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UNRAVELING GENE VARIANTS FOR SCHIZOPHRENIA AND DEPRESSION:

A Profile of Elliot S. Gershon, M.D.

by Anne B. Brown

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Somewhere in the massive haystack of the human genome, Dr. Elliot Gershon believes, there are a few precious needles that could change forever the way doctors treat psychiatric disorders.

“Even in college, I was always fascinated with the biology of human behavior,” says Dr. Gershon. “When improved psychopharmacology agents became available, they reopened the notion that there are important biological components to psychiatric illnesses. Around that time, genetics was developing very quickly, but not until development of the DNA markers in 1978 and the completion of the maps of the human chromosomes published in 1987 was significant progress made in genetics. Also, advances in statistical analysis helped to improve genetic studies.”

Dr. Gershon, chair of the department of psychiatry at the University of Chicago and a member of NARSAD's Scientific Council, is a renowned researcher in psychiatric genetics. Before coming to the University of Chicago, he headed the Clinical Neurogenetics Branch at the intramural program of the National Institute of Mental Health where he was instrumental in developing the methodology to start the large

genetic collaborative studies on psychiatric illnesses. Collaborate studies are very important in solving the complicated puzzle of genetics and environment. Scientists must study hundreds of families affected by an illness. The more families examined, the easier it becomes to build a statistical case for which genes are and are not involved in a disease.

According to Dr. Gershon, “genetic research to date has yet to identify susceptibility genes for most psychiatric disorders, including bipolar disorder and schizophrenia. Nonetheless, significant progress has occurred in statistical genetics, completion of the human genetic map, and new technologies for rapid sequencing of large numbers of genes. In addition, there have been several promising genetic linkage findings. Combined with collections of large samples of affected families, these advances are laying the groundwork for the ultimate identification of susceptibility mutations for these psychiatric disorders.”

“I moved to the University of Chicago for the opportunity to develop a group of laboratories,” explains Dr. Gershon. Members of Gershon's lab track about 400 genetic variations in each of his bipolar subjects as well as their immediate family members.

By studying hundreds of genetic family trees, or pedigrees, Dr. Gershon's lab is also slowly closing in on a genetic culprit of schizophrenia. Dr. Pablo Gejman, director of schizophrenia genetics research at the University of Chicago, has identified a region of chromosome 6 that appears to play a role in the disease. Studies by other researchers confirm this result, and some scientists think additional suspects lie on part of chromosome 13. Regions of chromosomes 13, 18, 21, and 22 appear to be involved in bipolar disorder.



Elliot S. Gershon, M.D.

Oligogenic Model

Dr. Gershon believes that by adopting a model of inheritance called the oligogenic model to the study of psychiatric disorders, significant advances could result. Under an oligogenic model, several genes may be required for an individual to develop the disorder. For schizophrenia and bipolar disorder, statistical analyses indicate that the most likely oligogenic inheritance pattern involves two or three genes, each having a small contribution to the risk to relatives. For these and other relatively common disorders, an oligogenic model would predict that each of these genes are very prevalent in the population as a whole, but that all of them are needed to increase an individual's susceptibility to developing the disorder.

In Dr. Gershon's view, "an incorrect assumption of a disease model of bipolar disorder and schizophrenia (in which a single, rare gene was responsible) may have accounted in part for frequent nonreplications of earlier positive findings of linkage. A second reason for inconsistent findings between studies is the

fact that large numbers of affected cases and family members are necessary to provide adequate power to detect linkage." Due to this problem, Dr. Gershon has used as a rule of thumb that a suggestive or significant linkage report must be replicated at least once to be considered worthy of further research.

Another area of focus for Dr. Gershon is on the possibility that, under an oligogenic model, bipolar disorder and schizophrenia may share susceptibility mutations. For instance on chromosome 18p, evidence for linkage has been reported for schizophrenia using the same markers earlier reported to be linked to bipolar disorder.

In his illustrious career, Dr. Gershon is most proud of "the people I have trained over the years including 10 individuals that have gone on to become full professors (including Drs. John Nurenberger of Indiana University, Wade Berrettini of the University of Pennsylvania, James Leckman of Yale University, Pablo Gejman of the University of Chicago, and Miron

Baron of Columbia University.)

