognizing the clinical entities for which treatments are being developed is a challenge. There is not only a genotype problem but also a phenotype problem.

A related issue is how to move new treatments into the real world. Just because a randomized controlled clinical trial has been conducted does not ensure that the results will be used. Even studying treatment effectiveness in broad populations and diverse real-world settings does not guarantee that new therapies will be disseminated with fidelity to the places where people seek care. Changing the behavior of health systems and clinicians remains a very difficult problem.

Training is another area of unfinished business. While NIMH has allocated considerable resources for minority training, the outcomes remain unsatisfactory. Further, the trend lines for new physicians entering serious independent research careers are most discouraging. More diversity is needed among the scientists entering the field of mental health research—not only with respect to ethnic and racial minorities but also in terms of the diverse skill sets needed to make progress.

Dr. Hyman concluded his remarks by stressing that he wanted to find ways to stay involved with NIMH in a helpful way. He looked forward to the opportunities to address the challenging problems ahead, and he thanked all for supporting his tenure at the Institute.

NIMH RESPONSE TO THE EVENTS OF SEPTEMBER 11

Dr. Farris Tuma, Chief of the Traumatic Stress Program in DMDBA, reported on the important role that NIMH played in translating research findings into implementation strategies following the events of September 11. Dr. Tuma recalled that, ironically, he and other staff members were organizing a scientific meeting about how data on behavioral and neurobiological responses to trauma might be used to develop and test early interventions that reduce the risk of mental illness when news of the September terrorist attacks was first reported. Since then, the Institute has been active on a number of fronts.

NIMH has a long history, beginning under the Alcohol, Drug Abuse and Mental Health Administration, of supporting research following natural disasters and human-caused emergencies that has allowed NIMH to provide some guidance regarding how to respond. NIMH quickly established communications with several agencies and departments that were mounting a mental health response on behalf of the Federal Government. This included briefings with the Secretary and others within DHHS as well as organizing and delivering educational information to the public and to clinicians and identifying clinical and training resources around the country. The intramural and extramural programs worked with a group of American and international research and clinical experts on violence, traumatic stress, and disasters to share knowledge with SAMHSA and other authorities in Maryland, Pennsylvania, DC, Virginia, and New York. After consultations with DHHS and NIH, useful information for the general public and clinicians who did not have trauma experience was posted on the NIMH Web site. In the 2-week period after the attacks, the Web site received approximately 60,000 hits for information.

The focus of early post-terrorist attack guidance fell into three areas. The first was helping the public to recognize that the widespread shock reactions for the vast majority of people in this country were normal and would dissipate with time. Secondly, practical advice was provided on how to reassure one another, particularly young children who needed to understand that responsible people were trying to make things as safe as possible. The third area was providing practical advice about seeking professional mental health care if problems persisted and interfered with the ability to continue daily activities. Guidance was provided about who was most at risk and might benefit from mental health services. Finally, information was disseminated about what is known about effective interventions for both acute and long-term mental health concerns. In sum, most of these were simple messages that widespread mental disorders were not anticipated and that reactions that many people were experiencing should not be over-pathologized. In fact, there is a risk of undermining normal recovery processes in some people by intervening too quickly or inappropriately. The more complicated message was that, based on prior research, unprecedented levels of mental illness, particularly in the most impacted communities, are anticipated and that effective care must be made available to those in need. It was rapidly evident that more research on the mental health ramifications of terrorism is needed and more needs to be learned about how to respond appropriately. More information is needed about the nature of the problems traumatized persons experience, the type of help that is needed, where it will be sought, and the capabilities of health care and human service systems to deliver effective care. The highest priority, however, must be placed on conducting such research with respect for issues of privacy, dignity, and sensitivity to the community so as to not impede the work of local service providers. Research following the Oklahoma City disaster found that post-traumatic reactions to large-scale trauma tend to be rapid, producing higher rates of anxiety and depression than those in response to other types of emergencies, including natural disasters. Nonetheless, people are resilient. The vast majority of those directly

exposed to the Oklahoma City bombing and to other kinds of disasters do not develop mental disorders.

Other important lessons have been learned. Beyond the immediate need for first aid, very practical assistance efforts (e.g., food and housing, supportive counseling and reassurance, resuming normal activities, having a meal with family members, and working out transportation needs) are most relevant to the vast majority of directly exposed persons. These efforts are not formal mental health interventions. Additionally, increased numbers of requests will be made for therapy and for medications to address troubling symptoms that most people experience.

More has also been learned about the nature of trauma-related anxiety and depression and about the treatment of these psychobiological disorders. Specifically, cognitive behavioral therapies that teach people coping skills—how to react differently to situations and to bodily sensations that trigger anxiety—coupled with medications that relieve sleep-related problems and other troubling symptoms can be very effective.

However, much of what is known comes from research on interpersonal violence and trauma or natural disasters. There is not yet adequate knowledge about the potential consequences of terrorist attacks like those of September 11 and how to mount adequate responses. More research is particularly needed on how various risk and protective factors impact the likelihood of adverse outcomes such as anxiety or depression after trauma. More also needs to be known about the neurobiological responses to traumatic stress. This knowledge will be key to developing effective interventions for all those who suffer. A better understanding of the content of interventions and the most appropriate timing for introducing either psychotherapy or medication is also needed.

Even as the Nation is struggling with recovery from September 11, NIMH has taken steps to foster more disaster research, recognizing that there is a public health need to learn from these tragedies and to be better prepared to assist those who need help after mass violence, wherever it occurs. Three approaches are being taken: (1) reactivating of the Rapid Assessment of Post-Impact Disaster (RAPID) grant program that facilitates research following an unforeseen event and has been used successfully in the past to learn from events like Oklahoma City (see <http://grants.nih.gov/grants/guide/notice-files/NOT-MH-01-012.html>); (2) providing supplemental funding for carefully selected and existing clinical research and epidemiological studies that could generate new information; and (3) adding questions to several nationwide cross-sectional surveys of health and mental health that might provide relevant information. To facilitate these activities, the Institute put together a multi-divisional interdisciplinary working group to review proposals for supplements to existing grants and applications for new research.

Immediately after September 11, the Institute had an enormous number of inquiries from mental health researchers and clinicians who wanted to do something and who were proposing a variety of activities. From this group, NIMH invited a number of applications for short-term studies intended to lay the foundation for longer-term data collection. These applications are under consideration for funding under the RAPID mechanism. The topics are varied, including the epidemiology of exposures in children and adolescents in the impacted communities as well as in the country as a whole. The services research applications relate to the settings where people present for care, as well as the health and mental health impact of bioterrorism and its threat. Other applications are being considered by the NIMH Center for Mental Health Research on AIDS through a similar fast turnaround process (see <http://grants2.nih.gov/grants/guide/pa-files/PA-99-132.html>). Although this area of research is taken very seriously, the Institute does not want to encourage or support any activity that would interfere with direct assistance efforts. Thus, any research under consideration must have direct linkages with local care activities.

Several enhancements to existing studies are underway. For example, one supplements a longitudinal study in New York that is examining psychopathology among a large number of Hispanic children and their families. The additional research will examine the pre- and post-attack effects on a wide variety of psychological and mental health problems, as well as educational and social variables within the sample. The possibility of looking at the risk associated with having a prior mental health disorder and subsequent trauma is most interesting. Other projects being considered focus on the impact of chronic threat and terrorism, the mechanisms by which trauma is linked to illness in children bereaved by the attacks, and whether the development of a chronic disorder after the attacks can be prevented in people who were already experiencing symptoms of mental illness.

Finally, NIMH is also supporting the addition of new research questions to a number of ongoing cross-sectional surveys, including a replication of the National Comorbidity Survey as well as the National Survey of African American Adults and Adolescents that collects information on mental disorders, impairments, and disabilities. Since a portion of this sample had been collected prior to September 11, it allows for interesting comparisons. Two other studies to which NIMH contributes that might shed light on this problem are the National Household Survey on Drug Abuse and the National Health Interview Survey, which collect information from large numbers of adults, children, and adolescents on an annual basis.

