

**National Institute of Mental Health
Alliance for Research Progress
January 2005**

Introduction

The National Institute of Mental Health (NIMH) held its Alliance for Research Progress Winter Science Meeting Monday, January 24, 2005 at the Montgomery County Conference Center in Bethesda, Maryland. At the first NIMH Alliance Meeting on July 19, 2004, patient and family advocacy groups indicated that they would be keenly interested in an update on NIMH research discoveries. The purpose of this second meeting was to provide research updates as well as to continue efforts to foster dialogue and education. During the discussion, Alliance participants had the opportunity to direct comments and questions to the NIMH Director and senior NIMH staff, as well as to engage the presenters in discussion on pressing needs in the mental health field.



NIMH Director Thomas R. Insel, M.D., opened the meeting with a welcome and discussion of the “State of the NIMH.” Alliance attendees at the Winter Science meeting heard presentations from these distinguished NIMH researchers:



Alliance speakers Drs. Giedd, Manji, Insel, Mayberg, and Lieberman (left to right)

Husseini Manji, M.D., Chief, Laboratory of Molecular Pathophysiology, and Acting Director, Mood and Anxiety Disorders Research Program at NIMH, described studies looking at the interaction of genes and the environment and the relationship this might have on the development of depression and anxiety. Jeffrey A. Lieberman, M.D., Chairman, Department of Psychiatry, Columbia University College of Physicians and Surgeons, presented an update on schizophrenia treatments and talked about the increasing demand for practical clinical trials. Helen S. Mayberg, M.D., Professor of Psychiatry

and Neurology at Emory University School of Medicine, spoke about brain imaging and depression. Jay Giedd, M.D., Chief of Unit on Brain Imaging in the Child Psychiatry Branch, NIMH, discussed gender differences in brain development.

The State of NIMH and the Priority Setting Process

“In these challenging times, we have enormous opportunities to do new things. However, serious priority setting is imperative; otherwise, we will be doing yesterday’s science,” said Dr. Insel. Reducing the economic and social costs of mental illnesses through research that informs how the science should be translated into patient care is the ultimate goal of this priority setting process, according to Insel. The NIMH uses three principles to judge the priority level for any given research proposal: (1) *relevance*—whether proposed activities pertain to the NIMH mission of reducing the burden of mental and behavioral disorders; (2) *traction*—which research areas are poised for rapid progress because of access to new research tools or recent scientific advances; and (3) *innovation*—emphasizing “discovery” science that may lack extensive pilot data, but which is extremely relevant and could provide an enormous pay-off.

“Because our resources are limited, we need to determine the most important discoveries we need to make to have the greatest impact on people with mental disorders,” said Insel. In his introduction, Dr. Insel raised the following additional points. He said:

What one discovery would change the life of someone with anorexia, bipolar disorder, schizophrenia, autism, or any other mental disorder? It’s actually no different than the question that we ask for cancer, hypertension, heart disease, or diabetes. The mental health field needs valid diagnostic tests. Being forced to look only at observable behavior to make diagnoses hampers the field because behavior is variable, complex, and often difficult to quantify. There is a frustration in the field that most medications we currently use are knockoffs of medications we’ve had for three decades. We need a ‘molecular pathophysiology’ for these disorders, just the way we are now putting together a molecular pathophysiology for breast cancer, prostate cancer, and for leukemia.

Dr. Insel emphasized that NIMH uses a bench to bedside to practice model and that the speakers would touch on different points of effort along this continuum.



Dr. Insel, Director of NIMH, describes the bench to bedside to practice model to Alliance members.

Speakers

Husseini Manji, M.D., “Anxiety and Depression Research: New Ideas from the NIMH MAP”



Dr. Manji shares the latest advances in anxiety and depression research.

Translating research into practice is critical, said Dr. Manji, Acting Director of the NIMH Intramural Mood and Anxiety Disorders Research Program, the largest program of its kind in the world. The program’s scope includes research on: major depressive disorder, neuroimaging, medication development, and genetic epidemiology. “Breaking down barriers between intramural and extramural research is a critical aspect of this program,” said Manji. “It allows for the translation of research to daily clinical practice that can only occur when all

levels of research (such as basic and clinical) work together.”

Throughout his talk, Dr. Manji brought human experience into the discussion of complex disease models. He described three overarching concepts in the field of mental health: human resilience, epigenetics (the study of genetic information within the cell that may contribute to mental illness), and plasticity. The quest to better understand human resilience—why some people develop depression and others do not and why some people recover faster—guides much of Manji’s program. According to the new field of epigenetics, individuals inherit specific genes and the environment helps to determine what genes turn on and off and when. “This gene and environment interaction is critical to understanding mental disorders,” said Manji. Plasticity (or malleability) refers to the ability of the brain to continually adapt to its environment.

