

# NARSAD *Research Newsletter*

National Alliance for Research on Schizophrenia and Affective Disorders

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**MOMENTUM**

*Center Section*

## *Genes, Brain, and Behavior*

### *A Profile of James L. Kennedy, M.D., FRCPC*

Dr. Kennedy's intrigue with neuroscience arose at age 16, during high school. While studying history and philosophy he became dissatisfied with the plethora of questions regarding human nature and the paucity of answers. As an undergraduate at York University in Toronto, he was influenced by the burgeoning field of physiological psychology, and he created a combined baccalaureate degree program for himself by taking the core courses in each of the departments of psychology and biology. The next step was a Master of Science degree in molecular neurobiology, studying messenger RNA in the rat brain. During his Masters degree, he realized that his interest in the relationship between the brain and human behavior was best studied within the context of medicine, where patients with psychiatric diseases would define some of the ways that brain mechanisms could go wrong.

During his first weeks in medical school, at the University of Calgary in Alberta, Canada, Dr. Kennedy focused immediately on psychiatry research, exploring what he felt were under-appreciated evolutionary connections between non-human primate behavior and human group behavior. In this process he visited and was influenced by Irving Yalom in Stanford and Michael McGuire and Lewis Baxter in UCLA. By the time he completed his internship, he finished a man-

uscript on evolutionary interpretations of processes in group psychotherapy with Roy MacKenzie that was submitted to the British Journal of Psychiatry and subsequently accepted as a lead article.

By now, Dr. Kennedy's motivation and curiosity regarding the origins of the major psychiatric disorders was in full swing, and he strode across the border to the USA to begin his residency training in psychiatry at Yale University. This was a very long way indeed from the tiny village of 200 people in rural Ontario where he was raised.

Dr. Kennedy chose Yale because of the strong tradition of research in psychiatry, and his clinical investigation skills were honed by the impressive faculty there including: Dennis Charney, Larry Price, Earl Giller, and Steve Bunney. In early 1987, the laboratory of Ken Kidd, in the Human Genetics department at Yale, became a high priority for Dr. Kennedy to visit to discuss the possibility of developing a research program that would add molecular genetics to his training in molecular neurobiology, human evolution, and clinical psychiatry. Dr. Kennedy arrived for his first appointment to meet with Dr. Kidd only to discover that the accomplished geneticist was nowhere to be found. Dr. Kidd had been called suddenly to Washington to speak at a press conference discussing the discovery of a gene for

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manic-depression in the Old Order Amish kindred.

Those were exciting times representing the early beginning of DNA laboratory studies in psychiatry, and Dr. Kennedy immediately became engrossed in Dr. Kidd's laboratory in the search for the gene for schizophrenia. Dr. Kidd had set up a collaboration with psychiatrist Lennart Wetterberg who had been studying a very large kindred in the far north of Sweden, and Dr. Kennedy was given the task of organizing the molecular genetic investigation in the laboratory. A year later in the spring of 1988 a major event occurred in Dr. Kennedy's life: he received news that he had won a NARSAD Young Investigator Award.

The NARSAD award had enormous impact. It guaranteed Dr. Kennedy's research efforts for the next two years, and allowed him to increase his time in the laboratory. He focused on testing the hypothesis that chromosome 5 was involved in schizophrenia in the Swedish kindred and, in November of 1988, his work was published in the journal *Nature*. Another series of experiments over the next two years involved testing genetic variation in new clones for dopamine receptors. With the collaboration of the late Dr. Hyman Niznik in Toronto, also a NARSAD Young Investigator, Dr. Kennedy co-authored another paper in *Nature* describing the genetic variation in the dopamine D1 receptor gene and discussing the implications for schizophrenia.

Dr. Kennedy applied for and received a renewal of his NARSAD Young Investigator Award in 1990. The renewal was invaluable in funding him through his next career transition as he moved back to Canada to take an

Assistant Professor position and start the Neurogenetics laboratory in the Department of Psychiatry at the University of Toronto. With very little in the way of operating funds for the new laboratory, the NARSAD award financed a large percentage of his work for his first year as an assistant professor. He was successful in using the NARSAD support to produce sufficient pilot data to bring him larger grants from Canadian agencies, and his research activities grew.

During this time Dr. Kennedy was working with another NARSAD Young Investigator, Dr. William Honer, to investigate a gene that was highlighted through Dr. Honer's work on antibody studies in post-mortem brain tissue from schizophrenia patients. The antibody strategy of Dr. Honer pulled from a brain library a gene that Dr. Kennedy identified as coding for a protein called alpha-3 integrin which is known to be involved in brain development. Further excitement ensued when Dr. Kennedy found that this gene was located among a group of important neurodevelopment genes on chromosome 17. Furthermore, the gene showed a modest degree of linkage with schizophrenia in a group of Italian families. However, additional studies revealed that the gene did not show linkage in the Swedish kindred or in Canadian schizophrenia families. Dr. Kennedy's first graduate student examined the expression of this gene in the mouse brain through development from birth to early adulthood to further characterize its function. Without replication of the initial findings in Italian families, it was not good



*James L. Kennedy, M.D., FRCPC*

use of limited resources to pursue the project further. However, Drs. Kennedy and Honer still wonder to this day whether the alpha-3 integrin gene may somehow play a role in schizophrenia.

Dr. Kennedy's research network among NARSAD awardees continued to grow in remarkable ways. He formed a collaboration in the early 1990s to work with Drs. Carlos and Michelle Pato to study schizophrenia and bipolar disorder on the Azores Islands. Dr. Kennedy applied for a NARSAD Independent Investigator award with Drs. Carlos and Michelle Pato to begin to recruit and diagnose families with schizophrenia on the islands. Dr. Kennedy was successful in obtaining NARSAD funding for this project in the mid-1990s, allowing the team to retain psychiatrists on the islands to trace geneologies and interview families. This paved the way for not one, but two subsequent NIMH R-01 awards that continue to support the Azores Islands project through the present time. Initial results from the laboratories of Drs. Kennedy and Pato in the first set of families collected suggest that Azorean fami-

lies with psychotic disorders may have a higher rate of unstable DNA in their chromosomes, leading to the possibility of unstable DNA being a risk factor for bipolar disorder and schizophrenia.

At the present time, Dr. Kennedy is examining the intriguing question as to what are the similarities and differences between the attentional deficits in schizophrenia and Attention Deficit Hyperactivity Disorder (ADHD). Dr. Kennedy's laboratory was the first to report, in 1996, the association between the dopamine D4 receptor gene and ADHD, a finding which has been replicated at least seven times to date. Dr. Kennedy's group has shown recently that the D4 gene association also exists in the adult ADHD population. Such a high degree of replication is rare in psychiatric genetics, and this finding may represent one of the few true genetic associations to date in molecular genetics of behavioral disorders.

As of July 1, 2000, Dr. Kennedy has been promoted to the rank of Full Professor in the University of Toronto, and promoted to Head, Department of Neuroscience, at the Centre for Addiction and Mental Health. ❖

*In 1996, Dr. Kennedy was invited to serve on the NARSAD Scientific Council. He was the first former NARSAD Young Investigator to be elected to this elite scientific group.*



## Books by NARSAD Scientists A Review

### **"I AM NOT SICK, I DON'T NEED HELP!" Helping The Seriously Mentally Ill Accept Treatment**

*A practical guide for families and therapists by Xavier Amador, Ph.D.,  
with Anna-Lisa Johanson, publisher, Vida Press.*

Xavier Amador, Ph.D., of Columbia University, recipient of a NARSAD Young Investigator Award in 1990, has written a book based on his clinical practice and his studies of patient and family behavior. His focus on family understanding and support is the central theme of this "Practical Guide."

Constance Lieber, President of NARSAD, had this to say in the foreword of this valued book. "There is probably no more difficult or more important responsibility for a family member in our society than meeting the needs of a mentally ill child, sibling or close relative. Daily life can be a struggle and the future impenetrable with uncertainty. Dr. Amador has taken up the challenge of guiding the family member in order to bring a better life to the afflicted patient and the responsible relatives. The unique combination of sensitivities he brings to this task reflect both his life experience as a sibling of an afflicted brother and his many years of broad clinical practice.

Reflecting his own profound empathy and insight, the book is a guide to the shocked, bewildered and too often hopeless close relative. It is no mere compendium of generalizations. It is a practical, step-by-step, program for achieving understanding and even expressing love in a situation where that love is difficult to convey.

His is a remarkable achievement and a great public service. Many lives of patients and their loved ones could be enhanced, often immeasurably, if copies of this book were given to the families of every patient who begins to show signs of psychosis. As people use this book, it will make the beginning of a sound remediation and even rehabilitation."

Herbert Pardes, M.D., President of NARSAD's Scientific Council, wrote the following in his preface: "I Am Not Sick, I Don't Need Help!" is essential reading material for family members battling with their mentally ill loved ones about the need for treatment. Dr. Amador provides an insightful, compassionate, and practical guide for handling the frustration and the guilt that inevitably arises when dealing with a sick individual who, by virtue of their illness, is completely unaware of the need for treatment.

What make this book especially poignant is Dr. Amador's inclusion of his own personal account of his lifelong struggle with his own brother who suffers from schizophrenia, as well as his detailed presentations of patient cases. He does an exceptional job summarizing the compelling science behind poor insight, or anosognosia, clarifying that the loved one's lack of insight is not a product of a psychological defense mechanism, but is a result of the very brain dysfunction that underlies the illness. Practical tips on how to help a loved one with poor insight accept treatment or how to proceed with civil commitment, if necessary, make this book especially useful. ❖

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# NARSAD Announces Independent Investigators

by Alan S. Brown, M.D.

NARSAD is pleased to announce the awarding of 50 Independent Investigator Grants in 2000. With the addition of this new commitment, NARSAD has now awarded, since the inception of its program in 1987, \$99 million to fund 2,403 grants to 1,237 scientists at 164 universities and medical research institutions.

The goal of NARSAD's Independent Investigator Program, which was initiated in 1995, is to provide support for investigators at the critical juncture between initiating independent research and achieving sustained funding.

These \$50,000 per annum, two-year grants are awarded to mid-level scientists, at the associate professor level, who are clearly independent and have won national, competitive support as a principal investigator.

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## **Anissa Abi-Dargham, M.D.,** *of Columbia University*

is conducting neuroimaging studies on chronic abusers of PCP ("angel dust") in order to examine abnormalities of brain function that might be similar to those observed in schizophrenia. Previous work suggests that one of the receptors on which PCP acts (the NMDA receptor) is underactive in schizophrenia. Dr. Abi-Dargham will use the following brain imaging techniques: positron emission tomography (PET) to examine the dopamine type 1 (D1) receptor; magnetic resonance spectroscopy (MRS) to quantify the neuronal marker n-acetyl-aspartate; and functional magnetic resonance imaging (fMRI) to measure blood flow activation following a working memory task. The findings from this study may help support the validity of NMDA receptor underactivation in schizophrenia, and further justify the search for new medications that enhance NMDA transmission in the treatment of schizophrenia.

## **David Allison, Ph.D.,** *of Columbia University*

is investigating the biological mechanisms that underlie weight gain caused by antipsychotic medications. It has long been known that antipsychotics can cause dramatic weight gains that may threaten health and reduce medication compliance. Dr. Allison plans to refine a mouse model of atypical antipsychotic effects on food intake and body weight using mice varying in the number of

serotonin type 2c (5HT-2c) receptor genes. In addition, the mechanism which prevents weight gain following treatment with ziprasidone, an atypical antipsychotic, will be explored. Finally, olanzapine, another atypical antipsychotic, will be tested to determine whether its weight gain properties are mediated by blocking the 5HT-2c receptor. For this study, transgenic mice (i.e. mice with extra genes for the 5HT-2c receptor) will be used. This work has important clinical implications, including the development of new antipsychotics which result in minimal or no weight gain.

## **Steven Arnold, M.D.,** *of the University of Pennsylvania*

is investigating the molecular mechanisms that underlie abnormalities of nerve cell connectivity in autopsied brains of patients with schizophrenia. Previous work has demonstrated abnormalities of the olfactory system (the system which governs the identification of odors) in schizophrenia. These abnormalities are believed to be caused in part by disturbances in brain development, as well as disruptions later in life. Patients with schizophrenia appear to have diminished innervation of the olfactory system. To investigate this question further, Dr. Arnold will examine autopsied brains of schizophrenia patients and matched controls in order to assess the distribution and intensity of specific proteins, such as cell adhesion molecules and growth factors that guide nerves to their appropriate targets and that establish connections with those targets in the olfactory bulb. This work may shed new light on the abnormal neural connectivity present in schizophrenia.

## **Karen Faith Berman, M.D.,** *of the National Institute of Mental Health*

is examining the brain mechanisms that underlie severe premenstrual syndrome, a cyclical disorder characterized by disabling mood-related symptoms. There are many indications that these symptoms are

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*Alan S. Brown, M.D., of Columbia University, is a frequent guest writer for NARSAD's Newsletter. He received NARSAD's Young Investigator Award both in 1993 and 1996, is a recipient of NARSAD's Independent Investigator Award in 2000, and was presented with the A.E. Bennett Research Award at this year's Biological Psychiatry Meeting in Chicago, IL. A summary of his award-winning paper is highlighted on Page 30.*

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related to the female hormones estrogen and progesterone, but the mechanisms by which abnormalities of these hormones are not well defined. Dr. Berman will use a safe medicine that temporarily turns off ovarian function in women with severe PMS and normal controls. She will then use several brain imaging tools, including positron emission tomography, functional magnetic resonance imaging, and magnetic resonance spectroscopy, to define brain changes during the absence of these hormones and during hormone replacement. This work may provide a better understanding of the brain alterations that cause this recurrent and disabling disorder.

**Alan S. Brown, M.D.,**  
*of Columbia University*

will examine the relationship between prenatal exposure to influenza and to essential fatty acid deficiency in patients with schizophrenia. Previous studies suggest associations between these two potential risk factors, but the findings have been generally inconclusive. To address this question, Dr. Brown will capitalize upon a precious and unique resource—stored maternal serum specimens drawn during the prenatal period—in subjects from a large birth cohort in which he has conducted a follow-up study for schizophrenia. Serologic analyses will be conducted to quantify these two potential risk factors, and cases of schizophrenia will be compared with non-schizophrenic controls from the cohort on these measures. The use of serologically obtained measures to define exposure status introduces an important methodologic advantage to previous studies, which generally relied upon data from epidemics or maternal recall of the exposure following pregnancy. Findings generated from this study have the potential to identify important strategies for prevention and result in a better understanding of the causal mechanisms which underlie this devastating illness.

**Charles J. Bruce, Ph.D.,**  
*of Yale University*

is investigating the neural mechanisms that underlie eye tracking dysfunction. A dysfunction of eye tracking is one of the most robust findings in schizophrenia. Dr. Bruce will examine, in rhesus monkeys, the two principal eye movement tasks that schizophrenic patients and their relatives typically demonstrate: smooth pursuit tracking; and memory saccades. These monkeys will be evaluated on these two sets of tasks after administration of drugs including PCP (“angel dust”) which induce symptoms of schizophrenia in humans. In addition, electrophysiologic studies and functional magnetic resonance imaging will be used to map sites in pre-

frontal cortex that contribute to these eye movements. Moreover the eye tracking tasks will also be tested during temporary inactivation to analyze the different roles of the brain areas within the prefrontal cortex. The results of this study will help to elucidate the relationship between frontal lobe function and eye tracking dysfunction in schizophrenia.

**Linda Brzustowicz, M.D.,**  
*of Rutgers University*

is attempting to identify genes that increase the vulnerability to schizophrenia. Her previous work suggests that a schizophrenia gene may reside on a specific region of chromosome 1. Using molecular genetic techniques, Dr. Brzustowicz will develop a fine genetic map of this region and screen ten genes in this candidate region for mutations. The mutations that appear the most promising will then be sequenced for their chemical composition. The identification of a gene involved in the susceptibility to schizophrenia will permit important insights into the origins of this disorder, as well as ultimately lead to preventive strategies.

**Brett A. Clementz, Ph.D.,**  
*of the University of California-San Diego*

is conducting a genetic study of schizophrenia among a unique isolated population. He will study five families, consisting of over 200 individuals, on the small Pacific island nation of Palau. Family members will undergo tests to identify eye movement and EEG abnormalities that are common in relatives of patients with schizophrenia and that likely have a genetic basis. These traits are easier to quantify than the clinical disorder, and provide information that is closer to the brain abnormalities which produce the symptoms of schizophrenia. The use of a population isolate provides a more homogeneous sample, facilitating the identification of causal genes. Blood samples and DNA markers have already been identified for most of the members of these families. This project has the potential to identify causal genes for schizophrenia and its associated neurobiological abnormalities, with important implications for prevention and for understanding the mechanisms that lead to this disorder.