Discussion

Dr. E. Cameron Ritchie commented on the military's mental health response to the Pentagon attack and reported on a recent conference on mass violence and early intervention that was organized by the Department of Defense (DOD) in conjunction with NIMH, the Department of Veterans Affairs (VA), and other agencies. Three local military hospitals (Andrews Air Force, Bethesda Naval, and Walter Reed Army) immediately sent mental health clinicians to blanket the Pentagon crash site and the surrounding buildings where many people assigned to the Pentagon worked. These clinicians provided a variety of interventions that were tailored to the needs of the individuals, including critical incident stress management, supportive therapy, memorial services, working with the chaplains, and repairing the organizational fabric. Additionally, the Departments of Defense and Justice, the Federal Emergency Management Agency, and other agencies established a Family Assistance Center at the Sheraton Hotel in Crystal City that initially only served family members of Pentagon employees but soon expanded to include family members of the victims on the American Airlines flight that crashed into the Pentagon. Compared to the New York efforts, those at the Pentagon were simple because the Pentagon was a contained environment where all the issues could be coordinated (e.g., determining who could be volunteers and how agencies could collaborate in identifying persons with legitimate needs). Currently, the Center for Health Promotion and Disease Prevention is surveying everyone who was in the Pentagon that day to determine occupational exposure to smoke and fire and to assess mental health symptoms at the time.

For nearly a year before the September attacks, the DOD had planned for a conference on mass violence and early intervention that was to include the literature and best practice treatment guidelines. In the past, the standard response after a terrorist event, school shooting, or similar disaster had been a critical incident stress debriefing. However, the existing literature is equivocal about this response. The conclusions from this recent conference were that a number of components of early mental health intervention—supportive therapy, psychological first aid, the reunion of family members, and making sure that people are comfortable and that the environment is not toxic—should be used and not just one or two of them. After the conference recommendations are published, DOD will develop training packages to inform mental health practitioners and policymakers of the wide range of post-tragedy interventions that can positively impact mental health outcomes.

Dr. Arons described how CMHS, which is part of the Federal Government-wide apparatus that responds to national emergencies, has a special unit that helps communities mobilize responses to the mental and emotional impacts of disasters. The CMHS also conducts an annual training program on disasters for individuals from all States. Immediately after September 11, CMHS began helping various communities mobilize their responses. Each State was invited to send 5 to 10 representatives from substance abuse, mental health, and emergency response organizations to a meeting in New York City. Many of these representatives are continuing to work there. In summing up, Dr. Arons repeated the lessons of the terrorist attacks: symptoms do not necessarily indicate psychopathology, although some individuals do have prolonged and stressful reactions that should not be stigmatized. Further, the remarkable examples of heroism and resilience that are manifested at such times reestablish one's faith that the common bonds of humanity are more important than that which drives people apart.

Dr. Tuma added that another important result of the terrorist attacks was the reaffirmation of linkages among SAMHSA/CMHS, DOD, VA, the Department of Justice, and other agencies around common interests. Mobilizing this coordinated ability to help people has been a very positive outcome of these tragic experiences.

Dr. Mary Durham said that she was impressed with the comprehensiveness of the projects reviewed by Council that resulted from the RAPID program. Nonetheless, she was curious about whether, 5 months after September 11, this mechanism was sufficiently responsive to gather needed information and contribute to essential research. Dr. Tuma responded that this was a difficult question. On the one hand, there is a need to move quickly to address immediate needs. On the other hand, this difficult process involves many sensitivities and the potential for doing harm. In the context of a disaster where there is a great deal of chaos and disruption of normal activities, caution must be exercised in encouraging research activities.

Dr. Nakamura interjected that, with Council's assistance, NIMH will continue to explore options for speeding up research. He complimented Dr. Tuma and staff for reassuring New York State that investigators would not be allowed to disrupt the provision of other immediate services.

Dr. Robert Freedman reiterated that Colorado had a very similar experience after the Columbine shootings, discovering that researchers created resistance if they moved in too rapidly. He also echoed the observation that any pathology of real concern to mental health workers emerges slowly. Mental health services are most needed now, several years after the tragedy.

Dr. Ming Tsuang congratulated Dr. Tuma on his overview of the NIMH response but suggested that the Institute should have its own capability to take rapid action in response to this type of disaster that would be instigated by the Director's office. He also suggested that more emphasis should be placed on studying the protective factors that seem to increase resilience rather

than the pathological consequences of trauma. Post-traumatic reactions may be not only psychosocial but also neurobiological. Large-scale disasters offer an opportunity to study underlying resilience.

Dr. Charles Nemeroff added that it might be appropriate to appoint a small Council subgroup to work with Drs. Charney and Tuma and, perhaps, with other agencies to recommend ways to establish a rapid research response to disasters. He was particularly interested in data indicating that early intercession after trauma prevents the development of psychopathology over time. This phenomenon relates both to susceptibility and resilience. Although the NIMH response to September 11 was remarkable, a more formal mechanism may be needed for organizing a rapid reaction since, unfortunately, this may not have been the last of these kinds of events. He suggested that consideration might be given to an NIMH—or even an interagency—task force. Dr. Nakamura agreed that this was a good suggestion and promised to report on how this was progressing at the next Council session.

Dr. Ritchie interjected that more needs to be learned about how to conduct a needs assessment in the immediate aftermath of a disaster. Lessons could be learned from preventive medicine and public health colleagues about how to go in—not necessarily offering immediate interventions—to assess the situation and determine what kinds of short- and long-term interventions would likely be needed.

Dr. Lester added a few comments about the NIMH response to bioterrorism, reminding everyone of the important role that people's curiosity about drugs and toxins has played over the past 150 years in developing what is known about neuroscience as well as in creating very effective medications. In the 19th century, for example, Claude Bernard figured out how synaptic transmission works by studying curare, the South American Indian arrow poison. Later studies detailed the effects on the nervous system of morphine, nicotine, LSD, and deadly nightshade, a plant containing numerous belladonna alkaloids, most notably atropine. Even later discoveries about transmission hinged on the use of botulinum toxin. In addition, tetanus taught us a great deal about how nerve transmission works and studies of PCP (angel dust) illuminated much about the central nervous system. Some people think that the Salem witch trials were caused by an infestation of the wheat supply in the Massachusetts Bay Colony by ergot, a fungus, which has effects on the nervous system that are similar to those of LSD. Additionally, all of these drugs and toxins have helped produce medications impacting mental conditions, including the selective serotonin reuptake inhibitors (SSRIs) and the benzodiazepines, as well as anesthetics.

RESEARCH TRAINING IN PSYCHIATRY

Dr. David Kupfer, Thomas Detre Professor and Chairman of the Department of Psychiatry and Professor of Neuroscience at the University of Pittsburgh School of Medicine, reported on a major challenge facing the mental health field—an acute shortage of physician-trained clinical researchers. The number of physician-scientists engaged in the workforce has declined rapidly over the past 15 years, while funding for translational projects has increased and new scientific insights have proliferated. This period saw a 30 percent decline in medical school graduates who expressed an interest in a research career and a greater than 50 percent decrease in the number of M.D. postdoctoral trainees supported through NIH fellowships and training grants. These decreases also apply to the numbers of research fellows in psychiatry between 1992 and 2001. If this situation continues to worsen, the ability to leverage advances in basic neuroscience and behavioral science into improvements in public health will be stymied.

Some of the posited reasons for the decline in physician interest in research careers include an increasing proportion of students with large academic debt; the longer time needed to develop a research career; and a perception among physicians that they will not be competitive with Ph.D.s in obtaining grant support and becoming independent researchers. A number of special problems in psychiatry contribute to the lack of interest in research. Medical school instruction in psychiatry typically does not connect clinical psychiatry with relevant science or foster an interest in psychiatric research. Also, fewer research track options are available for individuals who enter specialty training in psychiatry. Finally, there are insufficient numbers of appropriate mentors in clinical psychiatry to encourage a research interest.

Many stakeholders are concerned with this problem, including Council members and NIMH staff, members of the American Psychiatric Association (APA), private foundations, industry representatives, organizations responsible for establishing standards for graduate medical education, faculty in departments of psychiatry, medical schools, and academic hospital centers, patients, and consumer advocates.

Recent efforts to address the training issue include a report by an American College of Neuropsychopharmacology study group, to be published by the *Archives of General Psychiatry*, that will likely stimulate discussion of such major issues as: How early in the pipeline should recruitment be addressed? How can a more diverse (with respect to gender, ethnicity, discipline, and geographic location) group of trainees be recruited to psychiatric research? At what points do nascent researchers lose enthusiasm and drop out from the research trajectory, and how can attrition be reduced? What strategies are needed to

ensure that highly qualified individuals compete for extramural support, including K awards? How can mentoring at all levels be increased? How can academic facilities support mentors?

In addition, the APA Council on Research met in May to begin joint planning efforts with NIMH for a workshop involving all essential organizations that train researchers and psychiatrists. The key stakeholders were convened in November at NIH to discuss strategies to enhance incentives for psychiatric research training. The meeting provided an overview of current NIMH research training activities, presentations relating to residency recruitment boards, and future strategies, including a proposed Institute of Medicine agenda. Four model programs for research training at Michigan, Yale, Columbia, and Pittsburgh were described to clarify issues that all academic departments confront in this arena.