Jeffrey Lieberman, M.D., “Update on the Treatment of Schizophrenia: Results from the CATIE Trial”



Dr. Lieberman, Chairman of Psychiatry, Columbia University, College of Physicians and Surgeons

Dr. Lieberman discussed CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness Trial). He reviewed the major questions of the CATIE study: are newer drugs more effective than the older drugs? How do newer drugs compare to each other, and which are more effective and safer? Consumers, who naturally want the newest and best medications, have a right to know if the new medications are really better. Currently CATIE is testing different classes of antipsychotic medications to determine if the newer drugs provide more benefit than the older, less expensive medications. In

addition, DNA collected from the CATIE trial will be stored at an NIMH repository and will become an important resource for future genetic investigators.

The increasing demand from the government, patients, and the healthcare system for practical clinical trials was a major theme of Dr. Lieberman's talk. The CATIE trial is a good example of a practical clinical trial because it includes the community at large and tests interventions that are currently in widespread use. CATIE includes 50 community sites, public health systems, and academic settings that have never before participated in clinical research. Several participants expressed concern that the findings of CATIE could be used as a justification to restrict access to certain treatments and services. Lieberman responded that his team would do their best to report the results in a way that encourages their adoption without promoting this restricted access. Results from this trial will be available in the summer of 2005. Dr. Insel then shared his views on the changing culture of clinical trials. In the past decade, the objectives of clinical trials have moved away from a focus on a pure diagnosis and toward a new focus on studying people with mental disorders who really reflect the broader population and may have multiple illnesses.

Helen S. Mayberg, M.D., "Imaging the Brain in Depression"



Dr. Mayberg, Professor, Psychiatry and Neurology, Emory University School of Medicine, discusses the latest research in brain imaging.

"If we really look at the problem in depression, we've been blessed with some reasonably effective treatments," said Dr. Mayberg. The problem is people commonly relapse, and often have recurrences. Mayberg emphasized that an unacceptably large number of patients fail to respond to treatment.

"Probably 10 percent, which may be an underestimation, do not get better no matter what we treat them with, and the high suicide rate is unacceptable overall," concluded Mayberg. Mayberg emphasized the need to determine what causes depression so that we can develop

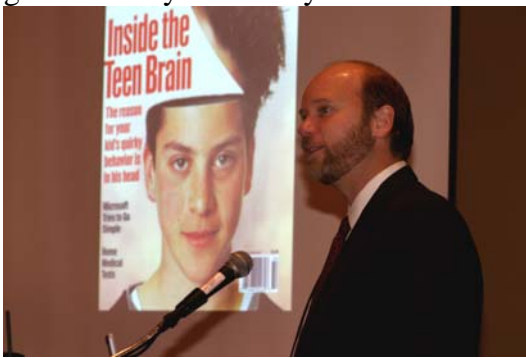
treatments that target its cause. Dr. Mayberg shared her clinical "wish list" for depression with Alliance members: to develop diagnostic tests that can determine illness subtypes, family members at risk, and relapse potential. This would pave the way for evidence-based treatment tailored to what a specific person needs. It would also allow practitioners to determine in advance what treatments would not work, thereby saving the patient from medications or therapy. Dr. Mayberg posed questions to the audience such as: How might brain imaging contribute to achieving this wish list? Can we use imaging as a way to have diagnostic tests? Who is at risk for relapsing? Might it alter how we provide treatment? Who can come off medications effectively? Do we have any clues from imaging that might help us to identify relapse potential?

Dr. Mayberg shared one important contribution of brain imaging to understanding and treating depression: brain imaging shows that medications and cognitive behavioral therapy activate different parts of the brain. This explains why combination therapy works better than one treatment alone. Dr. Mayberg argues that we need more of this type of evidence-based medicine for mental disorders. Her talk intrigued many of the

Alliance attendees, who considered the potential inherent in Dr. Mayberg’s presentation: indeed, it stimulated much conversation during the meeting’s later discussion section.

Jay Giedd, M.D., “Child and Adolescent Psychiatry: New Views from Brain Imaging”

The brain changes significantly during adolescence, and determining the relationships between these structural changes and behavioral changes is an important goal of ongoing brain imaging studies, according to Dr. Giedd. Imaging studies indicate that the development of gray matter in the brain follows a U-shape development with regional variation while the development of white matter increases in a linear pattern with less regional variation. For example, temporal lobe gray matter thickness peaks at 16 years in both boys and girls while parietal lobe gray matter peaks at approximately 10 years in girls and 12 years in boys.