**Raymond F. Deicken, M.D.,**  
*of the University of California-San Francisco*

is using a technique called proton magnetic resonance spectroscopic imaging (MRSI) to quantify subtle manifestations of nerve cell dysfunction in patients with major depression. Previous work suggests that connections between frontal, limbic, and subcortical brain regions are important in the regulation of mood. Dr. Deicken will use MRSI to

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quantify levels of n-acetyl-aspartate (NAA), a neuronal marker that is very sensitive to nerve cell loss or maldevelopment. He will test the hypothesis that neuronal integrity is compromised, as evidenced by reduced NAA, in specific brain regions in the fronto-limbic-subcortical circuit among patients with major depression. In addition, the study will examine whether abnormal connectivity exists between these brain regions in the white matter. Finally, the hypothesis that greater duration and severity of depressive illness is associated with increased NAA reductions will be tested. This work may have important implications for treatments aimed at reducing the severity and frequency of depressive episodes.

**Gary Duncan, Ph.D.,**

*of the University of North Carolina-Chapel Hill*

is aiming to investigate the mechanisms of action of antipsychotic medications in schizophrenia. Previous work suggests that diminished function of the NMDA receptor may play a role in schizophrenia. The atypical antipsychotic drugs, clozapine and olanzapine, suppress brain activation induced by ketamine, an agent which blocks the NMDA receptor. Dr. Duncan will compare ketamine-induced alterations in brain metabolism with alterations observed in mice which are deficient in a specific NMDA receptor during the prepubertal and postpubertal developmental stages. In addition, he will examine the effects of atypical and typical antipsychotic medications using this experimental model. This work has the potential to lead to the identification of not only how antipsychotics work, but also the abnormal biochemical and developmental mechanisms that could be involved in schizophrenia.

**Rif S. El-Mallakh, M.D.,**

*of the University of Louisville*

will examine whether patients with bipolar disorder have an abnormality in a chemical called digoxin-like factor (DLF). This chemical, which resembles a medication called digoxin, appears to be decreased in the brains of subjects with mania. In the present study, it is hypothesized that patients with bipolar disorder may not make this hormone correctly when they are under stress, and that it could play a role in the development of mania. Dr. El-Mallakh will quantify DLF in bipolar patients before and after exercise, which normally increases levels of DLF. It is anticipated that healthy controls will show the expected increase, but bipolar subjects will not. If group differences are found, a larger, more extensive study will be conducted to establish whether this DLF abnormality is a characteristic of bipolar disorder.

**Carol A. Glod, Ph.D.,**

*of Northeastern University*

is conducting a double-blind, placebo-controlled, 8-week trial aimed at comparing the effectiveness of bupropion (Wellbutrin) SR and fluoxetine (Prozac) in the treatment of adolescent depression. It is hypothesized that both medications will significantly reduce the severity of depressive symptoms compared with placebo. There will be 150 subjects recruited; a total of 75 are expected to complete the trial. Subjects will receive rating scales which measure depressive symptoms and clinical functioning before and during the trial. This work may provide important new evidence for the use of bupropion in major depression in adolescents.

**Benjamin D. Greenberg, M.D.,**

*of Brown University*

proposes to study a technique called deep brain stimulation (DBS) as a treatment of severe obsessive-compulsive disorder (OCD) in patients who do not respond to standard treatments. DBS is believed to work by blocking abnormal activity in brain circuits in a region called the internal capsule. In this project, stimulating electrodes will be placed into the internal capsule and connected to a battery pack which will be placed under the skin. An intensive five-day preliminary trial will begin, followed by a longer-term outpatient phase. In addition, positron emission tomography (PET) scans will be performed to quantify how the stimulation changes activity in brain circuits believed to underlie OCD symptoms. This work will provide preliminary data on the safety and effectiveness of DBS in OCD patients who do not respond to conventional treatments.

**Robert D. Hawkins, Ph.D.,**

*of Columbia University*

will investigate the mechanisms which underlie abnormalities in presynaptic proteins in schizophrenia. These proteins are involved in the release of neurotransmitters at the synapse (the connection between adjacent nerve cells). These abnormalities could be related to changes in long-term potentiation (LTP), which is thought to contribute to the establishment and fine-tuning of cortical circuitry during development and learning. Dr. Hawkins will investigate whether alterations in presynaptic proteins represent changes in synthesis and transport of the proteins, local redistribution of the proteins, or increased exposure of the antibody binding sites of these proteins. These studies should provide information that may explain the causes of abnormal presynaptic protein levels in the brains of patients with schizophrenia.

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**Tadafumi Kato, M.D.,***of the University of Tokyo*

will examine whether abnormalities of calcium regulation in a cellular organelle called mitochondria occur in patients with bipolar disorder. The mitochondria are the energy-producing components of the cell. Based on previous work, it is hypothesized that mitochondrial dysfunction causes increased levels of calcium and increased vulnerability to cell death, leading to rapid-cycling in bipolar disorder. Cell lines produced from platelets and the olfactory mucosa (the tissue responsible for the sense of smell) will be immortalized, and biochemical processes causing an enhanced calcium response in bipolar patients will be investigated. This work has the potential to result in new medications which improve the symptoms of bipolar disorder by reversing abnormalities of calcium regulation.

**Kwang-Soo Kim, Ph.D.,***of Harvard University*

will investigate the control mechanisms underlying the expression of the human norepinephrine transporter (NET). The NET is responsible for the reuptake of the norepinephrine, a neurotransmitter implicated in depression; consequently, the NET is a prime target for antidepressant medications. Regulatory sequences of the NET gene critical for its expression will be defined using mice with altered genes and cell culture experiments. The results from this proposal will generate critical information that will likely be of value in better understanding and treating major depression.

**David G. King, Ph.D.,***of Southern Illinois University-Carbondale*

will study the correlation between bipolar disorder and a phenomenon called binocular rivalry, which occurs when different, conflicting visual images are separately but simultaneously presented to the two eyes. It is hypothesized that this perceptual function occurs more slowly in bipolar patients. In addition, the project will determine whether binocular rivalry abnormalities show genetic anticipation, that is, do they become more extreme with successive generations? A finding that both bipolar disorder and binocular rivalry disturbances show this pattern would strengthen the conclusion that these phenomena share a single underlying mechanism. Several hundred individuals, with an emphasis on pairs of first-degree relatives, will be studied.

**Gregory G. Kolden, Ph.D.,***of the University of Wisconsin-Madison*

will refine and pilot-test a comprehensive treatment for recurrent depression. This treatment is called Integrative Therapy for Recurrent Depression (ITRD), which blends components of two demonstrably effective psychotherapies, Interpersonal Therapy (IPT) and Dialectical Behavior Therapy (DBT). ITRD specifically targets and promotes emotional stability and relapse prevention by emphasizing both the interpersonal focus of IPT and the emotion-focused strategies of DBT. The study will be conducted in two phases. In the first phase, a manual will be constructed, staff will be trained, and pilot testing will occur. In the second phase, patient volunteers will be recruited to receive ITRD in addition to continuing their medication treatment. This project may lead to a promising new strategy for treating individuals with recurrent depression.

**Edward H. Koo, M.D.,***of the University of California-San Diego*

is investigating whether abnormalities in a biochemical pathway called the Wnt/beta catenin pathway is one contributor to the mechanisms that control complex neuropsychiatric behaviors. The Wnt family of proteins play key roles in embryonic development. Animals in which the gene for a related protein is “knocked out” have abnormal social behaviors and reduced prepulse inhibition, both of which are observed in patients with schizophrenia. Dr. Koo will determine which biochemical pathway is required for the behaviors noted in these knock-out mice, and will test at which stage of brain development the mutation is required for these behaviors. This work may provide compelling evidence that some of these abnormal behaviors are a consequence of developmental disruption, possibly from “miswiring” of the nerve cell contacts. Such work may have implications for better understanding the developmental origins of schizophrenia.

**Mary F. Kritzer, Ph.D.,***SUNY-Stony Brook*

will examine ovarian hormone regulation of dopamine and serotonin in brain areas linked to the causes and treatment of schizophrenia. The effects of hormone manipulations on dopamine transmission in mature rhesus monkeys will be examined. In addition, the project will probe for regulation of serotonin, abnormalities of which have also been demonstrated in schizophrenia. This work has the potential to further elucidate the biochemical basis of schizophrenia, and the relation of female hormones to these neurochemicals.

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**Jayashri Kulkarni, M.B.B.S., M.P.M., Ph.D.,**  
*of Monash University-Australia*

will conduct a placebo-controlled study of a skin patch containing estrogen plus an antipsychotic medication in postmenopausal women with schizophrenia. Previous work demonstrated that oral estrogen and estrogen administered via a skin patch improved symptoms more rapidly and had a more sustained response than taking antipsychotic medication alone. This work may provide an important new additive treatment for schizophrenia, and have implications for the hypothesis that estrogen may protect against the symptoms of schizophrenia.

**Herbert M. Lachman, M.D.,**  
*of Albert Einstein College of Medicine*

will analyze all brain expressed genes on chromosome 22q11 in order to identify a gene that increases susceptibility to bipolar disorder. Previous work has demonstrated that velocardiofacial syndrome, caused by a deletion on chromosome 22, is associated with a variety of psychiatric outcomes, including bipolar disorder. This work will capitalize on the recent publication of the entire chromosome 22 DNA sequence. Dr. Lachman will attempt to identify several candidate genes on chromosome 22q11 for mutations that underlie the vulnerability to develop bipolar disorder. The identification of genes for bipolar disorder has important promise for prevention, and unraveling the pathogenesis of this illness.

**Adrienne C. Lahti, M.D.,**  
*of the University of Maryland-Baltimore*

will conduct imaging studies using a cognitive task in relatives of patients with schizophrenia who perform poorly on a smooth pursuit eye movement (SPEM) test. SPEM abnormalities occur much more frequently in patients with schizophrenia and their family members, suggesting that SPEM dysfunction represents a biological marker of the genetic vulnerability to schizophrenia. Identified first-degree relatives of schizophrenia patients will be scanned and complete a battery of neuropsychological tests. Patterns of brain activation will be contrasted between relatives with and without SPEM abnormalities, normal volunteers, and schizophrenia patients. The relationship between learning and memory measures and patterns of brain activation will be examined in relatives. This work has the potential to identify the neural mechanisms underlying cognitive dysfunction and SPEM abnormalities that are related to the genetic liability to schizophrenia.

**Jose de Leon, M.D.,**  
*of the University of Kentucky*

will investigate whether lack of tolerance and response to risperidone (Risperdal) is due to deficiencies and excesses, respectively, of an enzyme called cytochrome P450. Patients with only 1 or 2 copies of this gene are considered poor metabolizers, and are hypothesized to have high blood levels of risperidone, even at relatively small dosages. Patients with three or more copies of this gene are considered rapid metabolizers, and are hypothesized to show a diminished therapeutic response to risperidone because of inadequate blood levels. This study will examine the reason for discontinuation of risperidone in 300 patients and have analyses conducted of the gene for cytochrome P450. This work may lead to new clinical guidelines for the use of risperidone, which are based on the type of cytochrome P450 gene present.

**Fabio Macciardi, M.D., Ph.D.,**  
*of the University of Toronto*

will apply a sophisticated molecular genetic called haplotype linkage disequilibrium analysis, in an attempt to isolate a gene that increases risk for schizophrenia. Previous work suggests that such a gene may reside on chromosome 22. The haplotype linkage disequilibrium test permits the evaluation of the joint effect of multiple genes, or of multiple variants within one gene. Dr. Macciardi will study a large sample of schizophrenic patients and their families in order to characterize the presence of one or more susceptibility genes in the region of chromosome 22 that has been associated with an increased risk of schizophrenia. The identification of such genes holds promise toward preventing and better understanding the pathogenesis of schizophrenia.

**Hari Manev, M.D.,**  
*of the University of Illinois-Chicago*

will investigate whether antidepressants can be used as a tool to elucidate the mechanisms of neurogenesis (new nerve cell growth). It has been previously demonstrated that antidepressants such as fluoxetine can stimulate the growth of new neurons. Dr. Manev will characterize the action of antidepressants on neurogenesis in cultured neurons of rats; investigate whether these effects can be induced after birth; characterize the selectivity of antidepressants in stimulating cell proliferation in the adult hippocampus; and characterize the contribution of serotonin to hippocampal proliferation induced by fluoxetine. This work promises to contribute significantly to understanding the pathophysiology of depression and other psychiatric disorders.

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**Laura Mufson, Ph.D.,***of Columbia University*

will conduct a pilot controlled clinical trial of interpersonal psychotherapy with adolescents suffering from dysthymia (chronic depression), major depression, and adjustment disorder with depressed mood. She will test the feasibility, acceptability and preliminary effectiveness of treating depressed adolescents with 16 weeks of group, as compared to individual, interpersonal psychotherapy. If interpersonal psychotherapy is demonstrated to be effective, it has the potential to be used in a variety of settings as a cost-effective and efficient way of treating the underserved depressed adolescent population.

**Andrew Nierenberg, M.D.,***of Harvard University*

will conduct a longitudinal examination of risk for affective disorders in 50 children of parents with bipolar disorder. These children and their parents received structured diagnostic interviews 5-6 years ago, and in the present study they will be re-administered these interviews. It is hypothesized that at the 5-year follow-up, children of patients with early-onset bipolar disorder who had received a diagnosis of disruptive behavior disorders, and one of several co-existing disorders, will demonstrate significantly greater rates of affective disorders than children of bipolar patients who did not meet criteria for these disorders. In addition, the investigators will attempt to replicate the findings of the original study. This work may represent the first stage in planning for a primary preventive intervention of children at risk for bipolar disorder.

**Jose N. Nobrega, Ph.D.,***of the University of Toronto*

is investigating whether alterations in non-dopaminergic receptors play a role in long-term side effects of antipsychotic medications. These side effects include tardive dyskinesia and can be tested in animal models by observing vacuous chewing movements (VCM). Dr. Nobrega will screen hundreds of genes to identify those that may be specifically associated with VCM vulnerability. Then, he will determine whether VCM and the accompanying gene alterations develop in mice lacking specific subtypes of dopamine receptors. This study should provide new and possibly fundamental important information about the nature of brain changes responsible for tardive dyskinesia and the role of dopamine receptors in that process.

**Michael J. Owens, Ph.D.,***of Emory University*

will examine the role of different receptors for corticotropin releasing factor (CRF) in regulating the stress response. Previous work has shown that CRF appears to control many physiological and behavioral responses to stressful situations. In addition, some depressed patients have overactive CRF systems. Dr. Owens will use viral particles that have been modified to selectively increase or decrease the synthesis of the CRF-2A receptor and urocortin (a neurotransmitter related to CRF) in the brain. Specifically, he will determine whether increases in function of CRF-2A and urocortin are responsible for the effects observed following administration of anti-stress/anti-anxiety medications. If they are important in mediating stress and anxiety effects of these medications, then these might be ideal targets for new types of medications.

**Laszlo Papp, M.D.,***of Columbia University*

will examine the effectiveness of cognitive behavioral therapy (CBT) in elderly patients who have both depression and anxiety disorders. Previous studies routinely exclude elderly patients with these conditions from pharmacologic trials and, in addition, elderly patients generally suffer more side effects to antidepressants. Dr. Papp will therefore administer CBT to 20 elderly patients with both depression and anxiety, in addition to CBT “booster” sessions. Non-responders will receive venlafaxine (Effexor) followed by a trial of mirtazepine (Remeron). The results from this study will be used to refine a CBT manual developed from this work, optimize pharmacotherapy for non-responders, and design a controlled study with a larger sample size.

**Daniel S. Pine, M.D.,***of Columbia University*

will use functional MRI (fMRI) to document abnormalities in the prefrontal brain regions of adolescents at high risk for major depression. A group of 20 high risk and 20 low-risk adolescents will be studied. At-risk status will be defined based on parental history of depression and prior history of childhood anxiety. For the fMRI scan, subjects will perform an emotional discrimination/attention task, previously shown to activate ventral prefrontal brain regions. Non-depressed adolescents at high risk for depression are expected to show abnormal activity profiles in ventral brain regions, relative to those at low risk for depression.