- The R25 Residency Research Track Program at the University of Michigan is designed to attract psychiatry residents into research before their residency—as soon as they enter or early in their training. They participate in an extensive and extended research experience as part of their residency and postdoctoral training. The goals of the innovative Michigan program are to provide a sequenced educational experience that motivates psychiatry residents to pursue careers in mental health research; to integrate clinical experiences with research training; and to offer psychiatry residents a very structured research experience that enhances and broadens their skills for making significant contributions to mental health research.
- The Clinical Neuroscience Mental Health Research Training R25 Program at Yale University has a strong tradition of neuroscience training. The program attempts to engage medical students, graduate students, postdoctoral fellows, and psychiatry residents in translational clinical research activities through a didactic curriculum that entails a carefully structured and mentored year-long training experience and integrates basic and clinical neuroscience with clinical psychiatry. One impressive and potentially exportable innovation is an extensive interactive electronic syllabus that covers many facets of the curriculum.
- Columbia University uses a T32 training model to prepare both psychiatrists and psychologists for careers in clinical or basic research focused on major mental disorders. Each trainee is assigned a mentor/preceptor who is an established and productive clinical investigator. The didactic curriculum includes statistics, research design, and research ethics, as well as modern neuroscience research techniques. Participants also learn laboratory techniques through collaboration with a laboratory-based researcher. Many of the graduates have successfully developed independent investigations and received career development awards.
- The University of Pittsburgh Early Faculty Development Model also uses the R25 mechanism to develop junior faculty scholars by contributing up to 25 percent of their salary support and offering a choice of two curriculum tracks that are relevant to translational or intervention research. The major focus in this effort is mentorship, although some faculty members who have done extremely well in this program find it useful to interact with colleagues/peers who are going through similar experiences. Other features like infrastructure and flexibility are also important components of the program.

Dr. Kupfer noted that the next steps for resolving this recruitment challenge and training a new generation of psychiatric researchers have been depicted as the four "Cs": consensus building, complexity, communication, and continuity. To build consensus, a variety of organizations must learn to coordinate their efforts to significantly impact the field. However, the complexity of this problem in terms of the diversity of stakeholders is immense, and many obstacles will need to be overcome. Also, the stakeholders must be more communicative with each other and strive for continuity in the progress made. It will be critical to engage more relevant groups in the research-mentoring enterprise and to support those already actively participating, determining the specific and important roles for each. Dr. Kupfer noted that agreement must be found on the role for industry.

Next, Dr. Steven Zalcman, Chief of the Clinical Neuroscience Branch, DNBBS, described the actions that NIMH has taken to address the serious shortage of researchers in psychiatry. This problem, he reiterated, is evident well before graduate education, but NIMH can most profitably address the issue at the medical school stage by trying to influence career choices and foster a diverse group of trainees. The challenge is both to repair the pipeline leaks and to stabilize the mental health clinical research enterprise.

Toward these ends, NIMH staff has participated in a number of activities since the presentation on research training at the January 2001 Council meeting. The Institute cooperated with an effort by the American Association of Medical Colleges to assess the mentored and patient-oriented K awards. A meeting was held with the Psychiatry Residency Review Committee (RRC) to explore reconsideration of the existing clinical training requirements and their impact on research training of psychiatrists. Additionally, there were a number of other workshops and study groups. As a direct result of these activities and

with the full endorsement of Council and Dr. Nakamura, NIMH staff has been working diligently to conceive and implement a comprehensive array of appropriate initiatives to address the following issues: inadequate numbers of medical students choosing to enter psychiatry; inadequate numbers of psychiatrists pursuing careers in research; insufficient mentoring at all career stages with a specific gap noted at the postdoctoral to junior faculty transition point; and the scarce resources that are available in this managed care era to address these issues.

The following initiatives are already being put in place:

- For medical students, a T32 mechanism will add slots on competitively reviewed NIMH training grants for both summer and academic year mental health research experiences. This will be a very low-cost program, roughly \$5,000 per summer student, but could have a substantial impact over time on the largely decreasing percentage of top-tier medical students who are choosing to pursue training in psychiatry.
- For residents, fellows, and junior faculty, three strategies are addressing the issues of indebtedness, enhanced research training opportunities, and decreases in the time required for both clinical and research training. As noted earlier, NIH has initiated an extramural loan repayment program. The R25 mental health education grant program is being revised to focus more on patient-oriented research, be more flexible, increase allowable costs to more realistic levels, foster more creative applications from networks of investigators with existing research infrastructures (e.g., various groups of center directors), and encourage leveraging of R25 support to obtain additional unrestricted funds from non-governmental sources.
- The NIMH also has endorsed an Institute of Medicine (IOM) study of the clinical training requirements for psychiatric residencies in an attempt to shorten the current 48-month focus on core competencies and, perhaps, to dedicate 12 to 24 months to specialization areas determined by the expertise of individual training programs (e.g., child-adolescent consultation liaison, geriatric and inpatient psychiatry, psychotherapy research, and psychopharmacology). Such a change could have a salutary effect on recruiting residents into research by foreshortening their core training by 1 to 2 years.

Discussion

Dr. Jeffrey Lieberman, while impressed with the tangible steps taken to ameliorate the problem of psychiatrist researchers, said he worried about the pacing of further steps because of the problems mentioned by Dr. Kupfer. The RRC, he noted, has a key role in any changes; however, the RRC must be attentive to the needs of many disciplines. Since he opined that the IOM report would be a most persuasive document in that regard, Dr. Lieberman concluded that NIMH and Council should focus on making certain that the study gets carried out in the most useful way.

Dr. Tsuang agreed that the issues were complex but, based on his experiences with several NIMH-sponsored research training programs for clinicians at Harvard University, said that mentors play a key role. However, they are asked to do too much and simply do not have sufficient time. Mentors, he argued, require more support to allow them the required time to counsel trainees to pursue a research track.

Dr. Charles Nemeroff concurred with Dr. Tsuang's comments, saying he was optimistic about progress. Since the revised R25 mechanism will allow immediate support of mentors, there is no need to wait for the IOM report or for a change in policy of the RRC. He commented that the new chair of the RRC seems quite open to the proposed changes and that it would be important for NIMH to immediately establish a dialogue with the new leadership.

Dr. Eric Nestler reiterated the severity of the situation. While NIMH has received well-deserved budget increases in the last few years, and hopefully will continue to do so, there may not be sufficient experts in the field a few years from now to use those resources effectively unless emphasis is now placed on this critical issue.

Dr. Roy Wilson added that non-traditional approaches to the problems of diversity and training would have to be taken and suggested that mid-career individuals in both medicine and other professional groups who have clinical practice experience may need to be enlisted in research-oriented careers. These front-line clinicians become very important when evidence-based work is translated into actual practice.

Dr. Cameron Ritchie noted that the largest psychiatry training programs in the country are at the local Bethesda Naval and Walter Reed Army hospitals and suggested that more partnering with psychiatrists in the military might be considered. While these personnel do not require research grants because they are salaried, the idea merits "out-of-the-box" thinking.

Dr. Megan Gunnar found it unfortunate that medical schools are not traditionally linked with undergraduate education, which might engage students at an earlier point in their education. There should be mechanisms in various universities to link undergraduate education with the research being conducted in medical schools.

TREATMENT DEVELOPMENT WORKGROUP

Dr. Wayne Fenton, Acting Deputy Director of NIMH, reported on the activities of Council's Treatment Development Workgroup that Dr. Hyman initiated to review the Institute's investment in developing new treatments for mental illness, particularly schizophrenia and depression. This Workgroup has engaged in a number of activities since its formation last May, including a June meeting with other Institutes and Centers to look at their models of treatment development; a follow-up meeting in August to narrow the scope of the Workgroup's activities; and clearance of three related concepts in September. The first Request for Proposals (RFP) from this initiative was recently released (see <http://www.nimh.nih.gov/grants/indexcon.cfm>) and a meeting on depression treatment is scheduled for April 15, 2002. Over 30 experts with wide-ranging academic, industry, and regulatory perspectives have been enlisted in this endeavor including staff from each division within NIMH, other Institutes, and the field. Representatives from the Food and Drug Administration (FDA) have been important participants from the outset of these activities.

The focus of this Workgroup is crucial because a plateau seems to have been reached in the development of therapeutics; although efficacious new medications are available, there is considerable room for improvement. The Workgroup identified the major reason for the lack of further progress in the development of therapeutics: a stymied focus on the same molecular and clinical targets. That is, medication development has targeted dopamine receptors and serotonin and norepinephrine reuptake mechanisms and has not focused on fundamental new molecular targets. Valid new pathophysiologically relevant molecular targets are sorely needed.