As co-author on a study that found evidence of a susceptibility gene for manic-depressive illness in chromosome 18, Dr. Gershon, along with Drs. Berrettini and DePaulo, received NARSAD's 1996 Selo Prize for outstanding affective disorders research. (See remarks on page 3, from Dr. Gershon's acceptance speech.) He is also honored to be on NARSAD's Scientific Council. "NARSAD fills a very important niche for research studies—helping promising studies get started."

Consequences of Genetic Revolution

Dr. Gershon believes that although it will likely be many more years before the genes for these disorders are all identified, we must begin thinking about the consequences of the genetic revolution for medicine and for society. Potential applications of identifying these genes include diagnostic tests of vulnerability, a new understanding of the biology of susceptibility, new treatments based on these understandings, and gene therapy.

Genetic tests can be developed to identify who is vulnerable to the disease. "If we can test to see who is at risk, we might be able to help them," says Dr. Gershon. Deciding if and when such tests should be used is a matter of debate. Even if tests for diseases caused by multiple genes are developed, they could only determine genetic susceptibility because they do not take environment into account. And until better treatments are available, some question the value of such testing as it can cause undue anxiety without offering options to circumvent the disease.

Remarks by Dr. Gershon in Accepting NARSAD's 1996 Selo Prize for Affective Disorders Research

Of course, there is also talk of gene therapy and other methods to alter the DNA and thereby minimize the odds that people will become ill.

Although exciting from the standpoint of preventive and treatment implications in mental illness, genetic research could also potentially shift to more subtle and complex genetic contributions to behavior. This could potentially become very controversial, if, for instance, couples wished to improve their future offspring's intellectual ability, or give them a desired personality trait. Furthermore, the precise knowledge of one's genetic risk will require a broadening of skills for genetic counselors, so that they may effectively become psychotherapists. Finally, one must consider the possibility that some of the identified genes, while increasing the risk of a psychiatric disorder, may simultaneously serve to protect against other disorders or confer desired traits such as creativity.

Despite these potential problems, Dr. Gershon thinks that the promise of genetic studies for the treatment of psychiatric disorders clearly outweighs these concerns. "These genes are targets for developing new treatments," believes Dr. Gershon, "and in the future, they may also lead to curative treatments." ❖

"The way I look at my work is that this is an enterprise of humanity that, fortunately, any of us who are so moved can pick up the task and do something for it. Not everybody will be so moved. But you people who participate as philanthropists, you people who participate as scientists, you people who participate by volunteering to reveal your most painful and intimate moments in yourselves and your families, you're all doing something for this, and you are all bringing things forward.

Apart from infectious and semi-infectious diseases, we have to deal with chronic mental illnesses. Mental illnesses are one member of the category, the hypertension is another, and the arthritic complaints are a third. These disorders are dominating medicine, and have for many years. They are only very recently yielding to the efforts of genetic research. One reason is that we have a new paradigm. It's a paradigm shift in science, which advances in these sort of jerky ways. The older paradigm is that you had to have a specific hypothesis about what the cause of illness might be.

With the new genetic paradigm, we don't have a previous biological hypothesis about how it might work, but we can find out in what genes this tendency resides. From that, we can find out which particular gene, and which particular indication of a gene is producing susceptibility. From that, we can turn to the biologists. The biologists, because they know what the gene is, can then find out what is wrong. That means that they then have the rational way to tell us how to fix it.

I think the chromosome 18 story is one of the first of the chronic disorders in medicine, in all of medicine, for which you found the genes by using advanced genetic mapping

with statistical analysis. We have been able to march in a way that's inexorably leading towards the genetic components of susceptibility.

So I think that this chromosome 18 work has been a breakthrough. When I say a breakthrough, I mean it in the sense that it's one of the first. The reason I call it a breakthrough is that it's like a crack in a dam. The scientific community is intensely competitive. When the other guy's out there saying, 'Hey, you know what we can do?' They are all rushing in there, and it's a wonderful thing because it's a human enterprise—whoever picks up the task has a very good chance, at least now, of helping see this to completion.

Now, where is that completion? I'm going to also talk science fiction. First of all, I expect that we'll have diagnostic tests. So right now, somebody comes into my office and as a psychiatrist I can talk to them, and I think I can do it reasonably well. Based on their history and the things that we talk about, I can figure out what their diagnosis is, but only in a very broad way. In thirty or forty years, the doctor will say, 'Oh, you have these schizophrenic or manic depressive problems and I think I can find out what's producing it, at least the genetic part. Come back tomorrow, and I'll be able to tell you exactly what it is.' The day after that, the doctor will be able to give this patient either gene therapy or a precision pharmacotherapy. Right now, anybody here who is a psychiatrist knows just how much this is trial and error. So I think we'll have the tests. We'll have the treatments and we'll also have, I hope, a better understanding of helping people deal with both the illness and the fact that it is familial. It's my hope that all of these things are going to get better, and a lot better."