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**Steven A. Rasmussen, M.D.,**

*of Brown University*

is using a neurosurgical procedure called gamma capsulotomy for the treatment of patients with severe obsessive compulsive disorder (OCD). Gamma capsulotomy is a new radiosurgical technique that focuses beams of cobalt gamma rays and lesions a small target deep in the brain, much as a magnifying glass focuses the rays of the sun. Because the gamma rays pass directly into the skull, the procedure does not require the neurosurgeon to open the cranium or enter the brain itself. Patients will be evaluated with a comprehensive battery of diagnostic examinations before, during, and following the procedure. This study should confirm the long term effectiveness and safety of this procedure in the treatment of severe OCD that has failed to respond to all other available treatments and should contribute to our understanding of the neural circuitry that appears to be involved in the pathogenesis of this disorder.

**Perry F. Renshaw, M.D., Ph.D.,**

*of Harvard University*

is using a technique called magnetic resonance spectroscopy (MRS) to quantify levels of a chemical called adenosine in the human brains of patients with major depression. Previous work suggests that levels of adenosine may be associated with response to antidepressant treatment. Dr. Renshaw will use a powerful magnetic resonance scanner to determine the extent to which brain adenosine levels are increased following the administration of S-adenosylmethionine (SAME), which increases adenosine and appears to have antidepressant efficacy. A study in 20 healthy volunteers will be followed by a clinical trial of SAME in 20 depressed subjects. This work has the promise of leading to new insights regarding the relationship between depression and adenosine levels.

**David Rosenberg, M.D.,**

*of Wayne State University*

will examine the effect of fluoxetine (Prozac) on brain levels of choline-containing compounds (cho) in children and adolescents with major depression. Abnormalities of brain cho are believed to be most pronounced in adult depressed patients who respond to treatment with serotonergic antidepressants. Dr. Rosenberg will study whether fluoxetine reduces cho levels in critical brain regions of pediatric major depressives, and if individual differences in cho concentrations determine resistance or sensitivity to fluoxetine's therapeutic effects. A non-invasive technique called magnetic resonance spectroscopy (MRS) will be used to monitor these

changes in cho. This work may eventually result in a new tool to predict which individuals respond to antidepressant medication.

**Randall R. Sakai, Ph.D.,**

*of the University of Cincinnati*

will investigate the hormone, brain chemical, and brain structural profile of animals exposed to prolonged stress. Recent studies suggest a valid animal model of clinical depression which makes use of a visible burrow system. Animals in this system have reduced social, sexual, and aggressive activity, changes in sleep cycles, and weight loss associated with lower food intake. In addition, nerve cells in the hippocampus of animals in this system undergo "remodeling" similar to that of animals which receive chronic doses of stress hormones. This proposal attempts to better understand this remodeling process as well as ascertain whether it occurs with concurrent changes in cell birth or death.

**Claudia Schmauss, M.D.,**

*of Columbia University*

will examine the distribution of a gene called c-fos in the forebrain of animals whose dopamine type 2 (D2) and type 3 (D3) receptors have been deleted (so-called "knockout mice"). C-fos is a molecular marker for neuronal activity. Dr. Schmauss will treat these mice with a single dose of a drug that stimulates dopamine type 1 (D1) receptors or with amphetamine. This experiment, and other proposed studies, will test whether the different types of pharmacological stimulation activate different neuronal circuitries. This work may lead to potential therapeutic benefit of intermittent activation of D1 receptors during chronic treatment with typical antipsychotic medications.

**Stephen M. Strakowski, M.D.,**

*of the University of Cincinnati*

will examine brain activity in recovered patients with bipolar disorder while they are performing a simple test of attention (the Stroop test). Previous studies have demonstrated that performance on the Stroop test is sensitive to mood state. Patients with bipolar disorder and healthy controls will receive the Stroop test while functional magnetic resonance imaging (fMRI) testing is performed. Differences in brain activation will be performed in response to different conditions on the Stroop test. These results may help to identify which brain regions are not functioning properly in patients with bipolar disorder to better understand its causes.

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**Jane R. Taylor, Ph.D.,***of Yale University*

will investigate the neurobiological underpinnings of cognitive impulsivity. The hypothesis to be tested is that cortical dopamine dysfunction, induced by prior long-term exposure to PCP (“angel dust”) or amphetamine, will produce cognitive impulsivity (deficits in response control, attentional function, and working memory). Alterations in dopamine transmission, and in an enzyme essential for the response elicited by dopamine receptor stimulation, will be examined in relation to cognitive impulsivity. This model system may have important implications for better understanding the biological abnormalities that underlie schizophrenia.

**Leonardo Tondo, M.D.,***of Harvard University*

will evaluate the effectiveness of mood-stabilizing medications in patients with unipolar and bipolar disorder. Patients will receive lithium and anticonvulsants with or without other adjunctive treatments. The effectiveness of these treatments will be evaluated with ratings of the frequency and duration of episodes, and the risk of suicide. This work may have important clinical implications for appropriate usage of mood-stabilizers in both unipolar depression and bipolar disorder.

**Stephen F. Traynelis, Ph.D.,***of Emory University*

will evaluate the effect of the selective receptor (PAR1) activating compounds in mice on NMDA receptor current responses. Previous work suggests that activation of protease receptors can increase the activity of NMDA receptors in the brain. Dysfunction of the NMDA receptor has been implicated in the pathophysiology of schizophrenia. Dr. Traynelis will use sophisticated techniques including whole cell voltage clamp of neurons in the deep layers of the cingulate cortex and subiculum, brain regions potentially relevant to schizophrenia. This work will help to determine the reasons behind the stimulating effect of PAR1 on NMDA receptor function. A better understanding of PAR1’s ability to enhance NMDA receptors may suggest opportunities for new medications to address diminished function of the NMDA receptor in schizophrenia.

**Eric E. Turner, M.D., Ph.D.,***of the University of California-San Diego*

is conducting a study on the basic mechanisms of brain development and gene regulation. In particular, he is examining the role of a regulatory molecule, called a transcription factor, which binds to

DNA in the nucleus of neurons and switches on and off the activity of specific neuronal genes. Recent work has led to the creation of genetically altered mice (“knockouts”) that produce a marker enzyme for the transcription factor Brn-3.0. Mice that are deficient in this factor sprout axons (neuronal projections) in many inappropriate places, often missing their targets. In this proposal, Dr. Turner will interbreed mice expressing this marker enzyme with strains of mice carrying genetic defects for control of neuronal path-finding and survival, to assess whether these defects resemble the axonal mistakes noted in the Brn-3.0 knockout mice strain. This work may lead to a better understanding of abnormal brain developmental mechanisms in disorders such as schizophrenia.

**Ralph M. Turner, Ph.D.,***of the Noyes Research Foundation-Pennsylvania*

is working to cross-validate a new theoretical model which views suicide as an emergent dynamic process, and not simply a linear summation of risk factors. In addition, he will determine the similarities and differences in the emergent process of suicide activation among schizophrenic, schizoaffective, and mood-disordered patients. For this purpose, 150 patients will be assessed on the primary variables in this theoretical model, and the adequacy of this model will be tested. This work may help to confirm the investigator’s hypothesis, with important implications, including the prevention of suicide in schizophrenia and mood disorders.

**Flora M. Vaccarino, M.D.,***of Yale University*

will investigate molecular events that are necessary for cell growth and the formation of new neurons in the adult brain of mammals. Previous work suggests that neuronal loss within the hippocampus of depressed patients is produced by stress, and these changes are due to a decrease in the proliferation of new neurons. Fibroblast growth factor-2 (FGF-2) is involved in the proliferation of these cells during embryonic development. It is hypothesized that FGF-2 is also required during the postnatal period for the formation of new neurons in the hippocampus and other brain regions. This study will test whether FGF-2 and a closely related molecule, FGF-1, are necessary for this neuronal proliferation. This work may yield essential new insights into the role of disturbances of neuronal growth and proliferation in depression.

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**Christopher H. Van Dyck, M.D.,***of Yale University*

will examine whether patients with Alzheimer's disease and major depression have reduced binding of serotonin receptors and reduced brainstem serotonin transporter binding, compared to Alzheimer's patients without depressive symptoms. Prior work suggests that depression may be related to dysfunction of the brain's serotonin system in Alzheimer's disease. The ability to relate the "serotonergic deficit" of Alzheimer's to depression is critical for a more coherent treatment of this condition. Positron emission tomography (PET) using specific ligands for the serotonin system will be used for this study. The results of this work should enhance our understanding of the pathophysiology and treatment of depression in Alzheimer's disease.

**Sophia Vinogradov, M.D.,***of the University of California-San Francisco*

aims to design a set of computer-based intensive cognitive training exercises which target key domains of neurocognitive impairment in schizophrenia. In a recent pilot study, a cognitive training program was applied to patients with schizophrenia. These findings suggest that this intervention improved symptom profile, verbal/symbolic memory, and verbal short-term memory. In the present study, Dr. Vinogradov will use this technique to target short-term memory, neuromotor sequencing, and cognitive flexibility. In addition, the symptom profile, quality of life, and neurocognitive performance will be evaluated before and after the intervention. Finally, the effects of the exercises will be compared to those of a non-specific control task. This work has the potential to improve psychosocial functioning, which is believed to be secondary to neurocognitive dysfunction, in patients with schizophrenia.

**Michael W. Vogel, Ph.D.,***of the University of Maryland-Baltimore*

will study the nature and localization of anatomic and neurochemical abnormalities that may contribute to the pathophysiology of schizophrenia. Previous studies have demonstrated dysfunction of "limbic" cortical regions of the brain, including the hippocampus, entorhinal cortex, and anterior cingulate in patients with schizophrenia. Dr. Vogel will pair anatomic and neurochemical measures to analyze postmortem brains of patients with schizophrenia in these brain regions and in the thalamus. The study will analyze markers for nerve cell structure and neurotransmitter systems in these brain regions. It is hypothesized that there will be a reduction in the activity of the glutamate hippocampal signals

from the hippocampus to its projection areas; this abnormality is believed to be related to delusions and hallucinations in schizophrenia. It is further hypothesized that these neurochemical abnormalities will be present in the same neurons which have altered density of synapses (the connections between nerve cells) and dendrites (the neuronal structures which receive signals from other neurons.) This work has implications for understanding the biological mechanisms that underlie the signs and symptoms of schizophrenia.

**Franz X. Vollenweider, Ph.D.,***of the University of Zurich-Switzerland*

will investigate differences in brain activation patterns underlying prepulse inhibition between first episode schizophrenic patients and healthy controls. Prepulse inhibition (PPI) represents a phenomenon known as sensorimotor gating, the ability to filter sensory inputs. Patients with schizophrenia have a deficit in PPI. Dr. Vollenweider will use positron emission tomography (PET) in combination with a test of PPI, in order to elucidate the neuronal activation abnormalities that underlie PPI dysfunction. In addition, the relationship between antipsychotic medications, PPI deficits, and brain activation patterns, will be explored. This work may eventually lead to an improved ability to characterize subgroups of schizophrenic patients in order to develop more specific treatments.

**Allan H. Young, M.D., Ph.D.,***of the University of Newcastle-upon-Tyne-UK*

will examine brain nicotinic acetylcholine receptors (nAChRs) in postmortem brains of patients with depression, bipolar disorder, and schizophrenia. It has long been noted that smoking is very common in individuals with schizophrenia and depression. This study will attempt to determine whether the apparent need or desire to smoke is reflected in changes in the nACh receptors. Dr. Young will compare the nAChRs between these three groups of patients and unaffected matched control subjects. The results of these studies should identify the involvement of nAChRs in these disorders, including their modulatory role in other neurotransmitter pathways, such as dopamine and serotonin.

**Mary Zanzarini, Ed.D.,***of Harvard University*

is conducting a double-blind placebo controlled trial of omega-3 fatty acids in borderline personality disorder. This disorder is a relatively common and severe psychiatric disorder characterized by intense feelings of unhappiness, severe mood swings, and self-destructive behaviors. Omega-3

fatty acids (a type of fish oil) appear to have mood-stabilizing and mood-elevating properties. In the present study, it is therefore hypothesized that omega-3 fatty acids will diminish the depres-

sion and mood swings found in borderline personality disorder. This work may lead to a promising new treatment of this disorder. ❖

## NARSAD ELECTS FIVE NEW SCIENTIFIC COUNCIL MEMBERS

**Pierre Blier, M.D., Ph.D.**, recently relocated to the University of Florida and is affiliated with Shands Hospital. Previously, Dr. Blier was a professor in the Neurobiological Psychiatry Unit at McGill University. He graduated with a B.Sc. in Biology and Psychology from Bishop's University, and later obtained his M.Sc. in Neuroscience, as well as a medical degree and doctorate from the Université de Montréal. Since 1978, Dr. Blier has been investigating the mechanism of action of antidepressant and anxiolytic treatments and conducting concurrently fundamental studies in animals and clinical research. The main goal of these research endeavors is to better understand the neurobiological basis for the antidepressant, anti-obsessional and anxiolytic responses by assessing the effects of the treatments presently available using electrophysiological and neurochemical approaches in laboratory animals. From such results, novel approaches are being designed to accelerate the onset of action and/or efficacy of the pharmacotherapy of such disorders. Dr. Blier also carries out such translational trials in the clinic, thus bridging the bench to the bedside.

**Marc G. Caron, Ph.D.**, is an Investigator of the Howard Hughes Medical Institute. He is also James B. Duke Professor of Cell Biology and Research Professor of Medicine at Duke University Medical Center. He graduated with a Bachelor's of Science in Biochemistry from the Laval University in Quebec, Canada, and earned his Ph.D., at the University of Miami. He completed his post-doctoral training at Duke University in biochemistry and then returned to Laval University as Assistant Professor Physiology before joining the faculty at Duke in 1977. His research interest focuses on the mechanisms of regulation of G protein receptors and regulation of neurotransmission.

**Alexander H. Glassman, M.D.**, is Chief of Clinical Psychopharmacology at New York State Psychiatric Institute, and Professor of Psychiatry at the College of Physicians and Surgeons of Columbia University. He received his Bachelor's of Science from the University of Illinois, and his medical degree from the University of Illinois College of Medicine. He completed his residency at Jacobi Hospital and a fellowship in psychiatry at

the U.S. Public Health Service. Dr. Glassman is an internationally recognized authority on depression and antidepressant drugs—he was the first to demonstrate inter-individual differences in metabolism of imipramine influenced clinical outcome, as well as to show that delusional unipolar depression responded poorly to only antidepressant drugs, and that these patients were more likely to commit suicide than non-delusional depressed patients. His recent work has focused on using MAO inhibitors in eating disorders treatment, and using an alpha-2 agonist to lessen withdrawal symptoms in the cessation of cigarette smoking.

**Anthony A. Grace, Ph.D.**, is a Professor of Neuroscience and Psychiatry at the University of Pittsburgh. He earned his Bachelor's of Science in Psychology-Biology from Allegheny College, and two master's degrees and a Ph.D. from Yale University. His research efforts focus on the study of central dopaminergic systems in an effort to define the neurobiology of mental disorders, as well as the modes of action of psychotherapeutic drugs. His current projects include an exploration of the relationship between the prefrontal cortex and antipsychotic drugs with subcortical dopamine systems to determine the neurobiology of schizophrenia, as well as a study to identify the function of dopamine neurons in the recovery of behavioral function after partial dopamine-depleting brain lesions, which mirrors the effects of Parkinson's disease in humans.

**Husseini K. Manji, M.D.**, is Founding Director of the Laboratory of Molecular Pathophysiology, and the Founding Director of the Schizophrenia and Mood Disorders Clinical Research Division, Department of Psychiatry and Behavioral Neurosciences, at Wayne State University School of Medicine. His research investigates the molecular and cellular mechanisms of action of mood-stabilizing agents and has helped to establish a new Neuropsychiatric Research Unit which conducts an integrated series of clinical and preclinical studies focusing on signal transduction pathways and mood disorders. The aims of his division are to research the etiology and pathophysiology of the major mental illnesses, and to develop applicable innovative treatments.

## Childhood-Onset Schizophrenia: *Latest NIMH Findings*

The study of early-onset cases often yields important new understandings of a disease's etiology and mechanisms of action. This is why **Judith Rapoport, M.D.**, chief of the child psychiatry branch at the National Institute of Mental Health, and a NARSAD Scientific Council Member, has gathered a multidisciplinary team for a long-term, multifaceted investigation of childhood-onset schizophrenia (COS).

When they invested similar efforts into looking at childhood onset of obsessive-compulsive disorder (OCD), the payoff was considerable. Although thought rare, OCD was found to be common. Most important, Rapoport explained, "the biological circuits with the basal ganglia became very clear... such as the connection with Tourette's syndrome" (Rapoport et al., 1992; Swedo et al., 1989). These links had never become clear by investigating OCD in adults. Rapoport presented the most recent findings of the childhood-onset schizophrenia project, which began in 1990 at the American Psychiatric Association's Annual Meeting in Washington, D.C. (Rapoport, 1999).