Additionally, both NIMH and the FDA have tended to focus on DSM-diagnosed disorders as clinical targets. While the FDA registers medicines for treating broad syndromes, like depression and schizophrenia, clinicians focus on the symptom complexes within diagnostic categories. For example, antipsychotic medications will alleviate the symptoms of psychosis, whether it occurs in bipolar disorder, schizophrenia, or Alzheimer's disease. Psychopharmacology requires new clinical targets that dip below the level of DSM diagnosis to symptom dimensions like delusions, hallucinations, cognition, or anhedonia that are closer to pathophysiology.

However, NIMH is only one of a large group of organizations with an interest in developing new treatments and medications. In contrast to the top five pharmaceutical companies in the United States, the Institute's budget for treatment development represents a fraction of its total spending. This recognition has forced NIMH to examine the strengths and the competencies that public and private organizations offer in treatment development. Private industry, for example, has been successful in refining existing mechanisms, such as those underlying the five current SSRIs, each one earning the industry over \$1 billion a year. Pharmaceutical companies also have large combinatorial chemistry departments that can screen over a million new compounds against molecular targets in a period of weeks, and they have well-developed toxicology, kinetics, and manufacturing programs.

By contrast, the strength of the NIMH is its ability to take greater risks where there is less opportunity for an immediate commercial payoff. This includes supporting studies that focus on clinical pathophysiology, basic neuroscience, the search for new molecular targets, and developing better measures for clinical targets.

An observation from meetings with the FDA is that the research efforts of private industry are significantly influenced by FDA requirements. Since FDA maintains DSM syndromes as valid endpoints for clinical drug registration, pharmaceutical companies have no incentive to focus on symptoms or illness dimensions that are not DSM-oriented. While the FDA has no fundamental objection to looking at syndrome-based clinical targets, such as fever and pain, the agency firmly states that it "will not accept a new clinical endpoint for the convenience of any single drug company." The FDA has strongly encouraged NIMH to find a role in drug development that uses its convening authority as an independent scientific entity to bring together industry, academia, and regulatory agencies to define new and valid clinical endpoints.

The various divisions within the Institute have been assigned special roles in this effort. DMDBA will focus on activities that foster new clinical targets and measurement tools; DNBBBS and the intramural research program will concentrate on basic science activities that foster discovery of molecular targets, probes, and radiotracers; and proof-of-concept trials for new mechanisms and effectiveness trials will be conducted by DIRP and DSIR, respectively.

The goals for the measurement development groups are to dissect DSM diagnoses into symptoms and syndromes that are closer to pathophysiology, to take the lead in defining syndromal dimensions as important new clinical targets deserving of

recognition by the FDA for drug registration, and to develop valid measures of clinical treatment endpoints in the context of testing novel treatment strategies. If this work is successful and if the FDA embraces these targets, private industry will have an adequate incentive to focus billions of research dollars on more productive treatment development efforts targeting the new clinical endpoints.

In FYs 2002 and 2003, NIMH expects to have concepts approved for forming a measurement development workgroup on cognition and schizophrenia and another to refine assessment in affective disorders. The Institute also is in the beginning stages of establishing a treatment development network to focus on therapeutic approaches to cognition in schizophrenia.

Schizophrenia is one example of a complex DSM diagnosis that can be dissected into multiple dimensions, including delusions and hallucinations, anhedonia and blunted affect, disorganization, and thought disorders or cognitive impairment. All patients do not experience all of these symptoms. However, an examination of the relationship between patient outcomes and the various illness dimensions of schizophrenia shows that delusions and hallucinations are not good predictors of outcome, even though these are the clinical targets of this illness on which all current medications focus. By contrast, the best predictor of a functional outcome in schizophrenia is remediation of the cognitive impairment that is characteristic of the disease.

Because a more effective treatment for schizophrenia would have great public health benefit, NIMH wants to shift the focus in studies of this disease to cognition. A great deal of Institute-supported research is already focused on fundamental mechanisms of cognition in both animal and human models, and a variety of pharmacologic theories and models of cognition have been developed. At least a half-dozen good hypotheses have been posited for neurochemical systems that may be involved in modulating cognitive processes in the prefrontal cortex and in other neurocircuits. Although the field recognizes the importance of cognition in schizophrenia, and an increasing number of scientific articles focus on this topic, almost no human clinical trials have been conducted in this area. Essentially, there is a large gap in translational research that translates new models into treatments that target patients' symptoms.

To remedy this deficiency, NIMH has just released an RFP on cognition that asks for academic partners to join with the Institute in organizing and convening activities that pull regulatory industry and academic leaders together to define the most important aspects of cognition in schizophrenia and to reach some consensus regarding the best off-the-shelf measures for this condition (see <http://www.nimh.nih.gov/grants/synopNIMHDM020006.cfm>). This group could then propose recommendations to formulate a research agenda for developing new measures so that, in 5 years, the research community will be better positioned to look at cognition as a dependent variable in schizophrenia treatment trials. The partners will be asked to assist NIMH in designing and conducting a comprehensive survey to explore the feasibility of NIMH entering into agreements with pharmaceutical and biotechnology companies to obtain access to compounds and/or compound libraries with the aim of identifying new chemical entities of potential utility to enhance cognition in schizophrenia; developing a comprehensive list of lead compounds potentially accessible for government/industry collaborative development; defining approaches to management of intellectual property issues bearing on government/industry collaboration that would impact NIMH's ability to negotiate access to a compound for collaborative development and/or human clinical trials; and recommending a structure for effectively creating models to test agents for cognition and schizophrenia, including an initial translational proof-of-concept trial.

A similar situation exists with respect to depression measurement and the shifting paradigm of molecular targets for depression treatment. Among the promising leads are antagonists of substance P, antagonists of corticotropin releasing factor, melatonin receptor agonists, and trace amine receptors. Many of the current measures of depression, such as the Hamilton Rating Scale for Depression (HAM-D), are over 40 years old. Consequently, clinical trials often do not demonstrate that medication use is superior to placebo use. Additionally, the scales used to measure effectiveness are probably not sensitive to the new mechanisms. Moreover, although the effectiveness of antidepressant medications is determined by measurement scale(s), the four most common depression measurements do not overlap very well with one another. More specifically, the most commonly used depression measurement, the HAM-D, does not consider the cognitive aspect of depression as an important factor.

The upcoming meeting of the Depression Measurement Initiative is set for April 15 and 16. A group of experts, including FDA representatives, will be convened to examine the best available off-the-shelf tools for assessing depressive symptoms as a dependent variable in treatment trials. These experts also will recommend a research agenda for identifying and refining or creating better assessment tools for evaluating new mood disorder treatments. This will be a mechanism for fostering a new generation of measurement development in depression.

Five workgroups on depression measurement have been designated. One, led by Drs. David Kupfer and Charles Nemeroff, will look at the implications of biological findings for the measurement of depression. Dr. Ellen Frank is the leader for the group examining depression assessment outcome in psychotherapy—which raises interesting questions with respect to whether the

same measures are appropriate for psychosocial and pharmacologic treatment. Another workgroup, chaired by Dr. Karen Wagner, will address the developmental aspects of depression assessment and treatment trials for children and adolescents. A fourth workgroup will address assessment in pharmacotherapy trials for adults under the direction of Drs. A. John Rush and Charles Reynolds; and the fifth group, led by Dr. Jack Gorman, will consider assessment of anxiety as a treatment target in pharmacotherapy of depressive symptoms. In FY 2003, NIMH plans to concentrate on developing a cognition treatment network, establishing a mood disorders strategic initiative, and fostering the discovery of molecular targets, probes, and radiotracers for mental health research.

Discussion

Dr. Fenton introduced Dr. Dennis Charney, Chief of the Mood and Anxiety Disorders Research Program at the IRP, NIMH, who chairs the Council Workgroup on Treatment Development, and Dr. Kenneth Davis, Chairman of the Department of Psychiatry, Esther and Joseph Klingenstein Professor of Psychiatry, and Professor of Pharmacology at the Mount Sinai School of Medicine. Both Drs. Davis and Charney deferred further comments but offered to answer any questions.

Dr. Tsuang agreed that this is the right time to emphasize schizophrenia and mood disorders and stressed that recent trends in the literature show that these two disorders overlap in several dimensions, including descriptive and neurobiological perspectives. The main task for the field, in his opinion, is not just to study mood disorders but also to reassess whether the dichotomy as reflected in the DSM descriptive categorizations is correct.