NARSAD's 2001 SARASOTA SYMPOSIUM— BIPOLAR DISORDER AND SCHIZOPHRENIA

by Anne B. Brown

This outstanding symposium was organized and sponsored by NARSAD Board Members, Lee and Bob Peterson, and NARSAD's National Leadership Council Member, Joyce Tate, under the leadership of Dr. Wade Berrettini of the University of Pennsylvania (a NARSAD Distinguished Investigator Awardee both in 1992 and 1999, and the 1996 Selo Prize Winner for Affective Disorder Research).

The symposium featured several speakers: Dr. Kay Redfield Jamison from Johns Hopkins University. Dr. Richard Jed Wyatt from the National Institute of Mental Health and Dr. Paul E. Keck, Jr. from the University of Cincinnati.

Kay Redfield Jamison, Ph.D.

Dr. Jamison is professor of psychiatry at John Hopkins University. She was awarded the NARSAD Falcone Prize for Affective Disorder Research in 2000. Her leadership in psychiatric research is broad. She is co-author of the seminal textbook, Depression, and author of studies on bipolar illness and its impact on leading writers and composers, as well as of a distinguished personal memoir, An Unquiet Mind: A Memoir of Moods and Madness, detailing her own struggles with manic-depression and suicidal thoughts.

CLINICAL ASPECTS OF BIPOLAR ILLNESS

Dr. Jamison discussed the major clinical problem with bipolar illness—keeping patients in treatment. Psychotherapy can help to increase treatment compliance by providing an understanding of the illness and improving social skills.

Dr. Jamison then tried to convey the enormity of the problem of suicide since there has been a tendency to think of it as a rare event. To illustrate her point, Dr. Jamison plotted the 10-year death rates

from the Vietnam War against the suicide committed during the same period in the United States. She found that there were as many suicides in young men in the United States as there were deaths from the Vietnam War.

“When you look at suicide attempts, the average person has a 1% chance of attempting suicide with no lifetime history of psychiatric illness,” explained Dr. Jamison. “However, when you look at individuals with bipolar disorder, the rate jumps to 25%-50%. As for completed suicides, the rate for a patient with bipolar illness is between 10-20%, with most of these deaths clustering early in the course of the illness.”

Symptoms in bipolar depression that put an individual at high risk for suicide include agitation, very severe anxiety, sleep disorders, and possibly psychosis. Lithium is one medication that has been shown in several studies to help prevent suicide due to its effect on aggression, some kinds of agitation, and certainly on impulsiveness.

Next, Dr. Jamison expressed a need to develop treatments that are much more specific to younger



Kay Redfield Jamison, Ph.D.

patients with bipolar disorder. She stressed that, “the things that help with non-compliance for somebody who is 30 will not work for somebody who has just been diagnosed at 16.”

Dr. Jamison finished up her talk with an encouraging downward trend in suicide for the 15- to 19-year olds in the United States over the last few years. One possible explanation for this trend is an increase in awareness of affective disorders and more individuals receiving treatment as shown by an increase in the number of prescriptions being filled for antidepressants during this same period.

Richard Jed Wyatt, M.D.

Dr. Wyatt is chief of the neuropsychiatry branch at the National Institute of Mental Health. He was a recipient of NARSAD's Lieber Prize for Schizophrenia Research in 1999. He has played a major role in psychiatric rehabilitation studies and programs nationally. He is a member of NARSAD's Scientific Council.

SCHIZOPHRENIA: NEW IDEAS ABOUT PREVENTION AND TREATMENT

Dr. Wyatt spoke about the need to intervene early in schizophrenia so that there is a potential to make it a less severe illness than it is now. He discussed studies looking at individuals with early symptoms—suspiciousness, depression, anxiety, tension, irritability, mood swings, sleep disturbance, and appetite changes—and putting them on a fairly mild form of treatment to develop a way of decreasing the conversion from what might be a normal adolescence to psychosis. A fairly large public health effort in the United States and abroad is attempting to identify youngsters early in their illnesses to try to decrease the conversion to psychosis.