The rareness of COS has been substantiated by NIMH's wide-scale efforts to locate childhood-onset cases. A review of 1,000 charts and follow-up screening of 300 families from the United States and Canada produced the current sample of 50 subjects (30 boys, 20 girls). The mean age of diagnosis was 10 years, and subjects had to have demonstrated the full Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnostic criteria for schizophrenia prior to age 12 to be enrolled. Because the

diagnosis of schizophrenia has been controversial in children, the NIMH group rigorously examined the phenomenology, neuropsychology and neurobiology of these children to establish that they are suffering from a disease that is "clinically and neurobiologically continuous with the adult-onset disorder" (Nicolson and Rapoport, in press).

The youngest child the NIMH group diagnosed with schizophrenia was 9 years of age; onset was thought to be at 7 years of age. The NIMH team has not concurred in the diagnosis of schizophrenia in children under the age of 7 who were screened, instead categorizing them as suffering from autism or brain damage. A group of aggressive and hyperactive children who only occasionally may hear voices were diagnosed by the NIMH group as suffering from a poorly understood form of atypical psychosis. Since many of the patients were initially recruited for a clozapine (Clozaril) trial, the majority are refractory to treatment with conventional antipsychotics. About half of those in the study have now responded with varying degrees of success to clozapine. Research on the efficacy of olanzapine (Zyprexa) in this group is ongoing.

In most respects, the children resemble "poor outcome adult cases," according to Dr. Rapoport. Their disease generally has an insidious onset, beginning with negative symptoms like social withdrawal and progressing to delusional thinking and hallucinations. Symptomatology parallels that seen in adults, although the content of children's hallucinations comes from their experiences. For example, although the paranoid subtype appears with the

same frequency as in populations of adult schizophrenics, children may hallucinate that a cartoon villain is their nemesis rather than the FBI. For example, Dr. Rapoport said, "One boy was convinced that the Mutant Ninja Turtles were dancing around him all the time, saying terrible things"; another was sure that "his parents weren't his real parents but impersonators who had taken their place."

### Developmental Abnormalities

Nearly all the children in the NIMH study group manifested some neurodevelopmental abnormalities years prior to the onset of frank psychosis. These were generally more severe than those reported in the histories of adult-onset schizophrenics. A number of independent studies have associated early-onset schizophrenia with such developmental anomalies and delays; these studies have suggested a link between them and a greater familial risk for schizophrenia (Alaghband-Rad et al., 1995; Hollis, 1995). In the NIMH sample, 52% of the subjects had language delays or other language abnormalities, and 56% had motor problems. Fifty-three percent met one or more criteria for autism such as lack of interest in peers, poor eye contact, circumscribed interests, stereotypes with hand/arm flapping, odd speech or echolalia. Nearly half of the sample had some form of learning disability, and over 64% had either failed a grade or been placed in special education classes. The COS patients' mean IQ test score was approximately 80 (potential subjects with scores below 70 before the onset of psychosis were excluded from the sample).



*Judith L. Rapoport, M.D.*

### **Familial Patterns**

Data from the first-degree relatives of the NIMH study COS subjects suggest that these children may indeed have a greater genetic risk for schizophrenia than do adult-onset patients. About 50% of the children studied have at least one first-degree relative with schizophrenia or a spectrum disorder. The rate of schizotypal and paranoid personality disorders (21%) among the first-degree relatives was remarkably high, a finding replicated in another ongoing study of childhood schizophrenia at the University of California, Los Angeles (Asarnow, 1999). The rates of the most disabling disorders (three first-degree relatives with schizophrenia and one with schizoaffective disorder) were similar to those seen in relatives of adult-onset schizophrenic patients. This finding may be skewed by the fact that the demands of participating in the study excluded some of the sicker parents from enrolling their children.

The prevalence of spectrum disorders in first-degree relatives correlated with premorbid neurodevelopmental abnormalities; 13 of the patients (72%) with relatives with spectrum disorders had

premorbid language abnormalities, while only seven (32%) without a similar family history had them (Nicolson and Rapoport, in press). A history of spectrum disorders in the family was also positively correlated with ventricle to brain ratio in the subjects ( $p=0.03$ ) Nicolson et al., in preparation).

The abnormal smooth pursuit eye tracking aberrations that have been reported in 40% to 80% of adult-onset schizophrenics, and about 25% of their first-degree relatives, were found in the NIMH group in about the same frequency according to unpublished data by Nicolson et al. Subjects with early language delays were also more likely to have a first-degree relative with eye tracking abnormalities.

### **Environmental Factors**

Obstetrical complications and early life stresses have been associated with earlier onset of schizophrenia in adults by some investigators (Kinney et al., 1994; O'Callaghan et al., 1992; Smith et al., 1998). When the NIMH group compared the birth records of 31 of the COS patients to 25 sibling controls, they found no significant differences in terms of obstetrical course between the groups. Nor did the children with COS suffer any unique environmental stresses or psychological trauma.

### **Genetic Findings**

Dr. Rapoport and her team also looked for relationships between candidate genes and the study group. They found no association between the disease and apolipoprotein E, human leukocyte

antigen or trinucleotide repeats, all of which have been implicated as susceptibility genes for other neurological disorders.

Some of the children in the NIMH group did have striking cytogenetic abnormalities: Turner's syndrome (one girl), balanced translocation of chromosomes 1 and 7 (one boy) and velocardiofacial syndrome (two boys and one girl). This is an extremely rare 22q11.2 gene microdeletion that has been associated with schizophrenia (Bassett et al., 1998; Gothelf et al., 1997), mild mental retardation (Swillen et al., 1997) and speech delay in other populations.

The NIMH team now intends to expand their patient population to 100, and their population of first-degree relatives to 250, so they can perform a full linkage study across the genome. "[Schizophrenia] is probably a polygenic disorder...We need to look at the way alleles are inherited within families," said Rapoport, adding that with such a young patient population first-degree relatives are more apt to be available for an entire linkage study.

### **Progressive Brain Changes**

Some of the most promising findings in the NIMH study have come from prospective, longitudinal magnetic resonance brain imaging of the COS subjects and matched controls at entry. The MRIs have been repeated at two-year intervals. So far, 20 patients (and their matched controls) have been screened twice, and 16 patients (and their controls) have undergone three MRI screens. The patients' scans on entry have resembled those of adult schizophrenics, with characteristically enlarged ventricles and slightly smaller overall brain mass. The

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second scans taken two years later demonstrate the ventricular enlargement to be an ongoing process, with the ventricles becoming more abnormal over time. But in those subjects who have now been screened a third time (at the end of adolescence), these changes appear to stabilize. Thus, by 18 to 20 years of age, the ventricular enlargement appears to cease (Giedd and Jeffries, in press).

On the initial screens, the COS patients did not have significantly decreased brain matter in the frontal and temporal lobes or decreased hippocampal volumes, findings that have been documented in adult schizophrenics. However, over the two-year follow-up interval, the COS subjects experienced a significant decrease in temporal lobe structures (Jacobsen et al., 1998), with hippocampal volumes also significantly decreasing. By the third screen, this diminishment had also stabilized.

The NIMH study constitutes the first longitudinal brain MRI study of healthy adolescents and, although it is well-known that synaptic pruning causes changes in the brain during adolescence, the cortical changes seen during the 13-18-year-old age range were quite robust for the control group (Rapoport et al., 1999). Dr. Rapoport explained, "Probably to increase efficiency even at the [expense] of plasticity...during [healthy] adolescence your cortex prunes down." The healthy controls lost cortical gray matter in the frontal (2.6%) and parietal (4.1%) regions (Rapoport et al., 1999). The COS group's losses were considerably greater from the frontal (10.9%) and parietal (8.5%) regions, and they also had a decrease in temporal gray volume (7%). This remained intact in the cortical group.

In the COS group, those with higher baseline Brief Psychiatric Rating Scale scores also showed greater volume decreases in temporal, parietal and frontal gray matter. Treatment with clozapine, even when very successful at alleviating symptoms, did not appear to have an impact on any of the brain changes observed. Dr. Rapoport interprets these findings as suggesting that childhood-onset schizophrenics undergo progressive, continuous brain deterioration during that window of adolescence when the normal brain undergoes certain fairly dramatic changes, and these deteriorative changes cease by age 18 or 19. She posits that there appears to be excessive synaptic pruning in these early-onset schizophrenic children.

Researchers who have attempted to visualize the progression of brain changes in adult schizophrenics have been largely successful, leading some to consider schizophrenia the consequence of a fixed brain lesion. Dr. Rapoport suspects that these researchers may have looked too late, after the progressive brain deterioration had already occurred. But, Dr. Rapoport explained, observing this process is most intriguing because it may lead to isolating what starts it in motion—the actual, probably genetic, triggers of schizophrenia.

Dr. Rapoport hypothesizes that the very same genes that trigger abnormal prenatal and early-childhood brain development may trigger the later changes associated with psychosis. Isolating these triggers might allow for pharmaceutical intervention before full-blown schizophrenia has developed. Using AZT's ability to stop viral replication in AIDS as a model, Dr. Rapoport suggested that treatment might consist of halting or slowing down the pro-

gressive brain changes that are integrally linked to the symptomatology of schizophrenia.

To confirm that the losses of brain volume are the result of excessive synaptic pruning, the NIMH team will perform MRI spectroscopy of subjects undergoing the critical period of brain transformation. Dr. Rapoport predicts that diminishing levels of N-acetylaspartate will substantiate that the process is driven by neural elements.

The COS project is also beginning in collaboration with Patrick D. McGorry, M.D., a professor in the department of psychiatry at the University of Melbourne-Australia, and a 1998 NARSAD Distinguished Investigator, who has collected longitudinal brain imaging data on subjects who first sought help from a college counseling service for emotional problems. From test scores, Dr. McGorry predicts that one-third of these subjects will have a diagnosis of schizophrenia. Their MRI scans, first taken before the evidence of frank psychosis and taken at regular intervals since, will be sent to NIMH for analysis. They may provide examination of the prepsychotic brain and the very earliest brain changes that occur in schizophrenia. NIMH also intends to enlarge its study of first-degree relatives by performing longitudinal MRIs on the COS cohort's siblings. NIMH would like to double their current sample of COS patients. ❖

*To contact the group for more information, please call Marge Lenane, M.S.W. at (301) 496-7962.*

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# NARSAD Researchers

## *in the News...*

### *Researcher Searches For Schizophrenia Genes*

In this age of the gene, [Linda Brzustowicz, M.D.](#), has her work cut out for her.

The 39-year-old brain researcher, who holds dual appointments from Rutgers University and the University of Medicine and Dentistry of New Jersey, is after big game.

A psychiatrist who spent five years in a genetics lab so she could combine the powers of the two disciplines, Dr. Brzustowicz is determined to discover whether schizophrenia, the common, devastating and mysterious mental illness, is genetic, passed along by families in their genes.

Because the disorder is suspected of being caused by a complex of genes, Dr. Brzustowicz knows the search for her quarry will lead her through the tangles of human genetic information.

She couldn't be conducting her inquiry at a better time. Due largely to the rapidly advancing international effort to crunch the raw information of genes and transform it into an understandable format, Dr. Brzustowicz is making remarkable progress, according to her peers. Her April 28 paper in the journal [Science](#) makes a powerful case that a tiny region of Chromosome 1 is a potent component in the disease.

Gene information is posted daily on arrays of computers by the Genome Project. Though technically the projects are not complete, enormous amounts of data are already available.

"In a matter of seconds, I can yank a gene sequence from a Web site," Dr. Brzustowicz said, referring to a specific area of chemical bases that give individuals their uniqueness.

"Without this information, I would have had to do the work myself, something that might have taken two to three years," she said. "And it's routine, mundane stuff—it would have taken time away from the real creative work we are supposed to be doing."

Five years ago, Dr. Brzustowicz and Anne S. Bassett, M.D., joined forces. Dr. Bassett, a psychiatrist at the University of Toronto, began collecting data on Canadian families, looking for those who seemed susceptible to schizophrenia. Over time, her study enlisted 22 local families of Celtic and German descent who seemed to suffer disproportionately frequent cases.

During their study together, Drs. Brzustowicz and Bassett examined DNA from the 288 family members. It wasn't always easy to get blood samples, especially in family members suffering from some of the paranoid delusions the disease often brings.

Dr. Brzustowicz, charged with the gene-mapping portion of the work, combed through the long strands of DNA unique to the individuals, looking for common genetic patterns on certain chromosomes. She then had to sort between the portions that were common to all family members and regions found only in members afflicted with the disease.

Eventually she struck gold.

In the [Science](#) paper, written by Drs. Brzustowicz and Bassett and three other researchers, they reported that a region in Chromosome 1 was common to schizophrenics in the families. The work also confirmed an earlier study that found a genetic basis for the disease on Chromosome 13.

Scientists say Brzustowicz's work, known as a linkage study, is also notable for the confidence level of its finding, a rigorous statistical rating that, in this case, was exceedingly high.

"That's very impressive," said Anil K. Malhotra, M.D., a molecular psychiatrist and schizophrenia researcher at Hillside Hospital of the North Shore-Long Island Jewish Health System in New York.

"Over the years, there have been a lot of linkage studies," Malhotra said. "Thus far, most have failed to stand up. So there are a lot of skeptics out there. This is the best statistical result so far."

The next step for Brzustowicz will be to pinpoint exactly what gene on Chromosome 1 causes schizophrenia. Her present work has led her to "know the neighborhood," she said. Now she must find the gene's specific address.

If she can isolate the gene and, more importantly, identify the mutation involved in causing the disease, she will look for similar mutations in people with schizophrenia from other populations, to determine the relevance of the finding to groups worldwide. The work might make possible a

## Researcher Searches for Schizophrenia Genes...

blood-based screening test for genetic susceptibility to schizophrenia.

“This does hold out the promise that someday we may be able to do screening for schizophrenia and possibly approach it from a preventive perspective,” she said.

She said people with a family history of the disease appear to be taking solace from the clearing picture of a genetic basis for schizophrenia. A diagnostic test for the disorder could allow for earlier intervention with traditional drug therapies and may lessen the severity of the disease. ❖

*Linda Brzustowicz, M.D., is a 1990 NARSAD Young Investigator.*

*Anne S. Bassett, M.D., is a 1997 NARSAD Independent Investigator.*

*Anil K. Malhotra, M.D. is a 1999 NARSAD Young Investigator.*

*Reprinted from the Sunday Star Ledger, May 21, 2000*

**Visit NARSAD's Website**  
[www.narsad.org](http://www.narsad.org)

Visit our website for newsletter articles, grant information, as well as the Study Search bulletin board onto which researchers recruit participants.

NARSAD also keeps its brochures (in Spanish and English) posted on the site, along with Frequently Asked Questions and Coming Events pages. Our newest addition is a page in which supporters of NARSAD can make contributions electronically—on a secured platform—using their credit cards.

## Emerging From The Shadows

*From an article by Emily Smith Martinez, writer for Southwestern Medicine*

**D**epression is a disease that usually begins with a whimper and too often ends with a bang.

### **A few facts about depression:**

About 10% of Americans will suffer through at least one period of depression during their lifetime; half as many men suffer from depression as women; men who suffer from depression are twice as likely to commit suicide than women; and while depression treatment works for 80 to 90 percent of patients, males as well as females, most men who need help are not getting it.

### **Running From Depression**

Underdiagnosis is considerably greater in men than women because of the negative images associated with mental illness, said Dr. Madhukar Trivedi, associate professor of psychiatry, principal investigator for UT Southwestern's depression and anxiety disorders program, and a 1992 NARSAD Young Investigator.

“Many men think that if they admit to depression they're less of a man. It's made worse because of the way the disease is manifested—through crying spells, lowered self-esteem and lack of sexual interest,” Trivedi said.

### **Uncovering a Hidden Enemy**

Untreated depression is the No. 1 cause of suicide, and depression is second only to heart disease in causing lost workdays in America, Trivedi said. “Only about 40% of people suffering from depression are properly diagnosed, and only about half of those get adequate treatment,” he said.

Besides a sad mood, characteristics of depression include difficulty sleeping, a change in appetite or weight, low energy level, feelings of worthlessness, thoughts of death or suicide, as well as difficulties with concentration and a loss of interest in favorite activities.