Dr. Giedd, Chief, Unit on Brain Imaging Child Psychiatry Branch, NIMH talks about the teenage brain.

Dr. Giedd explained that genetics, nutrition, toxins, bacteria, viruses, hormones, and many other factors may have an effect on neuronal pruning, wherein there is a decrease in gray matter over time in the brains of children and adolescents, a process in which connections between cells are eliminated. Some researchers suspect that a “use it or lose it” principle guides adolescent pruning (brain connections that are used will survive and strengthen while connections that are not used will die).

If this hypothesis is true, then behaviors may have a powerful influence on the physical development of adolescent brains. Conversely, later development of the prefrontal cortex (important in controlling impulses) may explain the higher propensity of adolescents and young adults to engage in risky behavior.

How both the environment and genetics influence this development is an important area of research. For example, the influence of peers, parents, medications, diet, and videogames on brain development remains unknown. However, imaging studies indicate that brain development is different for boys compared with girls. In addition, studies show that cortical thickness in the brain varies with a particular gene status: the APOE E4 allele. Twin studies indicate that the environment strongly influences the development of the cerebellum (the structure behind the brain stem), which may be a key to understanding childhood disorders, suggests Dr. Giedd. “Brain imaging in children is all about group average—we are not good at determining the usefulness of individual brain scans yet,” said Giedd. He concluded:

In my private practice of child psychiatry, I’m always frustrated by how rarely my two worlds interact in terms of what we are trying to do with imaging and genetics in terms of what it actually does on the front lines. It’s almost all trial and error.

Discussion

Evidence-Based Medicine

Several major topics of discussion emerged throughout the day. The idea that different mental disorders might have similar genetic and/or environmental pathways was raised. Alliance members agreed that their individual diseases and research needs overlap and that comorbidity (having two or more diagnosable conditions at the same time) is a major reason for this overlap. They discussed the issue of symptom overlap and the importance of treating symptoms instead of exclusively treating diagnoses. Mental disorders are more difficult to understand, diagnose, and treat compared with diseases such as diabetes, breast cancer, or heart disease. Dr. Insel commented that the mental health field needs to develop better diagnostic tests. "Currently, we don't have a diagnostic test for either bipolar or for borderline personality disorder other than behavioral assessment and interviews. That, I think, is still a major hang-up for us," concluded Insel.

Dr. Mayberg stressed that the mental health field needs to be like every other aspect of medicine: it needs tests that help clinicians make decisions about how to treat and that allow them to know in advance what treatments won't work. She vividly demonstrated her point through the following example:

When you have chest pain, the first thing is to be diagnosed. If you just sit at home and think its indigestion, you could be dead. But it's really easy to diagnose the heart attack. They can look at your cardiac vessels and they know that cardiac vessels are instructive to know about how the heart works, and we don't have that for depression. With depression, the issue is not the diagnosis. The issue is you don't sit in the emergency room and negotiate with the cardiologist: 'I promise to eat less Big Macs. I promise to exercise.' The doctor doesn't make the decision based on what your Aunt Mabel was treated with, what you believe to be true, what you saw in the New York Times last week. They do another test, because EKG doesn't tell you the underlying problem or how to treat, and cardiologists have been smart in that they've done evidence-based studies. We don't have the test, but we have clues, and now what we have to do is systematically do the evidence-based studies to see how do our scans, when there's variability, match up to what kind of treatment people should best receive, and that is what we are trying to work on.

Many participants agreed that the mental health field needs to move more toward evidence-based interventions and at the same time evidence-based practice should not be used to restrict access to care. Evidence-based treatment requires that the best available, current, valid, and relevant scientific evidence—combined with clinical judgment and careful consideration of consumer goals and preferences—guide decisions about health care.

Personalized health care—where the best treatment is tailored to the individual patient—would allow doctors to identify who is at risk before the first symptoms appear and to provide more rational lifetime care. Dr. Insel continued this thread of discussion:

We want to be able to predict who will respond to what treatments—to identify a person who is at risk for schizophrenia before the first break in just the same way we identify who is at risk for heart disease before the first heart attack. Current studies look at population effects (i.e., 50 percent of patients get 40 percent better). We take for granted now that you manage someone’s diet, exercise, and cholesterol well before their first heart attack, and most cardiologists now spend most of their time with patients who have not had a heart attack rather than doing rehabilitation for those who have. That’s exactly where this field ought to be in 10 years, and that’s what we would call personalized health care with presymptomatic prevention and lifetime care.



Valerie Porr, M.A., thanks speakers.