Dr. McClelland asked whether this particular approach is necessarily the way to proceed for a disease like schizophrenia that, presumably, has some very deep underlying molecular causes that produce the immediate types of deficits that are the focus of current treatment and, in turn, contribute to the functional deficit that is observed on the surface level. Although pursuing drugs that directly address the surface phenomenon seems to be a thoughtful and well-reasoned approach, he suggested it would be important to look at the developmental pathology and assess what can be done to block those genetic pathways.

Dr. Charney responded that he and Dr. Hyman, in initial discussions of this area, agreed on the importance of the problem posed by the absence of credible drug targets in schizophrenia. A comparison of the treatments for Alzheimer's disease and schizophrenia is informative in this regard. Whereas much is known in Alzheimer's disease about amyloid precursor protein processing that results in a great number of drug targets, little is known in schizophrenia about what is happening on the molecular, cellular, and genetic levels. The consequence is the lack of credible drug targets. Drug discovery must be a priority program within NIMH. This may be accomplished by shifting some emphasis, for example, in the Conte Centers (see <http://grants2.nih.gov/grants/guide/pa-files/PAR-98-056.html>) toward new targets—or a program that can begin to develop new targets. Given the advancements in genetics and proteomics and the rapid screening of large numbers of proteins and genes, it will soon be possible to develop credible new targets.

Dr. Gunnar commented on her enthusiasm for the direction being taken and sees the approach as a real opportunity to understand the developmental processes involved and to move away from the DSM towards more specific behavioral targets. However, as the neurobiology underlying these disorders unfolds during development, there is a real likelihood that the behavioral targets will show developmental change. She urged that the issue of developmental change in behavioral targets be kept in mind while the neurobiology is under study, especially given the widespread use of medications in children and the real possibility that the DSM categories are not particularly good for identifying emerging disorders.

Dr. Freedman congratulated Dr. Fenton on the steps that NIMH is taking to speed the translation from its supported basic research to the clinic. In his experience, NIMH program staff has been particularly helpful in pointing out leads for potential new drug development and in making needed contacts with the FDA.

Dr. Nemeroff expressed his enthusiasm for the collaboration between the extramural and intramural programs in this major effort. Reaching out to the academic community and to industry requires a serious examination of pathophysiology utilizing the new approaches in proteomics and genomics to discover the new targets. However, many patients remain desperately ill, and the focus cannot be on pathophysiology or therapeutics alone.

Dr. Charney stressed that the clinical armamentarium, particularly in schizophrenia, is very deficient for patients. The pharmaceutical industry is continuing to develop new medications. While industry does this better than the Institute possibly could and compounds do exist that are credibly efficacious for cognition and schizophrenia, they are off-patent drugs that have no home. Hence, it seems appropriate for Government to facilitate trials that can answer questions regarding the efficacy of those compounds. Given that the regulatory environment is not conducive to looking at symptomatic rather than syndromal treatments, it appears that the Government must conduct these kinds of trials.

With respect to the adequacy of DSM, Dr. Charney noted that the APA and NIMH recently held a series of conferences and formed workgroups to examine different aspects of the DSM-V, and white papers were produced. One positive outcome, at least in relationship to the committee that Dr. Charney chaired that looked at the role of neuroscience and the future of diagnosis, was the recognition by all groups that DSM does not map neatly onto pathophysiology or therapeutic response. As a consequence, it was suggested that parallel research diagnostic criteria be developed that are more appropriate in terms of pathophysiology and therapeutic response. That approach is going forward.

Dr. Charney additionally stressed that the mood disorder workgroup is very sensitive to developmental issues. For the upcoming April meeting, a separate workgroup will focus on measurement of change in children and adolescents in order to ensure that developmental-specific symptoms are included in available measures.

Mr. McNulty complimented Dr. Charney on the efforts toward developing a strategic plan for mood disorders—an area that needs reassessment. He noted that those living with schizophrenia know that atypical antipsychotics do significantly alter symptoms for some patients but also that the field has been static in terms of medication development for 10 or more years. The situation is similar with antidepressants. It appears that NIMH will need to provide leadership to move treatment development forward.

CLINICAL TRIALS WORKGROUP

Dr. Grayson Norquist, Director, DSIR, reported on the large-scale clinical trials that DSIR is overseeing and asked Council to consider forming a clinical trials workgroup. He noted that the large patient populations with a variety of mental disorders that have been assembled for these trials might be appropriate candidates in the future for some of the treatment development studies already discussed. Before summarizing the status of the five largest clinical trial contracts, Dr. Norquist reminded Council that each trial is overseen by an external group of independent scientists.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial has enrolled more than 1,800 participants at 12 sites—with a goal of 4,000 enrollees. The Treatment for Adolescents with Depression Study (TADS) has enlisted about half of the target population—230 out of a goal of 430 participants. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project includes two trials that are looking at the effectiveness of atypical antipsychotics for treating either schizophrenia or Alzheimer's disease. Both trials have enrolled about 35 percent of their target populations. Sequenced Treatment Alternatives to Relieve Depression (STAR*D), a clinical trial of treatment-resistant depression, has recently initiated recruitment and has about 400 study subjects (10 percent of the goal of 4,000 people). The Research Units on Pediatric Psychopharmacology (RUPPs) are being reconstituted and expanded. The new Request for Applications (RFA) (see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-02-002.html>) has solicited a number of responses that will be reviewed soon.

Dr. Norquist introduced Dr. William Harlan, an internationally known expert in clinical trials whom the Institute recruited as an advisor, and invited his comments. Dr. Harlan remarked that, since the clinical trials must compete for very scarce resources—including participants, time, investigators, and money—it is extremely important that they answer critical questions that will move the field forward and directly impact medical practice. His own experience, Dr. Harlan noted, was primarily in cardiovascular trials that have made a remarkable impact on heart disease mortality and morbidity over the past 15 to 20 years. The questions asked by the NIMH-sponsored clinical trials have similar potential but will require resources, time, and the making of wise choices by the investigators who are involved.

Dr. Norquist reported that the field has been very responsive to the RFAs for clinical trials. The adult treatment portfolio for FYs 2000 and 2001 received 11 multisite applications in the fundable range, representing a total of \$9.2 million or about 44 percent of new and competing adult monies. Five more multisite applications have been received in FY 2002 for a potential \$9.2 million of the adult monies. In the child field, four sets of applications in FYs 2000 and 2001 received \$8 million—about the same percentage of new and competing monies as that for adults. For FY 2002, one fundable application for a child trial is requesting \$3.5 million. The multisite trials funded under investigator-initiated collaborative R01s are increasing and becoming a larger percentage of the NIMH portfolio.

However, there may be some imbalance in the portfolio among the types of disorders receiving funding and those that should be targeted. For example, no applications for bipolar grants were received this round, although this is an understudied area. Other disorders that constitute a small percentage of the portfolio are eating disorders, sleep, and dementia. Of particular concern is the large number of very expensive multisite grants that will consume a disproportionate share of the Institute's limited resources. Therefore, NIMH needs expert advice about how to balance the clinical trials treatment portfolio, what areas to target, and what messages to relay to the field about future directions for the clinical trials supported by NIMH.

Dr. Norquist requested that Council consider establishing a clinical trials workgroup comprised of Council members and extramural experts in the operational and scientific aspects of clinical trials—including consumers, providers, and the stakeholders. Such a workgroup would need to examine the treatment portfolio carefully before making recommendations; this might take a year or more to accomplish.

Discussion

When Dr. Nakamura asked Council to authorize the formation of a workgroup to review the clinical trials treatment portfolio, Mr. McNulty made a motion to this effect that was immediately seconded and passed without opposition. Dr. Nakamura then noted that Dr. Lieberman had graciously agreed to chair such a group and solicited more volunteers from Council members.

BREAKING GROUND, BREAKING THROUGH: A STRATEGIC PLAN FOR MOOD DISORDERS RESEARCH

Dr. Dennis Charney, Chief of the Mood and Anxiety Disorder Research Program, DIRP, was the next speaker. After thanking Dr. Karen Babich and Ms. Joan Cole for their help in working with NIMH staff, extramural scientists, and members of constituency groups in developing the mood disorders strategic plan, he reviewed the goals of the plan and other aspects of the program.

The three goals of this strategic plan are: (1) to describe the current status of scientific activities in depression and bipolar disorders research; (2) to identify gaps in knowledge and the challenges and opportunities ahead; and (3) to develop a list of objectives and implementation strategies to address knowledge deficiencies. This initiative is an outgrowth of several different surveys that recognized the seriousness of mood disorders as a public health problem and the World Health Organization's acknowledgment of depression and bipolar disorder as two of the most disabling and costly health conditions. NIMH accepted the challenge to develop a plan for improving both knowledge of the pathophysiology and the treatment of serious mood disorders.