Over the past few decades, UT Southwestern's depression program has gained an international reputation for innovative clinical treatment and groundbreaking research. Trivedi collaborates with other physician-scientists such as Dr. A. John Rush—vice chairman for research in psychiatry, holder of the Betty Jo Hay Distinguished Chair in Mental Health and the Rosewood Corporation Chair in Biomedical Science, a 1991 NARSAD Distinguished Investigator, and a world-renowned expert on mood disorders—on multiple research projects.

Trivedi and Rush recently participated in a national study that found a combination of drug treatment and psychotherapy overwhelmingly more effective than either medication or therapy alone in treating chronic depression. Eighty-five percent of patients who received a combination of nefazodone hydrochloride (Serzone) and psychotherapy responded positively, while medication alone led to a 55% positive response, and psychotherapy alone was 52% effective.

Another recent study directed by UT Southwestern researchers revealed that atypical depression—which features symptoms such as weight gain instead of the more common weight loss, and excessive sleeping instead of the usual sleeplessness—was effectively

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treated with either drugs or cognitive therapy alone.

Trivedi currently is working with radiology faculty members to study blood flow in the brain and determine how the flow differs among depressed patients and non-depressed people. Another study, done in conjunction with the Cooper Institute for Aerobics Research, is evaluating the effectiveness of exercise as a treatment for milder forms of depression. A UT Southwestern study at Children's Medical Center of Dallas is looking at sleep, attempting to determine how sleep patterns vary among depressed and nondepressed adolescents.

In addition, numerous drug studies are underway among adult and adolescent patients. An evaluation of St. Johnswort, sponsored by the National Institutes of Health, is the first major study in the United States to consider the safety and efficacy of the well-known herbal preparation.

German researchers recently found that men who are severely depressed have lower levels of the male hormone testosterone than men who are healthy. Though it's still not known whether a deficiency in testosterone contributes to depression, it could help explain why sexual function is often impaired in depressed men. Researchers also have found that men with depression are more than twice as likely to develop coronary disease as nondepressed males.

Women, it is documented, have a considerably higher predisposition to depression during certain periods of life, such as premenstrual and postpartum. Also, studies indicate that the rate of depressed women is always higher than that of men, even in different cultures and among different

classes. The statistics are convincing proof that hormones play a major role in depression and may explain in part why women report more depression than men.

Curiously, rates of depression among children of different genders are almost identical, said Dr. Graham Emslie, professor of psychiatry and holder of the Charles E. and Sarah M. Seay Chair in Child Psychiatry. "Only in later adolescence—after age 15 or 16—do you start seeing female dominance in depression," he said.

Rates of suicide and suicide attempts among depressed young people, however, foreshadowed rates among adults. "Suicide attempts are substantially higher among female adolescents, just as they are among adult women, but boys are eight times more likely to actually kill themselves," Emslie said.

One reason for the higher rate in boys is the same as for adult males; they choose more violent, effective means for self-destruction.

If parents are able to get their young sons and daughters psychiatric help, 70 to 80% will show notable improvement, Emslie said. If the depression is caught early enough, sufferers may avoid common problems that accompany it in both adults and young people, such as alcohol and substance abuse.

The recurrence rate is lower among depressed youngsters, possibly because of the hormonal factors. But most individuals diagnosed with depression need to view it as a lifetime disease, Trivedi said, similar to diabetes and hypertension. Like those diseases, though, depression is highly treatable.

*For more information about depression treatment at the University of Texas Southwestern Medical Center at Dallas, please call 214-648-8333.*

## ***Explanations and Answers***

A malfunctioning of the brain's neural circuits, which regulate mood, thinking, sleep, appetite and behavior, brings on depression. Neurotransmitters—chemicals used by nerve cells for communication—are out of balance. Genetic research indicates that depression often is a consequence of certain genes interacting with environmental factors, such as stress and grief. "If your father or mother suffered from depression, you're much more likely to," Trivedi said.

Antidepressants have been available since the 1950s. But the introduction in recent years of serotonin reuptake inhibitors—Prozac, Zoloft, Paxil, Celexa and Luvox—has revolutionized treatment. They improve moods by activating and altering chemical-messenger pathways in the brain and have fewer, less-serious side effects than other drugs. Successful treatment can return patients to previous levels of normal functioning.

National Institute of Mental Health research also has shown that psychotherapy, especially cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT), can help alleviate depression. CBT helps patients change negative styles of thinking, while IPT helps them work through difficult personal relationships that may prompt depression.

Another highly successful, though still controversial, treatment method is electroconvulsive therapy, known in earlier times as shock treatment. Advances in technique have greatly reduced the side effects, and short-term success rates are high—though relapse is common. ❖

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# M O M E N T U M

## *NARSAD's Board of Directors Elects Chairman*



Jerry Callaghan of New York City has been named Chairman of NARSAD's Board of Directors. At a recent Board meeting, Mr. Callaghan accepted his appointment and stated that a top priority would be to increase the amount of funds raised for research.

Mr. Callaghan is a managing director of Wall Street Access, a discount brokerage firm in New York City. Prior to this position, Mr. Callaghan was a managing director of Lehman Brothers, Inc., responsible for the firm's Trading Services Group from 1993 to 1998. Mr. Callaghan has also served as president of the Securities Processing Group of Shearson Lehman Brothers and head of the

Securities Information Group of American Express. Before joining Lehman Brothers, he was general partner at Bear Stearns and a member of its Management and Operations Committees.

In addition to his extensive experience in the financial services industry, Mr. Callaghan has volunteered for a number of not-for-profit groups. He worked for Covenant House, a non-profit organization for troubled young people, and most recently as a sponsor of the "I Have a Dream" Foundation, a nationwide program dedicated to keeping at-risk youth in school.

Mr. Callaghan lives with his wife, Karen, in New York City.

In other business, NARSAD Directors named Grover Heyler as Secretary of the Board. Hal Hollister, Constance Lieber, J. Robert Peterson, and Jeanne Robertson were re-elected to the Board. Harriet Vicente was also named to the Board.

## *NARSAD President Receives Awards*

Constance E. Lieber, President of NARSAD, was honored with several awards in recent months. Presenting her with the honorary degree of Doctor of Humane Letters, Christof M. Kimmich, President of Brooklyn College, stated that the honor was given "in recognition of your long efforts on behalf of mental health and your generous philanthropic support of research in psychiatry and neuroscience." The degree was awarded at the college's 75th commencement exercises on June 1. In 1999, Mrs. Lieber received a Doctor of Humane Letters Degree from Williams College.



The Society of Biological Psychiatry presented Mrs. Lieber with its first Humanitarian Award at its annual meeting in Chicago on May 12, "for her untiring dedication in support of research and care for the mentally ill." Organizations in her own community also recognized Mrs. Lieber's work and the work of NARSAD. Human Development Services of Westchester County, New York, made her the honoree of their annual reception on June 4. The National Alliance for the Mentally Ill of Westchester County presented her with an award for outstanding leadership and dedication to research in brain disorders at their gala dinner of August 2. In her acceptance remarks Mrs. Lieber spoke of NARSAD's progress and the ongoing challenge. She said, "The dedicated scientists we have all supported and whose careers we have helped to advance are proving that we are not on Mission Impossible, we are on Mission Overcome."

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# M O M E N T U M

## NARSAD's Gala Awards Dinner

NARSAD's Gala Awards Dinner will be held on **Friday, October 13th** at The Pierre Hotel in New York City. This year entertainment will be provided by the recipients of many "gold" records, The Platters. The dinner will also highlight the recipients of the largest prizes in psychiatry, The Lieber Prize for Outstanding Research in Schizophrenia and The Nola Maddox Falcone Prize for Outstanding Research in Affective Disorders.

## NARSAD's 12th Annual Scientific Symposium

The cornerstone of NARSAD's educational efforts, its **Annual Scientific Symposium**, will take place on **Friday, October 13th, and Saturday, October 14th**, at Le Parker Meridien in New York City. Fifteen NARSAD Investigators will speak on their research which will include the areas of basic science, affective disorders, and schizophrenia.

Please call the NARSAD Office at 516-829-0091 if you have not received your Save-The-Date card for our Gala Awards Dinner and Scientific Symposium.

## *Pre-Opening Benefit Preview of "The View"*

On **Friday, September 8, 2000**, chef Chris Melville and his staff are planning an exciting match of wines and comestibles at the **Grand Opening of "The View,"** a new gourmet restaurant in Birmingham, AL.

Enjoy food and drink while taking part in a silent auction and listening to the music of Rosalind Rust.

Tickets are \$250 each, with \$150 being divided between NARSAD and the Mental Health Association of Central Alabama.

For further information about this event, please contact 205-995-0002 in Birmingham or 1-800-462-5602.

## Staglin Music Festival

**Saturday, September 16, 2000**, is the date of the **6th Annual Staglin Family Vineyard Music Festival**. Once again, hosts, Shari (NARSAD Board Member) and Garen Staglin are inviting NARSAD supporters and guests to share in the festivities at their beautiful family vineyards in Rutherford, CA.

A Scientific Symposium will be held the next day, Sunday, September 17th.

For more details contact the Staglin Family Vineyard at: P.O. Box 680, Rutherford, CA 94573 or call 707-944-0477 or e-mail: [info@staglinfamily.com](mailto:info@staglinfamily.com)

## *Regional Symposium — Ohio*

*Featuring Investigators from  
Case Western Reserve University*  
**SUNDAY, OCTOBER 15, 2000**

**1:30 - 4:00 PM**

**CLEVELAND RACKET CLUB**

*Hosted by Jean and Homer McDaniel*  
**For More Information: 216-464-7385**

## *"Moods & Music" — Sarasota, FL*

The evening of **January 20, 2001** will be a very special one for the community of Sarasota when the **4th Annual NARSAD Gala Dinner & Concert, "Moods & Music,"** will be presented at the Van Wezel Performing Arts Hall. The Florida West Coast Symphony, conducted by Leif Bjaland, will perform familiar works by world renowned composers who suffered from mental illness. Dr. Kay Redfield Jamison, a professor at Johns Hopkins School of Medicine, author and expert on manic depression, will provide commentary about the composers.

Other NARSAD events that will be held at the Van Wezel include an educational research symposium scheduled for the morning of January 20, and a free concert for Arts Day patrons on Sunday afternoon, January 21.

These gala events will serve the dual purpose of both educating and entertaining the public while raising funds for NARSAD.

# M O M E N T U M

## FUND-RAISERS FOR NARSAD

### *Running for a Cure*

Meredith Barrows will run the New York City Marathon and is soliciting sponsors to raise money for NARSAD Research.

*“I have decided to try to help a little as we search for better treatments and possibly cures for my family members, my friends, and the millions of others who suffer with mental illness.”*

### *Getting Creative*

A group of individuals from the University of Maine and NAMI of Central Aroostook have designed and crafted pins and a quilt, and have scheduled a candle-light walk to kick off **Mental Health Awareness Week, October 1-6, 2000.**

The design of the pins and the quilt consists of three hearts; blue representing people living with mental illness, black in remembrance of those that have lost their lives to mental illness, and white to represent hope for increased understanding through research.

Aroostook Steal Company has donated funds to purchase the materials needed to craft these items, so that all proceeds from their sale will be donated to NARSAD.

If you are interested in purchasing a pin, bidding on the quilt, or would simply like more information, please contact Shirley Rush from the University of Maine at 207-768-9427.

Special thanks to Heather Lister for her efforts in organizing these activities.



### **Silver Ribbon Campaign For The Brain**

These metal lapel pins show you care about someone with a brain disorder. They help break down the barriers to treatment and support as well as eliminate stigma. They show that you know there is HOPE through education and research.

To order pins for yourself, your family or your group, call **NARSAD Artworks** at 1-800-607-2599.

### **NARSAD Golf Classic**

Year after year Peppino Puleo exhibits his exceptional commitment to NARSAD by organizing an annual golf classic...and this year he's done it again!

On Monday, June 19th, *The Ninth Annual Michigan NARSAD Golf Classic* took place at Gowanie Golf Club in Mt. Clemens, MI.

Sixty-eight golfers participated in the annual event helping to raise over \$11,000 to fund research. The weather was ideal and participants say it was the best golf classic yet.

Thank you Peppi!

### **KEEP YOUR CALENDAR OPEN...**

**JUNE 18, 2001**

**THE TENTH ANNUAL MICHIGAN  
NARSAD GOLF CLASSIC**

**Contact NARSAD for further information.**

### *The Shopping Benefit at Bloomingdale's*

On **TUESDAY, OCTOBER 24, 2000**, NARSAD will participate with other Long Island charities in "The Shopping Benefit." Held at the Bloomingdale's stores in Roosevelt Field Shopping Center and Walt Whitman Mall, "The Shopping Benefit" will feature live entertainment, fashion events and storewide savings.

Make a \$10 contribution to NARSAD and receive a ticket to "The Shopping Benefit." Upon presenting your ticket at one of the Bloomingdale's stores mentioned above, from 10 am to 10 pm on the day of the event, you will be entitled to a 15% discount on all purchases. Bloomingdale's will donate an additional \$5 to NARSAD for each person who holds a pre-sold ticket stamped with our name.

If you are interested in purchasing or selling tickets: **CONTACT** Beth McManus **NO LATER THAN** October 17th at 516-829-0091 or e-mail Beth at: [bmcmamus@narsad.org](mailto:bmcmamus@narsad.org)

*Your contribution to NARSAD is fully tax deductible.*

# M O M E N T U M

## FUND-RAISERS FOR NARSAD

### *Walks for Research*

On May 13, 2000, the **6th Annual Minnesota Mental Health Walk for Research** was held at Lake Nokomis in Minneapolis. Despite the weather being cold and overcast, friends and members from various mental health organizations came out to walk—raising over \$4,000 for NARSAD.

The day's festivities included food, music, speakers and prizes which were raffled off to the walkers. Speakers at the event remarked that the Walk brought hope by raising funds for research, but also challenged the stigma of mental illness by raising awareness.

NARSAD would like to thank the many individuals who performed, volunteered, walked, and sponsored the event, with special thanks to Walk leaders Kathy Brennan of the Mental Health Association, Laura Kahler of Supportive Living Services, and Tom Johnson of NAMI in Minnesota.

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NAMI Olmsted County, Rochester, MN, held its **7th Annual Walk for Research** on May 20th. More than 145 walkers participated and \$11,890 was raised for NARSAD. NAMI OC was especially pleased to welcome its NARSAD Research Partner, Seong-Gi Kim, Ph.D., 1999 NAMI Olmsted County Independent Investigator, as a participant in the Walk. Dr. Kim, a researcher at the University of Minnesota, is investigating the relation of brain flow and oxygen consumption during increased neural activity. Sun Country Airlines donated round trip airfare for two to any of its domestic destinations as a prize for the top fund-raiser. The winner of the airline tickets raised over \$2,700! NAMI OC continues to be pleased at the participation and response from the community for this important event.

NARSAD extends its gratitude to the participants, sponsors, and organizers of this event, and looks forward to a continued *Partnership in Research* with NAMI Olmsted County.

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In an effort to increase the awareness, understanding, and treatment of brain disorders, the National Alliance for the Mentally Ill (NAMI) of Dane County, Wisconsin is organizing its **1st Annual "From Discovery to Recovery" Walk for Research**.

Help support brain disorder research by joining the walk or pledging to support a walker.

**SUNDAY, SEPTEMBER 17, 2000**

**1 - 3 P.M.**

*All proceeds from this event will be donated to NARSAD.*

For further information contact NAMI of Dane County at: 608-249-7188 or [www.amidane@chorus.net](http://www.amidane@chorus.net)

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### *Putting Polo on the Map in Yuma*

The **Second Annual Polo Match** to benefit mental health was held at Scott's Arena in Yuma, Arizona, on May 6th. This year's match has grown since its inception last year and the proceeds, totaling close to \$4,000.00, were once again donated to NARSAD's research programs.

NARSAD's congratulations and sincere thanks go to Susan Barenholtz (member of NARSAD's National Leadership Council), and all her friends at Beta Sigma Phi Eta Beta.

# New Psychiatric Medications in Development

by Kristi Dodson

The new millennium is destined to see breakthroughs in the treatment of brain disorders and other illnesses. The recent completion of a draft of the human genome will revolutionize medicine by paving the way for new drug treatments. The human genome—the so-called “book of life”—maps the chemical sequences for human DNA. This genetic blueprint is already helping researchers zero in on gene variations that contribute to disease. Each mutation that is found brings scientists one step closer to developing new and better treatments.

Meanwhile, 103 medications are already in clinical trials or awaiting FDA approval to treat psychiatric disorders from depression to schizophrenia to Alzheimer’s disease, according to PhRMA, the organization representing U.S. pharmaceutical companies. Among the drugs in development, 26 target depression and 16 treat schizophrenia. NARSAD, in a continuing effort to provide its readers with the most current information, has compiled a report of potential treatments.