Dr. Wyatt then highlighted research studies now underway to investigate potential environmental causes of schizophrenia. This work arises from the observation from identical twin studies that if one twin has schizophrenia, the chances that the other will not is 50%. Investigators are using databases on pregnancies from 40 years ago in the United States and other countries to identify the environmental component to the possible cause of schizophrenia.



Richard Jed Wyatt, M.D.

One finding to arise from these studies is that a mother who is substantially overweight before becoming pregnant has about a threefold risk of having a schizophrenia offspring. Another finding that has been replicated several times over the years is that older fathers have a greater likelihood of having schizophrenia offspring. This finding may be a result of changes in the father's germ line that occur as his age increases.

Other findings have looked at starvation during the beginning of pregnancy (as in Dutch Hunger Winter of 1944-45) and have found a significantly increased risk of schizophrenia in the offspring. Infection of the mother during pregnancy, including first trimester rubella, and influenza and other respiratory infections, are also associated with an increased risk of schizophrenia. One public health measure to prevent schizophrenia could be the inoculation of potentially pregnant women for influenza and other respiratory disease. Finally, evidence suggests that Rh incompatibility and lack of oxygen at birth may be risk factors for schizophrenia.

Paul E. Keck, Jr., M.D.

Dr. Keck is a professor of psychopharmacology at the University of Cincinnati.

NEW TREATMENTS FOR BIPOLAR DISORDER

Dr. Keck discussed research efforts in two major groups of new treatments for bipolar disorder—antiepileptic drugs and antipsychotic medications. First, Dr. Keck began with a review of anti-epileptic drugs for treatment of bipolar disorder.

USE OF ANTI-EPILEPTIC DRUGS

Lamotrigine (Lamictal)

Although this drug appears to be an effective antidepressant medication, lamotrigine is not an effective mood stabilizer. Studies examining long-term effects of lamotrigine suggest that it might be a good drug for preventing depressive symptoms in those individuals with a type of bipolar illness usually characterized by depressive episodes. However, its ability to prevent manic episodes or even potentially depressive episodes in bipolar I patients is unclear.

Gabapentin (Neurontin)

This medication is frequently added to lithium or to divalproex (Depakote) when patients with bipolar disorder have breakthrough symptoms. Unfortunately, available evidence from good controlled studies suggests that gabapentin does not have much effectiveness as a genuine mood stabilizing medicine when used alone. On the other hand, there is evidence that gabapentin might be a



Paul E. Keck, Jr., M.D.

good drug for treating severe symptoms of anxiety of sleep disturbance, since it appears to be safer than some benzodiazepines, such as diazepam (Valium).

Topiramate (Topamax)

This medication is one of the few drugs in psychiatry to actually cause weight loss and is being studied for obesity. Unfortunately, topiramate's effectiveness at reducing manic symptoms is unclear and requires further studies.

Zonisamide (Zonegran)

This medication has recently received FDA approval and appears to be similar to topiramate but causes less severe side effects (i.e. sedation and mental confusion).

Oxcarbazepine (Trileptal)

For over 20 years, this medication has been available for the treatment of bipolar disorder in Europe. Further studies are needed to prove its effectiveness in manic symptoms over haloperidol (Haldol) and lithium. Oxcarbazepine does seem to be a better tolerated drug than carbamazepine.

USE OF ATYPICAL ANTIPSYCHOTICS

Dr. Keck then reviewed research findings for the use of atypical antipsychotics for bipolar disorder treatment. He noted that most of the atypical antipsychotics studied for bipolar disorder have focused on the treatment of mania with no studies to date looking at the effects on depression.

Clozapine (Clozaril)

Although clozapine has been observed to have antidepressant and anti-manic effects, Dr. Keck emphasized that good double blind randomized control trials have not been performed. This is due to the fact that clozapine is typically given to bipolar patients when all other treatments fail because of its association with a number of toxic reactions, including agranulocytosis, seizures and cardio-respiratory complications. In case reports, clozapine has been reported to have a remarkable response rate of 70%.

Risperidone (Risperdal)

One study Dr. Keck reviewed had looked at whether risperidone in addition to lithium, or in addition to divalproex, was equal to or better than lithium or divalproex alone (i.e. mood stabilizer alone versus mood stabilizer plus risperidone). The combination of treatments in both groups was better than the mood stabilizer alone at reducing manic symptoms.