Valerie Porr, President of the TARA National Association for Personality Disorder, thanked the speakers for providing presentations that put her “10 light years” ahead of most of the professionals her organization deals with on help-lines and at meetings. This new knowledge will allow Alliance members to educate their constituents, who can then take this valuable information into their individual communities.

Jane Honikman, President of Postpartum Support International, thanked the NIMH for bringing

consumers to the table. She asked for help with phrases she uses to get her point across—specifically that one of the greatest potential complications of pregnancy is depression. “I don’t have any proof. I’ve asked that at all sorts of meetings, and never gotten an answer. We need to get that statistic—my stakeholders think that if statistics are bigger, they are better—I think it is important to stay with the science,” asserted Honikman. Dr. Insel replied, “Approximately 30 percent of women who have a history of depression will relapse in the peripartum period. This is a big challenge, and we need to know how it happens—we still have a lot to learn in this area.”



Dr. Insel converses with Jane Honikman, President of Postpartum Support International, and Lydia Lewis, Director, Bipolar and Depression Support Alliance.



Cynthia Folcarelli (National Mental Health Association), Lynn Grefe (National Eating Disorders Association), and Melissa Plotkin, M.L.S., (National Association of Anorexia Nervosa and Associated Disorders)

Cynthia Folcarelli, Executive Vice President of the National Mental Health Association, said her organization is excited about the CATIE trial—particularly because it is looking at things like employment and personal relationships. Symptom reduction is not the only treatment goal.

“Getting a person back into society so that he or she can have a good quality of life is critically important,” continued Ms.

Folcarelli. She expressed concern that as resources become more limited, efforts to restrict treatments to only those that reduce symptoms will increase. This minimalist approach will not help them to live a full life. She thanked Dr. Lieberman for conveying the message that “one size does not fit all” in his presentation.

Lynn Grefe, CEO of the National Eating Disorders Association, emphasized that anorexia nervosa has the highest premature mortality rate of any mental illness. “Unless we get rid of the stigma that surrounds eating disorders, people will not seek treatment. Eating disorders are different because it’s not just the neck up—it’s all the way down to the toes. The people dying are young and I’m meeting many of the parents who are losing their children. It’s very sad, so unnecessary, and each memorial fund resulting from an eating disorder fatality reminds us of the need for more research and wider access to treatment,” said Grefe. Dr. Insel responded that we don’t have the scientific evidence that a specific treatment predictably works for this illness and we need randomized, controlled trials. Insel continued, “The irony is that you only get health insurance coverage once you collapse and go to the intensive care unit.” Dr. Giedd suggested that more work needs to be done to pursue the biology of eating disorders.

Educating policymakers about the seriousness of mental illnesses is a priority to key stakeholders and was a concern of many group representatives. For example, Mr. Sperling from the NAMI suggested that the mental health advocacy organizations work together to become more active in educational efforts on Capitol Hill. It is clear that there is still not a universal public understanding about mental illnesses; that they are very real, are one of the largest sources of disability worldwide, and are quite treatable in most cases. In fact, there was some discussion of the possibility of future attacks on science related to mental illness issues including what constitutes effective treatments. One participant suggested that having better statistics on the cost of specific mental illnesses would help to illustrate the seriousness of these diseases. Everyone appreciated the research updates and agreed this knowledge would allow them to better serve their constituents. Participants agreed that working together, especially in these uncertain financial times, is critical.

Prioritizing Research in Challenging Times

NIMH faces an enormous challenge in fulfilling its mission to reduce the burden of mental and behavioral disorders through research on the mind, brain, and behavior. The need is vast: mental disorders account for four of the top five causes of premature death and disability among 15-44 year olds in the Western world. For many of the disorders, there is some form of treatment; for most, there is no cure. Even for the disorders with extremely successful treatments, too many people do not have access to these treatments. For instance, about 16 percent of Americans ages 15-54 have experienced major depression in their lifetime and just over half of those experiencing it in the past year received treatment. While this is an improvement over previous years, it indicates the need for progress in treatment delivery.

Suicide is another real and enduring threat. While suicide rates are lower than they were 30 years ago, the rates are still alarming. Thirty thousand people in the U.S. die from suicide each year; far more than die from homicide. Suicide is high among several ethnic minority groups.

NIMH's goal is to generate research that will transform the prevention of, and recovery from, mental disorders. To achieve this goal, our grantees, scientists, and other staff must work closely with the Institute's stakeholders, Advisory Council members, and other experts in the field. The meetings of the NIMH Alliance for Research Progress are important components of the Institute's priority-setting activities as are consultations with the American public about NIMH's progress and future directions.



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