## AFFECTIVE DISORDERS

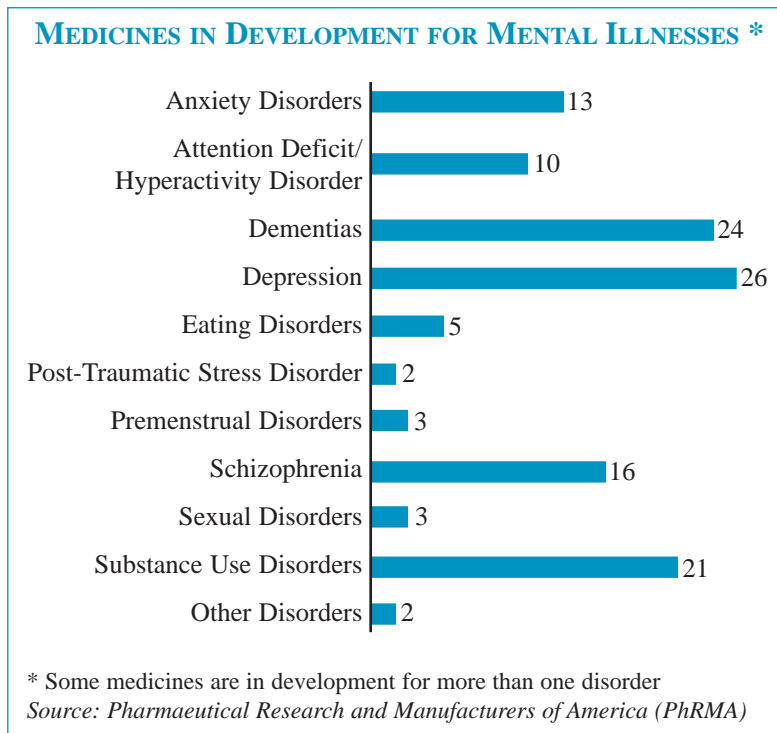
### Reboxetine

Researchers have considered norepinephrine an important pathway since its depletion is associated with symptoms such as lack of energy and interest, along with loss of motivation.

Reboxetine is a selective norepinephrine reuptake inhibitor (NRI) which has low affinity for adrenergic and muscarinic receptors. There is evidence that chronically depressive people have dysfunctional and atypical noradrenergic systems, which appears to impact drive and motivation.

In studies, reboxetine appeared to be as effective as a TCA (tricarboxylic acid) for severe depression. It also appeared to be well tolerated over the long term. The most frequently reported side effects were sweating, blurred vision, insomnia, and dry mouth. In studies done in Europe and Brazil, researchers claim that reboxetine is related to improvements in negative self-perception and to active social behavior.

The company announced, in February of this year, the FDA has



issued a second approvable letter for reboxetine mesylate tablets. This action requires the company to conduct an additional U.S. clinical study to augment the original New Drug Application (NDA). The original NDA was accepted for filing by the FDA in June 1998, based on studies conducted outside the U.S. Pharmacia and Upjohn is in the process of conducting this additional U.S. study.

Reboxetine is currently marketed in 18 countries.

### Duloxetine

Duloxetine is a dual reuptake inhibitor with serotonin and norepinephrine.

Prozac and similar antidepressants generally take four to six weeks to show maximum benefit. Early findings show that depressive

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symptoms may be impacted in as quickly as one to two weeks with duloxetine. Further studies are necessary, as many claims of more rapid onset of action of antidepressants have not proved accurate after intensive scrutiny of data. It also appears the medication has fewer side effects than Prozac and is generally well tolerated.

*Duloxetine is currently in Phase II trials for the treatment of depression. Eli Lilly reports the initial submission to the FDA is expected in 2002.*

### **Topiramate**

Johnson & Johnson's Topiramate is currently on the market under the trade name Topamax for adjunctive therapy in partial and generalized tonic-clonic seizures in adults and children. Topiramate is currently being studied for treatment of bipolar illness. Open clinical trials in monotherapy and in add-on therapy have indicated that 50-60 percent of patients respond successfully, including treatment resistant, rapid-cycling, or mixed-mania patients.

The mechanism of action of topiramate may involve facilitation of GABA transmission, inhibition of AMPA/kainite glutamate transmission, modulation of NA and neuronal Ca channels, and inhibition of carbonic anhydrase. The most frequent side effects found in studies of epileptic patients are numbness or tingling, drowsiness, psychomotor slowing, headaches, nausea, and weight loss. Most side effects are dose and titration rate dependent, and transient. Side effects are also more frequent with add-on therapy. If topiramate is added to other mood stabilizers, lowering the other mood stabilizer may be helpful.

*The Robert Wood Johnson Pharmaceutical Research Institute (RWJPRI) is conducting Phase II trials of topiramate in patients.*

### **Zyprexa - New Indication**

Eli Lilly and Company has announced that the U.S. Food and Drug Administration (FDA) has approved Zyprexa (olanzapine) for marketing for the short-term treatment of acute manic episodes associated with bipolar disorder. "In short-term clinical trials, it appears that Zyprexa acts as a mood stabilizer to manage the manic phase of bipolar illness easily, safely and effectively. Additionally, unlike some other medications, Zyprexa does not require blood monitoring," said Mauricio Tohen, M.D., Ph.D., a 1991 NARSAD Young Investigator, and lead investigator for Lilly Research Laboratories. "Zyprexa can stabilize mood in a range of bipolar patients with manic symptoms, potentially avoiding impulsive or reckless behavior that can lead to serious problems."

The FDA's approval of Zyprexa for the treatment of acute manic episodes associated with bipolar disorder was based on results from two placebo-controlled trials involving patients with a primary diagnosis of bipolar disorder: one three-week trial involving 67 patients and one four-week trial involving 115 patients. The trials included patients with manic and mixed episodes, with or without psychotic features, and with or without a rapid-cycling course. Zyprexa led to a significant improvement in mania, as measured by the Young Mania Rating Scale (YMRS). Zyprexa was generally well tolerated, with four adverse events reported significantly more frequently in the Zyprexa group than in the placebo group: somnolence (drowsiness), dry mouth,

dizziness and asthenia (loss of strength). No participants discontinued the study due to any of these events. Other common events that did not separate statistically from placebo were constipation, dyspepsia (indigestion), increased appetite, and tremor. The recommended beginning dose of Zyprexa to treat acute manic episodes is 15 or 10 milligrams, taken once a day, at any time, without regard to meals.

### **Tamoxifen**

Tamoxifen (Nolvadex), the non-steroidal anti-estrogen drug used to treat or prevent breast cancer, may be effective in treating acute mania in patients with bipolar disorder. Although the report is small and preliminary, results are encouraging, and further studies are planned.

In a single-blind case series, Hussein K. Manji, M.D., recipient of a NARSAD 1998 Independent Investigator Award and the 1999 Falcone Prize for Affective Disorders Research, and colleagues report on seven patients with bipolar I disorder and acute mania who received tamoxifen in doses ranging from 20 to 80 mg daily for three weeks.

Like lithium and valproate, tamoxifen affects protein kinase C (PKC). PKC plays a pivotal role in regulating neuronal excitability, neurotransmitter release and long-term synaptic events, according to Manji. Tamoxifen is the only selective PKC inhibitor available for human use.

The study sought to determine if tamoxifen would have a faster onset of action than lithium or valproate, which can take days or even weeks to work.

While lithium and valproate are not chemically similar, they have

similar effects on PKC, which led Manji and his colleagues to question if dampening PKC faster would result in treating mania faster.

The recommended daily dose in product labeling for breast cancer is 20 to 40 mg daily. Manji reports that most patients needed 60 to 80 mg per day by mouth to inhibit PKC.

The results show significant changes in scores of the Young Mania Rating scale (YMRS), and Clinician Administered Rating Scale for Mania (CARS-M). Researchers stress tamoxifen is not a long-term treatment, but rather for fast stabilization of acutely manic patients.

Only one patient reported an adverse effect, mild flushing on dose titration. The patient was able to tolerate a dose of 60 mg daily.

Manji says a larger, double-blind study of tamoxifen vs. lithium or valproate is planned to begin during the summer of 2000. Data should be available within two years.

*Adapted with permission from Manisses Communications Group 800-333-7771*

## PSYCHOTIC DISORDERS

### ORG 5222

ORG 5222 is a novel antipsychotic drug with a pharmacological profile that is different from that of the classic antipsychotics, haloperidol and chlorpromazine, and also different from that of the atypical antipsychotic, clozapine. It combines dopamine D1 and D2 antagonist properties with antagonism at a variety of serotonin receptor subtypes. This is reflected in behavioral pharmacological

effects that suggest antipsychotic properties and a low propensity to induce catalepsy (loss of voluntary motion) in rats.

*ORG 5222 is currently in Phase II clinical trials and is being developed by Organon.*

### Iloperidone/Zomaril

Novartis Pharmaceuticals Corporation is currently expanding the global ReALiZe (Research to Assess the Long-term Impact of Zomaril) Program, which is examining iloperidone (Zomaril) in the treatment of schizophrenia and schizoaffective disorders, as well as a wide range of symptoms associated with these disorders. This novel Phase III program provides expanded access to clinical trials for patients previously denied such access, including those with schizoaffective disorder and comorbid polysubstance use.

In animal models, iloperidone (Zomaril) has demonstrated expanded action across all monoaminergic receptor systems, which it is hoped will translate to benefit over currently available agents in patients. Further, clinical trials are currently evaluating whether its multiple antagonistic activities which produce a complex interplay of receptor blockade and release inhibition, will impart improvements in psychotic symptoms, as well as cognition and mood dysregulation, and whether it can reduce the overall liability to side effects, including extrapyramidal symptoms.

The ReALiZe program uses a range of world wide trials to investigate the safety, efficacy, and utility of this dopamine modulator in a variety of age and ethnic populations. Investigations include standard examinations of psychotic symptoms, but also entail the impact of iloperidone

(Zomaril) on depression, anxiety, cognition, disease insight, and health economics, as well as potential new technologies including pharmacogenomics.

*Currently, global recruitment is underway to study ILP3005 comparing iloperidone (Zomaril) to the antipsychotic risperidone.*

### Aripiprazole

Aripiprazole is a novel antipsychotic being developed by a collaborative relationship between Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co., Ltd. The results of the first pivotal Phase III trial demonstrate aripiprazole to have unsurpassed efficacy and tolerability in the treatment of acutely psychotic patients with schizophrenia or schizoaffective disorder, according to the companies.

Aripiprazole was tested in a double-blind, four-week comparison involving four hundred hospitalized patients with a DSM-IV diagnosis of acute relapse of schizophrenia or schizoaffective disorder. Patients in the study were given either 15 mg of aripiprazole, 30 mg of aripiprazole, 10 mg of haloperidol, or placebo. The efficacy of both doses of aripiprazole and haloperidol were significantly superior to placebo on the total score on the Positive and Negative Symptom Scale (PANSS), as well as on the positive and negative symptom subscales. However, the responder analysis (30% decrease from baseline in PANSS-total at last visit) indicated that both doses of aripiprazole were significantly better than placebo while the response rate for haloperidol was not significantly different from placebo. Tolerability data indicate that aripiprazole produces numerous meaningful advantages relative to haloperidol including fewer extrapyramidal symptoms

## THE DRUG DEVELOPMENT AND APPROVAL PROCESS

*It takes 15 years on average for an experimental drug to travel from the lab to U.S. patients.  
Only five in 5,000 compounds that enter preclinical testing make it to human testing.  
One of these five tested in people is approved.*

Early Research/ Preclinical Testing		Clinical Trials				
Years	6.5	Phase I	Phase II	Phase III	1.5	15 Total
<b>Test Population</b>	Laboratory and animal studies	20 to 80 healthy volunteers	100 to 300 patient volunteers	1,000 to 3,000 patient volunteers	Review process/ approval	Additional post-marketing testing required by FDA
<b>Purpose</b>	Assess safety and biological activity	Determine safety and dosage	Evaluate effectiveness, look for side effects.	Confirm effectiveness, monitor adverse reactions from long-term use	1 approved	
<b>Success Rate</b>	5,000 compounds evaluated	5 enter trials				

*Source: Pharmaceutical Research and Manufacturers of America (PhRMA)*

and lack of hyperprolactinemia, a condition often produced by antipsychotic medications that can cause symptoms such as sexual dysfunction and loss of menstruation in women. Aripiprazole also appeared to be associated with minimal incidence of weight gain and sedation.

Aripiprazole is currently being studied in additional Phase III trials in schizophrenia. It is also being tested for efficacy in the treatment of acute mania and psychosis associated with Alzheimer's Disease. There are plans to study aripiprazole in selected pediatric patients suffering from serious psychiatric disorders.

### Clozaril - New Indication

Clozaril is an atypical antipsychotic medication used for the management of treatment-resistant schizophrenia. Preliminary clinical studies have demonstrated that treatment with Clozaril reduces the risk of suicide in patients with schizophrenia. To

confirm these findings, the suicide prevention trial of InterSePT, a controlled trial of clozapine and olanzapine in 900 patients with schizophrenia and a history of suicidality, is currently underway. Results from this trial will be available in 2001 and should provide valuable data on patients with schizophrenia and a high risk of suicide.

### Ziprasidone (Zeldox)

Ziprasidone is an antipsychotic, which like other recently developed antipsychotics, has a high 5HT<sub>2A/D2</sub> receptor binding ratio, which is believed to underpin beneficial effects on both the positive and negative symptoms of schizophrenia with a low risk of movement disorders.

Ziprasidone also affects many other brain neurotransmitter receptors. It is a potent antagonist of 5HT<sub>2C</sub> and 5HT<sub>1D</sub> receptors, a potent agonist of 5HT<sub>1A</sub> receptors, and a moderate inhibitor of norepinephrine and serotonin re-

uptake. These characteristics may further enhance the efficacy of ziprasidone in the treatment of depressive symptoms, negative symptoms, and improvement in cognition. Ziprasidone is a relatively modest antagonist of alpha-1 histaminin (H<sub>1</sub>) receptors and has a negligible affinity for muscarinic (M<sub>1</sub>) receptors. These characteristics may enhance the tolerability profile compared with some newer antipsychotics.

In its clinical trials, oral ziprasidone was very well tolerated and appears to have a very low liability for inducing movement disorders (such as Parkinsonism and akathasia), postural hypotension and weight gain.

The rapid acting intramuscular formulation was developed for the acute control and short-term management of agitated psychotic patients before initiation with oral therapy. In clinical trials significant effect was apparent one-hour after injection, without evidence of profound sedation.

Pfizer re-filed a New Drug Application with the FDA for the antipsychotic Zeldox. Following consultation with the FDA after it issued a non-approvable letter for Zeldox in 1998, Pfizer undertook a specially designed clinical trial to more fully characterize the electrocardiogram (ECG) changes seen with Zeldox. Data from this trial and the underlying clinical development program demonstrate the absence of a significant risk associated with the ECG changes. Pfizer found that Zeldox has a favorable effect on blood lipids and causes little or no weight gain. An FDA advisory panel voted 9 to 1 that Zeldox was safe enough to be sold in the U.S. market. Winning the panel's support is a major step forward for Zeldox.

## ADD/ADHD

### Tomoxetine

Tomoxetine is the first in a new class of drugs to be studied for the

treatment of ADHD in children and adults. Tomoxetine Phase II studies have been completed and have shown promising results in children and adults with ADHD.

Tomoxetine is a non-stimulant norepinephrine enhancer that affects attention and inappropriate behaviors. Unlike the psychostimulants currently being prescribed for ADHD, such as methylphenidate, tomoxetine is not expected to be a controlled substance and does not require a mid-day dose.

*Eli Lilly is currently conducting Phase III trials on tomoxetine.*

### d-methylphenidate

Celgene Corporation announced in April of this year that it has granted an exclusive worldwide license (excluding Canada) to Novartis Pharma AG for the development and marketing of d-methylphenidate, its chirally pure version of Ritalin.

Celgene has previously reported the positive clinical results of its two pivotal Phase III efficacy trials for d-methylphenidate. In these trials, the d-methylphenidate product demonstrated its effectiveness in controlling the symptoms of Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder (ADD/ADHD) in school-aged children to a very high degree of statistical significance. The d-methylphenidate product also demonstrated a longer duration of action than Ritalin in these studies. Celgene plans to file a New Drug Application (NDA) for the product in the third quarter of this year.

This long-acting formulation will eliminate the mid-day dose, which has been identified by physicians, parents and school staff as a significant unmet medical and market need.