Olanzapine (Zyprexa)

Studies have shown that the initial starting dose of olanzapine is important in improving manic symptoms—requiring a higher dose than in schizophrenia. Olanzapine seems to be especially

effective in treating patients with so called “mixed manic and depressive episodes” along with rapid cycling.

Quetiapine (Seroquel)

Although this drug might have promise in treating manic episodes and especially as a good stabilizer, there have been no studies in this area.

Ziprasidone (Geodon)

Because of its serotonin and norepinephrine reuptake effects, ziprasidone is a very unusual antipsychotic medication. In fact, the degree to which ziprasidone blocks the reuptake of these neurotransmitters is very similar to antidepressants, but it does not worsen mania (unlike antidepressants). Studies have found ziprasidone to be effective in the treatment of mania.

Dr. Keck concluded his talk with the observation that if any of the atypical antipsychotic drugs are ever going to be used as long-term treatments for bipolar illness, research needs to show what effects these medications have on treating depressive symptoms and their long-term effects in preventing manic depressive episodes. ❖

NARSAD would like to thank the sponsors of the symposium: AstraZeneca Pharmaceuticals, Janssen Pharmaceuticals, Pfizer Inc., Wyeth-Ayerst Pharmaceuticals, Salomon Smith Barney, Northern Trust Bank, Sarasota Memorial Health Care System, Bayside Center for Behavioral Health, and Century Foundation of Sarasota Memorial Hospital.

MODIFIED *DSM* CRITERIA HELP CLINICIANS DIAGNOSE DEPRESSION IN CHILDREN

Preliminary results from the first federally funded study of depression in preschoolers suggest that using modified DSM-IV criteria is effective in detecting depressive symptoms.

Even preschoolers can be depressed, but their symptoms may not fit the *DSM-IV* criteria, a situation that may lead to underdiagnosis and inadequate treatment. The preliminary results of a new study funded by the National Institute of Mental Health show that modified *DSM* criteria may help clinicians improve their ability to identify depression in young children.

“The main purpose of the study is to determine whether preschool children have clinically significant depressive symptoms using modified *DSM-IV* criteria. Another aim is to validate the modified criteria using the same strategies that validated psychiatric syndromes in adults and advanced the *DSM* system,” said principal investigator **Joan Luby, M.D.**, at the October meeting of the American Academy of Child and Adolescent Psychiatry in New York City.

Luby, an associate professor of child psychiatry, and her colleagues at Washington University School of Medicine in St. Louis, modified the *DSM-IV* criteria for depression by eliminating the two-week minimum duration for symptoms and one core symptom so that either depressed mood or loss of interest in previously enjoyed activities was required instead of both, said Luby.

“In contrast to the stability we see in adult mood disorders, young

children have symptoms that can fluctuate from week to week and range in affect,” said Luby.

The preliminary results of the five-year study show that 18 preschoolers were diagnosed with depressive symptoms using the modified criteria, compared with three diagnosed with the *DSM-IV* criteria.

She and her colleagues also added questions during interviews with each child’s primary caregivers that are relevant to the child’s life experience. For example, mothers in the NIMH-funded study are asked about signs of sadness or destructive behaviors when their child plays, said Luby.

“Current *DSM* criteria focus on symptoms at work or in relationships that are irrelevant to preschoolers,” she noted.

“The validity of the modified *DSM* criteria was tested against four other measures used to detect depression in young children. These are a family history of psychiatric disorders, scores on the Achenbach Child Behavior Checklist (CBCL), a child’s self-reported symptoms of depression and anxiety, and salivary cortisol taken from the child at assessment,” said Luby.

Three groups of preschoolers were assessed with the four measures: the 18 preschoolers who met the modified *DSM-IV* cri-

teria; 11 preschoolers who met the *DSM-IV* criteria for attention deficit/hyperactivity disorder (ADHD), and 23 preschoolers in the control group who had no *DSM-IV* psychiatric disorder.

“We chose ADHD for the psychiatric comparison group because it is a known disorder in preschoolers, and we wanted to know whether the symptoms we found were specific to depressive disorders,” Luby explained.

“The most significant result was that depressed children had more relatives with major depression, affective disorders, and suicide attempts and/or completions compared with the ADHD group and the control group,” said Luby.

“There was also a significant correlation between the children’s self-reported symptoms of depression and the depressed group in particular on the self-reported social inhibition and internalizing symptoms using an age-appropriate puppet interview,” according to Luby.