To date, a number of tasks have been accomplished. In January 2001, the perceived opportunities and gaps in this field were used to outline tasks for the workgroups, and members were selected. Last March, a meeting in Pittsburgh brought the chairs, workgroup members, and NIH staff together to identify the most important questions and outline a plan for addressing them. Since then, a series of conference calls and e-mail correspondence led each workgroup to produce drafts, papers, and manuscripts that are forming the knowledge base for building the strategic plan.

Nine separate groups carefully considered multiple aspects of mood disorders, ranging from genetics to service delivery, in selecting the important challenges for research in this area. The NIMH professional staff provided important assistance by consolidating the recommendations of each group, refining the objectives and potential implementation strategies, and providing additional scientific material that will be part of the strategic plan document.

A nine-member Executive Committee composed of senior NIMH staff has responsibility for overseeing drafts of the plan, developing and prioritizing objectives based on the subcommittee reports, and developing feasible implementation strategies. In terms of format, this strategic plan will have an executive summary, an introduction, and four major sections: Basic and Clinical Neuroscience: A Foundation for Discovery; Dimensions of Age and Disease; Treatment, Services and Prevention: Improving Care and Outcomes; and Infrastructure Investments for the Future. There will be a summary statement at the end. Each major section will have an introduction to set the stage, a review of the current status of the field, an opportunities subsection that outlines the challenges and vision for new directions, and recommendations for the top research objectives and implementation strategies.

This strategic plan is not yet completed and awaits Council's input. The workgroup manuscripts that serve as an indepth review of each of the areas covered in the strategic plan (genetics, neural and behavioral substrates, preclinical models, developmental issues, aging and medical comorbidity, pharmacological and somatic treatment development, psychosocial treatment, clinical and translational treatment and services delivery and prevention) will be published in a special issue of *Biological Psychiatry*. Pending the Council's endorsement of the plan, the reports will be posted on the NIMH Web site for public comment.

Discussion

Mr. McNulty, after congratulating Dr. Charney on the mammoth undertaking, expressed some concern about the status of bipolar disorder research, especially in light of the lack of grant application submissions in this category for this round of Council. Considering the psychosocial disease burden and the cost of bipolar disorder, the structure of the NIMH grants

portfolio outlined by Dr. Norquist causes even more alarm and a call for immediate corrective action. Dr. Charney responded that the soon-to-be-issued strategic plan recognizes large gaps in knowledge about the pathophysiology and genetics of bipolar disorder as well as its treatment.

Dr. Lieberman, clarifying that the strategic plan will summarize the status of the field in various areas and lay a foundation for subsequent research, asked Dr. Charney to elaborate how this plan will be tied to funding mechanisms and how intramural-extramural components will be involved. Dr. Charney replied that the Executive Committee will address these questions. One of its tasks will be to recommend priorities among the approximately 50 primary recommendations submitted by the workgroups, recognizing that the budget will not support immediate implementation of them all. As currently drafted, each of the primary objectives has an associated implementation strategy. The Executive Committee recognized that, over time, one mechanism might prove more desirable than another for funding particular research.

TRANSLATIONAL RESEARCH IN BEHAVIORAL SCIENCE

Dr. Bruce Cuthbert, Chief of the Adult Pathophysiology and Prevention Research Branch, DMDBA, reported on the successful translational research and behavioral science program that Dr. Hyman fostered in 1998 by forming a special Council workgroup on the topic. After spending almost a year examining the general field of behavioral science and the Institute's portfolio in this area, the workgroup concluded that NIMH supported a strong basic behavioral science effort but did not sufficiently encourage the application of findings to pressing public health issues. An implementation group of NIMH program staff was then formed to implement the Council workgroup's recommendations regarding translational research—defined as "addressing how basic behavioral processes inform the diagnosis, prevention, treatment, and delivery of services for mental illness, and conversely, how knowledge of mental illness increases an understanding of basic behavioral processes."

This NAMHC Behavioral Science Workgroup's report, "Translating Behavioral Science into Action," can be accessed on the NIMH Web site (see <http://www.nimh.nih.gov/tbsia/tbsiatoc.cfm>). It addresses three priority areas: (1) basic behavioral processes in mental illness; (2) the features of syndromal illnesses that impair patients' functional abilities; and (3) such contextual influences on mental illness and its care as social, cultural, and health delivery systems. The program's goal was to develop and implement translational research in all three priority areas, beginning with basic behavioral processes. However, the implementation group comprised of NIMH staff decided that the best way to proceed would be to address all three areas simultaneously. Further, a decision was made early on to explicitly require collaborations between basic behavioral researchers and clinical/services researchers; otherwise, given the disciplinary and settings boundaries, neither group would likely appreciate the contributions and activities of the other. Hence, collaborations between basic and clinical researchers have become a cornerstone of the translational research program.

In November 2000, the first RFA to develop translational research was issued. The announcement endorsed three different mechanisms: 3-year networking R21 grants to foster new collaborations between basic and clinical researchers by getting them together to explore issues and design options; 5-year R21 grants to develop translational research capabilities (e.g., methodological and scientific infrastructures, pilot studies, and new instruments); and full-fledged translational R01 grants by single researchers or groups of investigators with appropriately focused projects. Even though the lead time for this RFA was relatively brief, NIMH received 36 applications and 6 of these have been funded. Most of these new projects support investigators who are conducting pilot studies and building a translational research capability.

The capstone of this program will be Translational Research Centers, funded under the P50 mechanism for up to \$1.5 million annually for 5 years and renewable once (see <http://grants.nih.gov/grants/guide/pa-files/PAR-01-027.html>). These will be comparable to the Conte Translational Centers, requiring multidisciplinary, multi-investigator research teams to approach a specific set of hypotheses with novel syntheses of basic and clinical science. As with all aspects of this program, the Translational Research Centers will encourage the integration of biology and neuroscience with behavioral science. The annual receipt date is October 22. The first round of submissions included some excellent applications that are currently under review.

Training, another priority recommendation by the Council Workgroup, will be addressed in the following ways. The Translational Research Center grants will encourage research apprenticeships; R25 education grants will support extensive curricula and summer workshops; and career K awards will be offered to new investigators who have mentors and to tenured faculty members in mid-career who can think creatively about new types of collaborations. Finally, trainees and junior faculty will be supported to attend workshops and conferences.

To date, a number of successful translational research conferences and workshops have been held. A Borderline Personality Disorder Conference was held in New York last summer, which included advocacy groups and provided junior researchers with an opportunity to meet senior faculty and discuss relevant research issues. Another two-part translational workshop

focused on close personal relationships. Basic researchers in such areas as animal models of relationships or genetic factors in the prairie vole met with investigators studying the psychology of attachment or marital and depression research. Some fruitful collaborations have resulted. NIMH also sponsored a workshop on cognitive science in clinical trials that asked cognitive neuroscientists to contribute their views about new clinical endpoints. A gratifying aspect of this program has been the new Program Announcements (PA) inspired by the translational research model. One invited R01s addressing basic and applied research related to Attention Deficit Hyperactivity Disorder. Another recent RFA asked for R01s on modular phenotyping for major mental disorders. An RFA soliciting exploratory developmental R21 grants in social neuroscience grew out of the workshop on close relationships and has elicited more than 90 innovative applications. An RFA to establish child and adolescent interdisciplinary research networks is still open, and two forthcoming PAs for building translational research will include the same successful formula used in the initial RFA: one PA will involve pilot/exploratory grants to initiate new collaborations among researchers and "developmental" grants to build a translational research infrastructure (see <http://grants.nih.gov/grants/guide/pa-files/PAR-02-062.html>), while the other PA is intended for fully implemented translational R01 projects (see <http://grants.nih.gov/grants/guide/pa-files/PA-02-061.html>).

RESEARCH ON BORDERLINE PERSONALITY DISORDER

Dr. Cuthbert continued with a presentation on borderline personality disorder after acknowledging the hard work by two NIMH staff members, Drs. James Breiling and Wayne Fenton.

Unfortunately, Dr. Cuthbert remarked, borderline personality disorder is one of the most stigmatized of all of the mental illnesses, starting with the derivation of its name from the out-of-date notion that the condition represented a borderline psychotic state. In fact, it is a brain disorder like other mental disorders and requires more attention to discover both its causes and better treatments than those presently available.