### Concerta

ALZA Corporation has received approval from the FDA for its new formulation of methylphenidate HCl in extended release tablets taken once a day for the treatment of children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD) ages 6 and older.

Two hundred and six children between the ages of six and twelve with a clinical diagnosis of ADHD completed a multi-center study. Patients were randomized to one of three blinded treatments for a period of 28 days, and were treated with either Concerta once daily, immediate-release methylphenidate three times daily, or placebo. The children were evaluated by multiple raters in various settings using standardized tests for behavior and attention. Based on this measurement, a significant improvement in attention and behavior was shown for Concerta

## Seroquel—Long-Term Use In The Elderly

Although typical antipsychotic medications have long been accepted therapy for elderly patients experiencing psychotic symptoms, the elderly are especially vulnerable to the side effects of these medications, particularly to movement disorders such as extrapyramidal symptoms (EPS). Researchers say Seroquel, an atypical antipsychotic may be an attractive therapeutic option in the elderly because it has not demonstrated treatment-emergent or dose related EPS.

The results of a 52-week, multicenter, open-label trial suggest that Seroquel may be a potential alternative to standard antipsychotic agents for long-term use in the elderly. The study was conducted with men and women at least 65 years of age (or 50 years or older for patients with Parkinson's disease) with psychotic disorders to explore the therapeutic utility and tolerability of Seroquel in the EPS-sensitive elderly population.

Significant improvement from baseline rating scales was noted at all time points measured (from 2 weeks onward). The most common adverse events reported in the 184 patients were somnolence and dizziness (side effects that can also be seen in younger adult patients treated with Seroquel) and accidental injury (events that are common in the elderly and are not necessarily related to the drug.)

and conventional methylphenidate when compared with placebo.

Concerta has a uniquely patterned plasma profile that minimizes the peak-trough fluctuations associated with methylphenidate given three times a day. The delivery pattern is designed to extend the duration of effect, provide consistent improvement in symptoms and overcome the need for repeated administration throughout the day.

Once daily Concerta had a similar profile to methylphenidate given three times a day. Adverse events related to treatment that occurred in more than 2% of patients taking Concerta include headache (9.6%), abdominal pain (4.8%), decreased appetite (3.8%), insomnia (2.9%) and vomiting (2.9%).

*According to ALZA, the drug should be available, by prescription, before the start of the 2000-2001 school year.*

## OTHER DISORDERS

### Fluoxetine hydrochloride - New Indication

The FDA has approved Fluoxetine hydrochloride (Sarafem), a selective serotonin reuptake inhibitor, for the treatment of [premenstrual dysphoric disorder \(PMDD\)](#). It is the first prescription medication indicated for the treatment of PMDD.

Sarafem is made from the same active ingredients found in Prozac. The FDA approved marketing the medication using a different name and color to note the difference between depression and premenstrual dysphoric disorder.

The FDA approval of fluoxetine hydrochloride for the treatment of PMDD was based in part on safety and efficacy results from

the randomized, double-blind placebo controlled trials presented. Patients were administered between 20 mg and 60 mg of fluoxetine hydrochloride or placebo daily for up to six months. The studies showed that women taking fluoxetine had statistically significantly greater improvements in mood and physical complaints and reduction in functional impairment compared with patients taking placebo. These improvements were recorded as early as the first cycle.

*Sarafem will be available in pharmacies August of this year.*

### Zoloft - New Indication

Pfizer Inc. announced in December of 1999 that the FDA approved its antidepressant Zoloft to treat [post-traumatic stress disorder \(PTSD\)](#).

A selective serotonin reuptake inhibitor, Zoloft is the first drug to receive FDA approval for the treatment of PTSD.

Patients diagnosed with PTSD who were treated with Zoloft showed significant reduction in the symptoms of PTSD compared to placebo, according to a study published in the [Journal of the American Medical Association](#). Patients in the double-blind, placebo-controlled trial also experienced a significant improvement in their quality of life and social and occupational functioning. The Zoloft study included 187 patients who had suffered from PTSD for an average of 12 years. Because more women than men experience PTSD, there were three times more women than men in these trials. Women also responded better to Zoloft than men.

Zoloft is indicated for depression, obsessive-compulsive disorder,

panic disorder and post-traumatic stress disorder.

### Exelon

Novartis Pharmaceuticals Corporation announced that the FDA has granted marketing clearance for Exelon (rivastigmine ttrate) capsules for the treatment of Alzheimer's, which belong to a class of drugs called cholinesterase inhibitors that block the breakdown of an important neurotransmitter called acetylcholine.

Acetylcholine is thought to play a role in memory and cognition; scientists have learned that levels of this neurotransmitter are dramatically lower in patients with [Alzheimer's Disease](#). Acetylcholine is broken down and inactivated by cholinesterase. Thus, by inhibiting cholinesterase, more acetylcholine is available for normal memory-related and cognitive functioning.

Exelon therapy has proven effective in multiple Phase III trials. In clinical trials, on average, the patients treated with Exelon were considered clinically improved compared to those on placebo at the end of six months. During the clinical trials, patients treated with 6-12 mg of Exelon per day were more likely to experience substantial cognitive improvement and less likely to show substantial decline than were patients receiving placebo. Moreover, at 26 weeks, 81% of those given 6-12 mg of Exelon daily had greater improvements and less worsening in cognitive function than did the average placebo-treated patient. Patients treated with Exelon demonstrated significant improvement compared to placebo in areas such as average total word recall and recognition, orientation and ability to speak. During the clinical trials, patients given Exelon demonstrated fewer delusions

than those given placebo and engaged in less purposeless activity. In trials, higher therapeutic doses of Exelon were associated with greater benefit.

The most common side effects seen with Exelon include nausea, vomiting, anorexia, dyspepsia, and asthenia, which are generally transient and mild to moderate in severity.

It is important to remember that while cholinesterase inhibitors, like Aricept and Exelon, can slow the progression of Alzheimer's disease, they are not a cure.

### **Paxil - New Indication**

SmithKline Beecham has submitted a Supplemental New Drug Application (sNDA) to the FDA for its antidepressant Paxil. The company is seeking marketing approval of Paxil for the treatment of **Generalized Anxiety Disorder (GAD)**, a condition characterized by excessive anxiety, worry and fear. Paxil, a selective serotonin reuptake inhibitor (SSRI), is currently indicated in the treatment of depression, panic disorder, obsessive-compulsive disorder, and social anxiety disorder.

### **1555U88**

Glaxo Wellcome is currently involved in Phase II trials for the treatment of **Mood Disorder and ADHD** with 1555U88, a noradrenaline reuptake inhibitor. ❖

## **NARSAD Investigator Receives the A.E. Bennett Research Award**

**Alan S. Brown, M.D.**, of Columbia University, received the prestigious A.E. Bennett Research Award for his research paper entitled Prenatal Rubella, Premorbid Abnormalities, and Adult Schizophrenia at this year's Biological Psychiatry Meeting in Chicago, IL.



In the study presented in this award-winning paper, Dr. Brown and his colleagues investigated the relationship between prenatal exposure to rubella (German measles) and adult schizophrenia/spectrum disorder. Previous investigations suggested that prenatal viral infection may play a causal role in schizophrenia outcome. In contrast, the present study utilized a birth cohort clinically and serologically documented with prenatal rubella infection, a well documented cause of other neurodevelopmental disturbances; and cases of schizophrenia/spectrum disorders were diagnosed by structured, face-to-face research assessments.

The rubella-exposed birth cohort was derived from the Rubella Birth Defects Evaluation Project (RBDEP), which recruited pregnant mothers who were clinically diagnosed during pregnancy with rubella infection. Serologic confirmation of infection was obtained in the vast majority of mothers and infants who were tested. The RBDEP cohort was administered longitudinal follow-up assessments of psychiatric, intellectual, neuromotor, and behavioral function during childhood, adolescence, and young adulthood. At the young adult assessment (administered at the age of 21-23), a subsample of the cohort received a computerized psychiatric interview, from which diagnoses could be made. In their first analysis of these data, Dr.

Brown and colleagues found a marked increase in non-affective psychosis (disorders with psychotic symptoms such as delusions and hallucinations, but without mood disorders) among members of this rubella-exposed birth cohort. That study was published in the American Journal of Psychiatry.

The present study was a follow-up of these cohort members further into adulthood (ages 33-35) for the presence of psychiatric disorders. This study utilized a more comprehensive and modern diagnostic interview than was administered in the young adult follow-up. This permitted the investigators to refine the diagnoses of the previous study. In addition, because nearly all of the cohort members will have passed through the age of risk for schizophrenia/spectrum disorders by their mid-30's, it allowed the investigators to identify new cases. Using sophisticated tracing methods, the authors traced, located, and assessed over 80% of the targeted sample.

In the first part of this study, Dr. Brown and colleagues found that 20.4% (11 of 53) of these rubella-exposed cohort members were diagnosed with schizophrenia or a schizophrenia spectrum disorder. This risk is 10-20 times higher than the risk of these disorders in the general population. Virtually all of the cases were exposed to rubella during the first trimester.

In the second part of the investigation, the authors tested whether rubella-exposed subjects destined to develop schizophrenia spectrum psychoses, as compared to controls (rubella-exposed subjects who remained free of these disorders,) had

more I.Q., neuromotor, and behavioral abnormalities during childhood and adolescence. For this purpose, the investigators capitalized upon a virtually complete dataset on these measures in the RBDEP cohort.

This hypothesis was confirmed. Dr. Brown and colleagues demonstrated that rubella-exposed subjects destined to develop schizophrenia/spectrum disorders manifested an *11-point decline* in the performance I.Q. score between childhood and adolescence, as compared to less than a 3-point I.Q. decline in rubella-exposed controls. These differences were statistically significant. The proportion with an I.Q. decline was 87.5% among subjects who later developed schizophrenia spectrum psychoses, compared to only 33% of controls. Moreover, the investigators found increases in

childhood and adolescent neuromotor dysfunction, mannerisms, and deviant behaviors among subjects destined to develop schizophrenia/spectrum disorders, as compared to the controls.

These findings provide the clearest evidence to date that a clinically and serologically documented prenatal exposure is related to the risk of adult schizophrenia/spectrum disorder. Given the size of the effect, the fact that the exposure preceded the outcome by many years, and an established literature on the teratogenicity of prenatal rubella, it appears probable that prenatal rubella exposure is a likely cause of schizophrenia/spectrum disorders.

Previous studies have demonstrated childhood intellectual, neuromotor, and behavioral abnormalities among subjects destined to

develop adult schizophrenia. This investigation adds a new dimension to this prior work by linking a known prenatal exposure, a deviant neurodevelopmental trajectory in childhood and adolescence, and schizophrenia spectrum psychosis in adulthood. These findings suggest that a dynamic pathogenic process, possibly involving abnormal elimination of synapses (the connections between adjacent nerve cells), begins long before onset of the illness, and ultimately becomes expressed as adult schizophrenia/spectrum psychosis. In future work, Dr. Brown and colleagues hope to replicate these findings in other cohorts, probe the mechanisms by which prenatal rubella might lead to adult schizophrenia, and examine potential interactions between *in utero* rubella exposure and genetic vulnerability to schizophrenia. ❖

## NARSAD Honors William and Marion Nicholson with The Peterson Award



*l-r: William and Marion Grable Nicholson with Lee and Bob Peterson*

On July 28, 2000, NARSAD awarded “The Peterson Award” for philanthropic leadership to William and Marion Grable Nicholson.

This is a significant award for NARSAD. It was started three years ago to recognize outstanding supporters of NARSAD for their long-term commitment and highly significant financial contributions. The first to receive it were Lee and Bob Peterson. NARSAD decided to make an annual award and to name it for the first awardees. Patsy and Hal Hollister were the second recipients of the newly named Peterson Award in 1998. The Hollisters started the NARSAD Artworks activity as a support organization for NARSAD and as a vehicle for mentally ill artists, twelve years ago. The next awardees were Constance and Stephen Lieber in 1999.

All who became involved with NARSAD in its very beginning recognize the vital role William Nicholson has played from its inception. He was the first to come forward with a gift for research funding. Bill’s catalytic role at the beginning was in itself enough to deserve special recognition as NARSAD has grown. But we cannot say how much we appreciate the increasing and highly significant role his and Marion’s contributions have directly played in NARSAD’s growth; his own contributions and those he and Marion have provided through the Grable Foundation.

More than merely playing a role in contributions, the guidance and leadership which the Nicholsons and the Grable Foundation have provided has been significant in NARSAD’s achievements. Bill and Marion pushed the first funding; the Grable Foundation has been a major contributor and has funded the translation of complex scientific reports into laymen’s language and, through Jane Berger, the foundation’s Executive Director, has been a wonderful guide to us. ❖

## NARSAD Recognizes Outstanding Young Investigators

The intriguing scientific research of six Young Investigators took center stage at NARSAD's Annual Klerman/Freedman Award ceremony at Le Parker Meridien in New York City in July.

Scientists were recognized for work that is helping to shape the direction of research in the coming decade. Awards covered a wide spectrum of fascinating projects, with top honors going to a Young Investigator studying side effects in elderly patients taking antipsychotic medications and to a Young Investigator researching certain brain molecules affecting learning and memory that may also play a role in mental illness.

Honorable mentions went to four additional researchers. Their projects include the use of transcranial magnetic stimulation to treat depression, the hunt for susceptibility genes for schizophrenia in patients with velocardiofacial syndrome, the use of PET imaging techniques to study functional changes in the brains of depressed patients, and a study of memory deficits in patients with schizophrenia.



l-r: Dr. Susan Schultz (Klerman Prize Awardee), Connie Lieber, and Dr. Edwin Abel (Freedman Prize Awardee)

### THE KLERMAN AWARD

The sixth annual Gerald L. Klerman Memorial Award was presented to Susan Schultz, M.D., of the University of Iowa. Honorable Mentions of the Klerman Award were given to Mark George, M.D., of the Medical University of South Carolina, and Sohee Park, Ph.D., of Northwestern University.

The Klerman Award Committee, led by Jan Fawcett, M.D., of Rush-Presbyterian St. Luke's Medical Center in Chicago, consists of Nina Schooler, Ph.D., of Albert Einstein College of Medicine, and Robert M.S. Hirschfeld, M.D., of the University of Texas Medical Branch in Galveston.

The Klerman Award was established in 1994 by Dr. Myrna Weissman, co-winner of NARSAD's Selo Prize (now known as the Nola Maddox Falcone Prize for Outstanding Research in Affective Illness), in memory of her husband, Gerald Klerman, M.D., to honor outstanding research achievements by NARSAD Young Investigators.

Dr. Klerman's distinguished career included innovative research in depression, outstanding teaching and mentoring, with research leadership at Yale University, Harvard Medical School and Cornell University.

### Susan K. Schultz, M.D.

Dr. Susan Schultz has conducted research on risk factors for tardive dyskinesia (TD), or involuntary motor movements, occurring as a side effect of antipsychotic drugs. Her study — *The Relationship Between Tardive Dyskinesia and Diabetes Mellitus in Elderly Patients with Schizophrenia* — investigated the presence of non-insulin dependent diabetes mellitus as a risk factor for TD in the elderly.

The treatment of schizophrenia can become complicated in older patients, as medical illnesses may interact with medications and worsen side effects. Specifically, the rate of TD increases with age. Dr. Schultz's study involved the use of a glucose tolerance test and a challenge test of phenylalanine (an essential amino acid) load, to determine whether either measure was able to predict the occurrence

of abnormal movements. Through her project, Dr. Schultz determined that early diabetes mellitus was associated with a greater likelihood of abnormal movements. She also found a possible relationship between lower phenylalanine levels in the pre-load fasting state and subsequent abnormal movements. The research suggests that the content of dietary protein may play a role in the development of abnormal movements.

Dr. Schultz noted that the findings are significant in that multiple factors are at work in determining why some individuals develop severe abnormal movements while others have none at all, despite similar exposure to antipsychotic medications. Her research findings were reported in an article in the [American Journal of Psychiatry](#) and at major scientific meetings.

Dr. Schultz, an assistant professor of psychiatry at the University of Iowa, earned her M.D. from the University of Nebraska Medical Center, College of Medicine in 1990.

She completed her psychiatry residence at the University of Iowa and a research fellowship with

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NARSAD Scientific Council member, Nancy C. Andreason, M.D., Ph.D., in her Clinical Neurobiology and Schizophrenia Training Program. Dr. Schultz is a recipient of a 1996 NARSAD Young Investigator Award.

### Mark S. George, M.D.

Dr. George investigated a novel neuropsychiatric tool called transcranial magnetic stimulation (TMS) to treat depression. The technique entails non-invasively stimulating the brain with an external magnet. When turned on and off, a small electromagnet placed on the scalp can excite nerve cells in the underlying superficial cortex. With slow stimulation, TMS can stimulate nerve cells, and with more rapid stimulation (rapid or rTMS), it can temporarily disable neurons.

Dr. George found that TMS is safe and more effective in treating depression than placebo. There was no difference between fast and slow stimulation. Although his research is exciting, Dr. George notes that much work remains in understanding which TMS parameters work best for treating depression—where best to place the coil, how much electricity is needed and how fast to turn it on and off.

Dr. George earned his M.D. degree in 1985 from the Medical University of South Carolina (MUSC). He spent four years at the Biological Psychiatry Branch of the National Institute of Mental Health as a Senior Fellow with Dr. Robert Post.

Dr. George, an associate professor of psychiatry, radiology and neurology at MUSC, received a 1996 NARSAD Young Investigator Award and a 1998 NARSAD Independent Investigator Award. He is Director of the Magnetic Brain Stimulation Laboratory at MUSC.

### Sohee Park, Ph.D.

Dr. Sohee Park examined the relationship between prefrontal brain functions and memory deficits in patients with schizophrenia. These deficits in working memory are often associated with significant social relationship problems encountered by this population. In her study, Dr. Park sought to elucidate neurocognitive components of schizophrenia and thus contribute to the understanding of the complex interplay between cortical functions and clinical symptoms.

Dr. Park found that **spatial** working memory deficits are present in acute and chronic schizophrenia patients and that they are stable over time. On the other hand, object working memory deficits improved with time as symptoms improved.

Dr. Park determined that spatial working memory can be improved in schizophrenia patients non-invasively by increasing affective arousal. In other words, when the stimulus is made more affectively salient (for example, by presenting faces, rather than plain circles,) the patients' performance on the spatial working memory task improved. It also improved when social reinforcement was provided by the experimenters after each trial. The results suggest an intimate connection between affect and cognition in the prefrontal system and also point to possible rehabilitation strategies.

Dr. Park, currently an assistant professor of psychiatry at Northwestern University, earned a Ph.D. at Harvard University in 1991. She received her first NARSAD Young Investigator Award in 1991, and was given a second NARSAD Young Investigator Award in 1996.

## THE FREEDMAN AWARD

The Freedman Award, inaugurated in 1998, honors a pioneer in biological psychiatry, the late Daniel X. Freedman, M.D.

His role as a founding member of NARSAD's Scientific Council typified his leadership in psychiatrically relevant brain research. His career spanned the era which initiated and developed psychopharmacology and neuroscience. His work at Yale and at the NIMH in the early 1950s led to a pioneering view of the reactions of brain systems to a range of both internal and external signals, which could be aided by drugs. He discovered the first link of hallucinogens to brain neurotransmitters—serotonin. In 1970, he became the Chief Editor of the *Archives of General Psychiatry*, and was president of the American Psychiatric Association in 1982. After 18 years at the University of Chicago, Dr. Freedman joined the faculty of UCLA as the Judson Braun Professor of Psychiatry and Pharmacology and subsequently became acting Director of the Neuropsychiatric Institute.

The Freedman Award Committee, headed by Ariel Deutch, Ph.D., of Vanderbilt University, consists of Paul Greengard, Ph.D., of Rockefeller University, Joseph Coyle, M.D., of Harvard University, and Eric Nestler, M.D., Ph.D., of Yale University.

The third Daniel X. Freedman Award was presented to Edwin G. Abel, Ph.D., of Columbia University, with Honorable Mentions to Bernice E. Morrow, Ph.D., of Albert Einstein College of Medicine, and Wayne C. Drevets, M.D., of the University of Pittsburgh.

*Samuel B. Guze, M.D.*

We mourn the loss of Dr. Guze, a founding member of NARSAD's Scientific Council, who died on July 19th from a bone marrow disorder. Dr. Guze had a remarkable and creative career in psychiatric research, clinical leadership, teaching and medical administration. He earned his medical degree from Washington University in St. Louis and built his career as he built the university's capabilities, notably in psychiatry. He served as vice-chancellor of the University and president of the Washington University Medical Center from 1971 to 1989. He was head of the Department of Psychiatry from 1975 to 1989 and again 1993 to 1997. He was Psychiatrist and Chief at Barnes-Jewish and St. Louis Children's Hospitals. At the time of his death, he was the Spencer T. Olin Professor of Psychiatry at Washington University.

He led and participated in many of the pioneering achievements which have brought psychiatry into the mainstream of medical research. He was among the first to use studies of twins as a means of identifying the role of heredity in psychiatric illness. He brought attention to the genetics of psychiatric disorders. In the words of a colleague, "He has been the most articulate and consistent advocate of clinical psychiatry as a scientific endeavor. He has been one of the people most responsible for the fact that in the last half of the twentieth century, psychiatry has moved into the mainstream of medical science."

Dr. Guze authored more than 200 scientific papers and several books. In 1980 he participated in creating the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSMIII).

Of great importance to him throughout the years, and to the field of psychiatry, was his teaching role where he trained hundreds of psychiatrists. Illustrative of his role as a teacher is the fact that in 1998 the winner of one of the most illustrious prizes given to Young Psychiatrists for outstanding research achievement by the Society for Biological Psychiatry was one of his pupils. That pupil, Wayne Drevets, M.D., spoke of his research by first acknowledging the guidance and inspiration of Dr. Guze. Dr. Guze took on many important responsibilities in his work as a volunteer on NARSAD's Scientific Council, including having been an original member of the Lieber Prize Committee.

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*Hyman (Chaim) Niznik, Ph.D.*

NARSAD mourns the loss of one of its most promising: Young Investigator and Independent Investigator Grantee, Hyman Niznik, Ph.D.

Dr. Niznik, professor of psychiatry and the Centre for Addiction and Mental Health, a rising star in schizophrenia research, died suddenly of a heart attack on March 31st. He was 43 year old.

He was widely known for his outstanding contributions in molecular neuroscience. His research provided enormous insights into the neurobiological underpinnings of some of the most distressing mental illnesses, in particular, schizophrenia. Professor Franco Vaccarino, vice president (research) at the Centre of Addiction and Mental Health, a close colleague and friend, told members of the Faculty of Medicine council April 17th, "In short, he was one of our very best."

Born in Montreal, Dr. Niznik received his B.A. from McGill University in 1979 and his M.Sc. from University of Toronto in 1983. Dr. Niznik received his Ph.D. in 1986, under the supervision of Philip Seeman, Professor of pharmacology. After a period of post-doctoral training, he accepted a faculty position in the department of psychiatry and the Institute of Medical Sciences as an assistant professor, and became an associate professor in 1994. He joined what was then the Clarke Institute of Psychiatry as head of the molecular psychobiology research section in 1991, a post he held until his death.



Dr. Niznik’s research interest in the relationship between dopamine dysfunction and schizophrenia developed during his Ph.D. training, and his later research characterizing and cloning key dopamine receptors helped set the foundation for a variety of medication development programs around the world. His research throughout the 1990s “stands as a model of excellence, creativity and perseverance,” Vaccarino said. “The impact of his work was felt worldwide.”

The author of over 100 articles, Dr. Niznik’s studies were published in some of the most prestigious scientific journals. In January of this year, he was the senior author of a groundbreaking study published in *Nature* on the discovery of a cellular communication method in the brain that could lead to improved treatments for schizophrenia and addiction. “There is little doubt that this work will rewrite textbooks in our field and permanently change our understanding of how brain cells communicate with each other,” Vaccarino said.

Dr. Niznik’s many achievements during his short career were recognized nationally and internationally. In 1987 he was among the first four recipients of the John Charles Polanyi Prize and in 1994 was co-winner of the first Prix Galen to be awarded in Canada, among other honors. Just days before he died he heard that he had received a prestigious Senior Scientist Award from the Medical Research Council. Dr. Niznik accomplished in his 43 years what many scientists do not achieve in a lifetime, Vaccarino noted.

“As a highly valued member of the scientific community, as a friend and as a cherished colleague, Chaim will be greatly missed.”

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*Donald A. Richardson*

It is with deep sorrow that we report the death of Donald A. Richardson on July 14, 2000. Mr. Richardson was one of the founding directors of NARSAD, having previously served as President of the National Alliance for the Mentally Ill. He served on the NARSAD board from 1986 to 1992. Over the years of his activity as a director and since, he brought a remarkable passion for the cause of the mentally ill and an impressive knowledge base built over decades as an educator and administrator. He was led to the fight against mental illness when the disorder struck two of his children. Thereafter he and his late wife gave of themselves unstintingly to the organizations dedicated to improving opportunities for the mentally ill.

His background qualified him to be a superb leader in this field. His military service in WWII encompassed vital roles as a hero of D-Day and the Battle of the Bulge. A graduate of the University of California at Los Angeles, he devoted his career to the academic world. Beginning as a teacher in the Los Angeles school system, his career, characteristically, took on increasing responsibilities of leadership, leading to his becoming assistant superintendent in the school system. After his retirement in 1980, he became a full-time leader as an advocate for mental health on both the national and state levels. He was President of the National Alliance of the Mentally Ill, a member of Rosalyn Carter’s National Advisory Commission on Mental Health and a principal contributor to the Surgeon General’s Report on “Mental Health 2000”. His extraordinary efforts were widely honored, including recognition as Los Angeles County’s “Volunteer of the Year,” receiving the California Psychological Association’s “Distinguished Humanitarian Award” and the United States Commission of Rehabilitation Services Award for “Outstanding Contributions to the Disabled in America.” In all of his activities he had the strong support of his wife Margaret, whom he married in 1943. She predeceased him.

NARSAD is deeply grateful for Don Richardson’s many contributions to our activities in behalf of better treatments and cures for the severe mental illnesses. We extend our condolences to his three sons and grandchildren.

**Edwin G. Abel, Ph.D.**

Dr. Ted Abel has worked with Dr. Eric Kandel at Columbia University in basic science research using genetic techniques to study changes in the strength of synapses (connections between neurons) in the hippocampus and other mammalian brain structures. Dr. Abel hypothesized that changes in the strength, or “plasticity,” of synapses affect learning and memory and may play an important role in a variety of brain disorders. Specifically, Dr. Abel explored the role of a molecule called protein kinase A (PKA) and how it affects neuronal mechanisms. PKA has been implicated in long-lasting changes in synaptic strength.

Using genetic engineering techniques to generate transgenic mice (mice with an extra gene that inhibited neuronal PKA), Dr. Abel found that PKA plays a critical role in the mammalian hippocampus, affecting long-term memory.

Dr. Abel earned his Ph.D. from Harvard University in 1993. He received a NARSAD Young Investigator grant in 1996, setting the stage for research that would later earn him two important NIH grants. In 1998, Dr. Abel moved to the University of Pennsylvania, where he is an assistant professor in the department of biology.

Dr. Abel credits NARSAD with providing the seed money that has enabled him to receive two major NIH grants totaling approximately 1.5 million dollars. In one study, he is investigating “*The Molecular Basis of Long-Term Memory Storage*.” In another, entitled, “*Sleep and Memory: A Molecular and Genetic Analysis*,” he is researching how sleep deprivation affects long-term memory. “NARSAD laid the ground work for these two grants,” Dr. Abel observed.

**Bernice E. Morrow, Ph.D.**

Dr. Bernice Morrow set out to find susceptibility genes for schizophrenia, which is prevalent in patients with velocardiofacial syndrome (VCFS), a genetic disorder associated with deletion of a small region within one of the two copies of Chromosome 22. Individuals with VCFS have a cleft palate, heart defects, characteristic facial features and learning disabilities.

Dr. Morrow defined specifically the region of Chromosome 22 that is associated with the psychiatric changes of VCFS, and has identified several genes in this region that may be critical. These studies are important not only in VCFS, but have offered new candidate genes that may be involved in psychiatric disorders such as schizophrenia.

Dr. Morrow, an assistant professor of molecular genetics at Albert Einstein College of Medicine, received her Ph.D. from Albert Einstein in 1985. Upon being awarded a NARSAD Young Investigator Grant in 1993, she pursued research of psychiatric disorders associated with VCFS and deletions on Chromosome 22. Her subsequent Young Investigator Award in 1996 allowed her to further explore the congenital and psychiatric disorders associated with VCFS.

**100% OF ALL GIFTS GO TO RESEARCH**

**NARSAD’s no overhead, no fund-raising costs pledge is possible because two family foundations have undertaken to pay all NARSAD administrative and fund-raising costs.**

**NARSAD has followed this “100% of all gifts for research go to research” policy since 1987.**

**Wayne C. Drevets, M.D.**

Dr. Wayne Drevets, using a neuroimaging technique called positron emission tomography (PET) to elucidate the chemical mechanisms underlying depression and other mood disorders, has studied the brains of healthy individuals and depressed patients.

Dr. Drevets studied an area of the brain that underlies motivation, psychomotor activity and reward-related behavior, which involves the dopamine projections from the midbrain into the ventral striatum and the medial prefrontal cortex. The dopamine system has become an important target for investigations of mood disorders, as evidence suggests that its function is decreased during depressive episodes and enhanced by antidepressant medications. Dr. Drevets was able to boost the dopamine system, developing a protocol that was safe and well tolerated by all subjects. Through the use of PET imaging, he found that depressed patients improved when their dopamine system was enhanced.

This NARSAD-funded study provided the preliminary data needed for Dr. Drevets to apply for NIH funding, and he has received two NIMH grants totaling approximately 1.5 million dollars. Dr. Drevets is currently using PET scans to evaluate the action of antidepressant medications.

Dr. Drevets, an associate professor of psychiatry at the University of Pittsburgh, earned his M.D. from the University of Kansas School of Medicine in 1983. He embarked on a career in neuroimaging with the support of the late Samuel B. Guze, M.D., a member of NARSAD’s Scientific Council, and is a recipient of a 1996 NARSAD Young Investigator Award and a 1999 NARSAD Independent Investigator Award. ❖

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## NARSAD Scientific Council

*The keystone of NARSAD's structure is its Scientific Council, which today consists of 65 of the most distinguished scientific leaders in the study and treatment of the severe psychiatric disorders. This body establishes policy and, as volunteers, reviews NARSAD's grant applications.*

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*NARSAD's National Leadership Council is a volunteer group bringing the message of new hope through research to communities throughout the United States in private and public gatherings.*

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## EDUCATIONAL MATERIALS AVAILABLE

NARSAD has the following educational materials available free of charge except for where noted. For organizations ordering large quantities of brochures, please call the NARSAD Office at (516) 829-0091 for pricing to cover our mailing costs.



### BROCHURES:

Qty.

- Understanding Schizophrenia (English & Spanish Editions)
- Conquering Depression (English & Spanish Editions)
- Search for Cures (Description of NARSAD)
- Grantee Listing by University
- Research Achievements (Selected Description of Research Achievements)
- Planned Giving Brochure
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-   NARSAD's \$100 Million Campaign Brochure




### NARSAD FACT SHEETS:

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- Late-Life Depression
- The Warning Signs of Suicide
-   The Treatment of Bipolar Disorder
-   Borderline Personality

### VIDEO TAPES:

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- I'm Still Here: The Truth About Schizophrenia Documentary (\$25)
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- Schizophrenia and Depression (\$10)
-   Hope is Here (Narrated by Mike Wallace) (\$10)
-   The Future of Psychiatry (Biological Psych. Mtg.) (\$10)
-   NARSAD's \$100 Million Campaign (*Free*)

### BOOKS:

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- Schizophrenia: New Directions for Clinical Research and Treatment (\$15)  
(Edited by Charles Kaufman, M.D. and Jack Gorman, M.D. of Columbia University)

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You may fax your order to (516) 487-6930. Orders containing video tapes and/or books **must be received by mail** accompanied by check made payable to NARSAD.

*Newsletter Design and Layout by  
Lorraine Divone*

**The National Alliance for Research on Schizophrenia and Depression** - represents the unified commitment for the support of research by the members of the country's largest mental health organizations: The National Alliance for the Mentally Ill; The National Mental Health Association and The National Depressive and Manic Depressive Association, our founders, and by our thousands of supporters.

In thirteen years, NARSAD has awarded \$99 million to fund 2,403 grants to 1,237 scientists at 164 universities and medical research institutions.

Because NARSAD seeks and has received grants for administration and fundraising, 100 percent of the funds contributed for research actually go to support research.

NARSAD has set itself an urgent goal: to raise \$100 million over five years through a national campaign. NARSAD welcomes support from all who believe, as we do, that research can and will provide better treatments of and, eventually, cures for mental illness.

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