The symptoms of this disorder include affective dysregulation, severely disrupted interpersonal relationships, impulsive behavior, self-injurious behavior, which may be non-lethal or suicidal, and a high use of mental health and medical services. While no currently reliable prevalence estimates exist, the DSM-IV claims that about 2 percent of adults have borderline personality disorder and nearly 75 percent of those are female. Rates of suicide completion are very high—at 8 to 10 percent, and approximately 20 percent of all patients with psychiatric hospitalizations have this diagnosis.

Unfortunately, little is known about the etiology of this brain disorder, although there is clearly genetic variability. First-degree relatives of these patients have a five times higher probability of getting this disorder than individuals in the general population. Environmental risks for this disorder also have been reported. Many people with borderline personality disorder often have reported a childhood history of neglect or abuse or sexual abuse by non-caretakers—although many do not have this background.

Over the past several years, NIMH support for research on borderline personality disorder has increased faster than that for other parts of the portfolio. A number of stellar investigators are examining neurobiological approaches to such specific components of borderline personality as impulsivity, emotional dysregulation, and suicidal behavior, as well as different treatment approaches, courses, and outcomes. One encouraging finding is that the disorder appears to be particularly severe during young adulthood but may remit or stabilize with age. The National Comorbidity Survey, an epidemiological study of a randomized sample of 10,000 adults and several thousand adolescents, is including questions about personality disorders (e.g., borderline) for the first time this year as a result of requests from advocacy groups.

A July 2001 conference in New York City on borderline personality disorders, which NIMH co-sponsored with the Swiss-based International Personality Disorder Research Foundation, resulted in a more explicitly translational research focus that will bring basic behavioral scientists and neuroscientists in the areas of impulsive behavior, personality and temperament, emotion, and emotional dysregulation together with eminent clinical researchers and clinicians. A valuable component of this successful meeting was participation by families, consumers, and advocacy groups, as well as the involvement of many young investigators—some of whom were already being mentored by pioneering researchers in the area and others who had a newly inspired interest in but no previous connection with the area.

A follow-up conference, planned for May in Minneapolis, will be co-sponsored by the University of Minnesota and the same Swiss Foundation. The same young investigators will be invited back to discuss research papers they have been preparing as a way of encouraging them to consider submitting grant applications, and invitations will be issued to other early-career scientists as well. NIMH will offer grant-writing technical assistance in this process. These conferences have stimulated much discussion and appear to be a mechanism for fostering interest that will later reap dividends and potentially further develop the research base.

Another conference focusing on family perspectives in borderline personality disorder is planned for October in New York as a way of helping relatives find the most appropriate treatments and ways to support their loved ones who have this disorder. This meeting is being organized by Dr. Perry Hoffman from Weill Medical College of Cornell University, who has an NIMH career grant entitled "Family Influences on Borderline Outcome," and will be chaired by former NIMH Director Dr. Herbert Pardes of New York Presbyterian Hospital. This conference also will feature participation by a number of consumer and advocacy groups.

A concept clearance will soon be requested for pilot and exploratory studies of this disorder (see NIMH Web site <http://www.nimh.nih.gov/council/conceptindex.cfm>). A number of poignant comments have been received from family members about the need for this funding initiative. The planned RFA will have a translational focus on initiating collaborations between basic and clinical scientists to stimulate innovative approaches. Additional workshops and conferences also are planned, and scientists in the field are encouraged to submit applications for conference research grants under the R13 mechanism (conference grant).

Discussion

Dr. Tsuang remarked that one ultimate goal of this effort should be to eradicate the stigma attached to borderline personality disorder and noted that persons in the beginning stages of schizophrenia or bipolar disorder sometimes have personality dimensions, but labeling the illness as borderline personality disorder is a misnomer. One aim of the DSM-V should be to eradicate this diagnosis. A better understanding of the neurobiological basis for this disorder may help rid the field of the erroneous label.

When asked by Dr. Ritchie what name he would substitute, Dr. Tsuang responded that borderline personality is a syndrome that could be divided into several subgroups. Descriptive terminology was initiated to increase clinicians' awareness of suicide risk and other dimensions. If a neurobiological substrate or specific risk factors within-or outside-the family can be found, these may be validated with a descriptive syndrome. He added that borderline personality can not be easily categorized since it is multi-dimensional and too heterogeneous to be classified as a single disorder.

Dr. Nakamura mentioned that he had been a member of the DSM-V workgroup that wrote the chapter on personality disorders. The white paper on the subject, which soon will be published, recommends a radically different approach to conceptualizing personality disorders.

CONCEPT CLEARANCE PRESENTATIONS

Concept to Study The Mental Health of Aging in HIV/AIDS (see http://www.nimh.nih.gov/council/cncptstover_102.cfm)

Dr. Ellen Stover, Director, DMDBA, explained that initiatives in the area of HIV/AIDS are sent to the NIH Office of AIDS Research a year or more in advance to ensure their compliance with the AIDS strategic plan. The proposed RFA focuses on individuals with AIDS who are over 50 years old, a population that has increased significantly in the last several years. Older adults with AIDS diagnoses now represent 15 percent of the total AIDS caseload, and, since people with HIV infection are living longer, the older population with HIV/AIDS is likely to expand. Evidence already exists that the natural history of HIV infection and symptom manifestation differs substantially in elderly compared to younger cohorts. Older adults living with HIV/AIDS have a more severe disease course, a shorter survival rate, more serious health problems at diagnosis, more opportunistic infections, and shorter AIDS-free intervals.

Because this vulnerable subgroup is still poorly understood and understudied, the RFA covers a wide range of topics, such as basic epidemiological and comorbidity studies of HIV-associated psychiatric disorders, the impact of neurocognitive dysfunction and substance abuse on clinical outcome and disease progression in people over age 50, physiological mechanisms responsible for disadvantages in older populations, and issues of compromised immune system and medical complications. Particular emphasis will be given to studying adherence to treatment and preventive interventions.

Motion: Without further discussion, a motion to accept this concept was unanimously approved by Council.

Concept to Support an NIMH Center for Collaborative Genetic Studies of Mental Disorders (see http://www.nimh.nih.gov/council/cncptmoldin_102.cfm)

Dr. Steven Moldin, Chief of the Genetics Research Branch, DNBS, described the critical need to accelerate the sharing of research resources that result from genetic studies. Data sharing in human genetics research is necessary to achieve sample

sizes with adequate statistical power to detect genes that produce vulnerability, to facilitate the rapid replication of new findings which are the foundation for further progress, and to ascertain discrepancies across different data sets when replication is not obtained—a situation that occurs rather frequently in genetics studies of mental disorders. Data sharing also reduces duplication of laboratory work because samples only have to be genotyped once after a single subject assessment and diagnosis, as well as duplicative costly data collection efforts. The sharing of data and DNA provides research resources on which new genomic tools and technologies may be applied and also stimulates multidisciplinary collaborations among basic scientists, clinicians, neurobiologists, molecular geneticists, and statistical geneticists. Lastly, data sharing attracts new young investigators to the field by providing them more immediate access to materials without going through a time-consuming and expensive data collection process.

Since 1996, NIMH's genetics initiative has distributed clinical and genotypic data, DNA samples, and cell lines. To date, over 23,000 DNA samples have been distributed on three diseases: schizophrenia, bipolar disorder, and late-onset Alzheimer's disease. Over a quarter of a million genotypes have been returned from investigators who analyzed these data. A total of 76 data analytic projects are currently underway: 56 in academia and another 20 by biotechnology or pharmaceutical companies. All data and biomaterials utilized in these projects were distributed under an NIMH contract that ends in FY 2002. This concept clearance is not only to continue those efforts but also to move the science to the next stage by enriching these research resources. The current contract supports making cell lines, creating databases, and distributing clinical and genetic data. The vast amount of genetic material already stored creates a new need for pooling and analyzing that data, for resolving discrepant genetic results, and for creating new meta-analytic approaches for pooling data.

The proposed RFA would fund one project through the U24 mechanism (Resource-Related Research Project, Cooperative Agreements) that creates and enriches research resources for the community and permits interactions between the NIMH staff and the awardee institution. The activities undertaken would include making cell lines and extracting DNA, maintaining databases, distributing the existing resources, and improving opportunities for subsequent pooling and meta-analyses of all the collected data. The long-term value of this effort will be to enrich research resources for genetic studies, facilitate data sharing within the scientific community, encourage collaborative research, promote analyses of full datasets, and accelerate gene discovery for mental disorders and, ultimately, therapeutic drug responses.

Discussion

Dr. Nakamura observed that the proposed concept deals with an already initiated activity. All of the NIH Institute directors recently decided that data sharing is a default activity; in the future all NIH applicants will be expected to include in their applications a data-sharing plan and justify any reasons for not sharing data.

When Dr. Nestler asked whether the program planned to expand to additional diagnostic syndromes beyond the three that were mentioned, Dr. Moldin explained that NIMH is currently distributing data for three diseases but has additional augmenting materials in the repository for those diseases. Available data on autism will come online in a few weeks, and families in large datasets on attention deficit hyperactivity disorder and obsessive compulsive disorder also will be available. Proposals have been made to collect data on other diseases that, depending on how the applications do in peer review, may also be included.

Dr. Nestler continued that he had heard an interest expressed in using NIMH's large-scale, multi-center clinical trials as a mechanism for expanding access to genetic material from a large number of patients. He added that the proposed center could be a critical component in using genetic information to resolve some of the scientific issues that arise in diagnosing illnesses, delineating their pathophysiology, and identifying novel drug targets.

Dr. Moldin responded that the Institute is actively investigating that option and considering extending this new resource to include clinical patients enrolled in the STEP-BD, STAR*D, CATIE, and TADS trials. Dr. Lieberman added that a solicitation for this has been issued and responded to by the principal investigators of these four large clinical trials contracts, with negotiations currently underway. He then commended Dr. Moldin on the proposed new initiative, which he thought was the right way to maximize an opportunity to realize the full scientific benefits of genetic and genomic information. He asked, however, whether the proposed work would be an extension or expansion of the existing initiative and whether NIMH expected that the research team currently distributing data and biomaterials would continue to do this.

Dr. Moldin explained that the solicitation will be open for competitive peer review and the Institute hopes the current contract awardee will apply, along with other investigators. The Institute anticipates receiving several highly competitive applications. The current contract was awarded to Washington University in St. Louis, with a subcontract to Rutgers University for establishing cell lines and extracting DNA. The contract experience has been very positive, with outstanding success rates in cell transformations of samples received from across the United States and from Taiwan, the People's Republic of China, Palau, Portugal, and Russia. The success rate for cell line transformation is 99 percent for both international and domestic

shipments.

Dr. Tsuang asked two questions: Can one center adequately handle this complicated task that involves various areas of expertise, and is collecting data on artificially categorized mental disorders the best way to proceed? He thought that the center should expand to other disorders, using categories that are based on clinicians' important observations. The current categorical approach to studying genetics needs to be abandoned. Dr. Tsuang added that NIMH has invested substantial monies in collecting data that are in the current repository and need to be capitalized on.

Dr. Moldin explained that the U24 funding mechanism can support a center comprised of an integrated team of investigators with expertise in molecular biology, statistical genetics, bioinformatics, and psychiatric genetics within a single institution or across institutions. Thus, the planned center is not constrained by one physical site. With respect to expanding beyond categorical assessments, some NIMH projects have included other measures (e.g., fMRI data collection in mood disorders, neuropsychological data, and psychophysiological measures in schizophrenia). When such projects are funded and included in the NIMH Human Genetics Initiative, those data are available for release to the scientific community.

Mr. McNulty asked if it might be appropriate for the Institute to think of a new way of categorizing mental illness that would be totally different from that described in the DSM-IV or forthcoming DSM-V, given their limitations, and Dr. Nakamura replied that a future Council meeting will have a specific discussion of issues surrounding the diagnosis of mental illness.

When Dr. Lester asked whether database and blood sampling activities are being coordinated with those of NINDS, which has similar interests, Dr. Moldin responded that DNBBS staff members have held several discussions with NINDS staff and have made considerable progress toward a joint data-sharing plan that was presented at the NIMH/NINDS Council session in September 2000. While NIMH has worked closely with NINDS on developing comparable resources, NINDS scientific priorities are driven by diseases such as multiple sclerosis, ALS, neurofibromatosis, and Parkinson's disease, which are different from the diseases of primary focus for NIMH.

Motion: Dr. Nakamura called for a vote on the concept clearance, which was approved without demurrer.

PUBLIC COMMENT

Dr. Darrel Regier, representing the American Psychiatric Association (APA) and the American Psychiatric Institute for Research and Education, opened the public comment period by describing the process to be followed in developing the DSM-V. The six white papers that have been produced, with the assistance of many NAMHC members, will soon be published and presented at the annual APA meeting in May. The second phase of DSM-V development will comprise an international conference to look at sub-diagnostic syndromes that correlate with modular phenotyping. The APA expects to facilitate research on prototypes of mood disorders that are more pathophysiologically and etiologically based than those described by current criteria. Depending on the research, the current trajectory for drafting the DSM-V is 2010. Not only the NIMH and APA but also NIDA, NIAAA, and WHO will collaborate in this international effort, as they did in simultaneous preparation of the ICD-10 and DSM-IV.

Dr. Regier also noted that the APA is extremely supportive of the proposed efforts to increase the flow of new researchers and is working on this with the Psychiatry Residency Review Committee. Further, the APA has a project underway on research ethics, which Dr. Lieberman is chairing. Lastly, the APA appreciated NIMH's leadership role in facilitating an international response to the September 11 events, particularly the international teleconference among experts in New York and Washington and at a World Psychiatric Association meeting in Madrid.

Dr. Tsuang stressed that the contribution of the DSM-III should not be minimized. This document facilitated the epidemiological catchment area research that first demonstrated the high prevalence of some psychiatric disorders. The field needs to move forward now by revising the diagnostic criteria with the assistance of pathophysiological categorizations. Dr. Regier added that the main value of the DSM—and the changes made in the 2nd, 3rd, and 4th editions—is to set forth hypotheses that can be proven or disproven in terms of their utility and validity. New information has now disproved some of those hypotheses as valid indicators of diagnoses for clinical conditions, although some have been very helpful for clinical treatment. The DSM was never meant to be reified and kept static; like all science, it has to move forward. Now is the time to incorporate a new understanding of etiology and pathophysiology into diagnoses.

Dr. Jerry Weyrauch, Executive Director for the Suicide Prevention Advocacy Network, commended Surgeon General Satcher for his contribution to creating the National Strategy for Suicide Prevention (see <http://www.mentalhealth.org/suicideprevention/strategy.asp>), saying that the production of that report entailed a unique

public-private partnership that still exists today. This includes, on the Government side, NIMH, the Health Research and Services Administration, CMHS, the Centers for Disease Control and Prevention, and the Office of the Surgeon General and, on the private side, the National Council for Suicide Prevention—an association of eleven non-profit groups. Dr. Weyrauch then prevailed on NIMH to implement Objective 10.1 from the Suicide Prevention Strategy, which calls for developing a national suicide research agenda with input from survivors, practitioners, researchers, and advocates. The existing partnership can be used for this purpose if NIMH will assume a leadership role. Dr. Cameron Ritchie agreed with the comments and observed that, since suicide is the second most common cause of death in the military following accidents, military representatives should be part of any partnership that aims to decrease suicide.

The next speaker, Ms. Valerie Porr, President of the Treatment and Research Advancements Association for Personality Disorders (TARA), expressed her gratitude for NIMH's emphasis on borderline personality disorder, as well as its discussions with the FDA on symptom-based research. Through its national telephone help-line, TARA has documented that the average consumer with borderline personality disorder receives four to five different diagnoses—supporting the desperate need for a better assessment instrument. Another dire need is for more treatment facilities for adolescents with borderline personality diagnoses. Too many of these children, according to their concerned parents, wind up with an explosive conduct disorder. Additionally, since no one drug is sufficient for treating borderline personality disorder, TARA supports any work with the FDA that will offset the current bias in judging drugs. Lastly, Ms. Porr appealed to NIMH to support a conference for families of persons with borderline personality disorder.

Dr. Carol Bush, representing the International Society of Psychiatric Mental Health Nurses, described the organization as an umbrella for three other nursing groups: the Association for Child and Adolescent Psychiatric Mental Health Nursing, the International Society for Consultation and Liaison Nursing, and the Society for Education, Research and Psychiatric Mental Health Nursing, organizations that NIMH has worked with in the past. Dr. Bush declared that there is also a critical need for developing more well-trained psychiatric nurse researchers, a similar situation to the need for the training of psychiatric physician researchers. Not so coincidentally, the index year for the initial decline in the number of psychiatry physician researchers, 1992, also marked the transfer of the education and training branch from NIMH to CMHS and a severe restriction in funding. The concept of better—and better funded—education and training for both clinical and research expertise among the various professions, including nursing, needs to be revisited.

Adjournment

Whereupon, the 199th meeting of the NAMHC adjourned at 1:50 p.m. on January 25, 2002.

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

Richard K. Nakamura, Ph.D.
Acting Chairperson

Appendices

- A. Review of Applications
- B. Council Roster