Depressed preschoolers also had significantly higher rates of internalizing symptoms than the group with ADHD and normal controls.

*Reprinted from Psychiatric News,
December 1, 2000.*

*Joan Luby, M.D., is a recipient
of a 1999 NARSAD Young
Investigator Award.*

HIGHLIGHTS OF THE INTERNATIONAL CONGRESS ON SCHIZOPHRENIA RESEARCH MEETING

by Alan S. Brown, M.D.

The International Congress on Schizophrenia Research Meeting, held at Whistler, British Columbia from April 28 to May 2, 2001, featured schizophrenia researchers from around the world. Begun in 1987, attendance at the meeting has grown several-fold. The purpose of the meeting is to provide a forum for investigators in schizophrenia to exchange information and be exposed to new ideas. Among its strengths are a mixture of basic and clinical scientists. The Congress has enhanced collaborations across the world, with a large proportion of investigators being from outside the USA.

Below is a sampling of presentations at the recent Congress meeting. Due to the large number of presentations and space limitations, many excellent papers could not be included in this review.

Epidemiology

Developmental Markers

Dr. Mary Cannon, of the Institute of Psychiatry, London, presented findings from the Dunedin Multidisciplinary Health and Development Study. This is a longitudinal investigation of a birth cohort of 1,037 children born in 1972-73 in New Zealand. This cohort received assessments on 10

Alan S. Brown, M.D., of Columbia University, is a frequent guest writer for NARSAD's Newsletter. He is a recipient of NARSAD's Young Investigator Award both in 1993 and 1996, and of NARSAD's Independent Investigator Award in 2000.

occasions between ages 3 and 26, and were assessed for schizophreniform disorder at age 26. She showed that the children who later developed schizophreniform disorder were significantly impaired in motor development, IQ, language, and interpersonal skills. Children who later developed mania or neurotic disorders had emotional and interpersonal problems but no difficulty in the other areas of function. These findings support a profile of early developmental impairment that appears to be specific for schizophrenia.

Untreated Psychosis

Dr. Helene Verdoux, of the University Victor Segalen, Bordeaux, France presented work that aims to assess whether a long duration of untreated psychosis (DUP) predicts poor clinical and social outcome, and whether this association is confounded by premorbid and clinical characteristics. She studied a sample of 24 schizophrenic patients admitted to the hospital with a first episode of psychosis and followed them up at 6-month intervals over two years.

As in other studies, she demonstrated that subjects with a long DUP had a poorer clinical outcome. However, after correcting for premorbid adjustment (the level of functioning before onset of illness), the association between DUP and clinical outcome was markedly reduced. This suggests that the relationship between long DUP and poor outcome may be explained by the fact that poor premorbid functioning is associated both with DUP and with poor outcome.

Increased Incidence

Dr. Jean-Paul Selten, of the University Hospital, Utrecht, the Netherlands, investigated the hypothesis that the increased incidence of schizophrenia observed in several migrant groups is explained by selective migration of patients predisposed to schizophrenia. In a previous study, conducted among Surinamese immigrants to the Netherlands, he demonstrated a markedly increased risk of schizophrenia. To address the hypothesis of selective migration, he made the assumption that all people genetically at risk for schizophrenia had left Surinam and that all new cases from the Surinamese-born population developed in the Netherlands. After adjustment for this factor, the increased risk of schizophrenia remained, although there was a moderate decrease in the size of the effect. These findings suggest that selective migration alone cannot explain the increased incidence of schizophrenia among Surinamese immigrants to the Netherlands.

Dr. J. E. Kelly, of the Institute of Psychiatry, London, presented results on changes in incidence of schizophrenia in Camberwell, South-East London from 1965 to 1997. A total of 1,055 new cases of schizophrenia were identified over this interval. The incidence of schizophrenia was found to double over this time period. The increase was greatest in subjects under 35, and was present for both males and females. The finding might be explained, at least in part, by an increase in the ethnic minority population over this time period.

Dr. Jim van Os, of Maastricht University, the Netherlands, discussed the results of a study aimed at testing whether psychosis-like symptoms have a similar geographical pattern to psychotic disorders. He evaluated 7,076 subjects with an interview that assessed the presence of psychotic disorders and of psychotic or psychotic-like symptoms. The study found that birth in an urban area was associated not only with psychotic disorder, but also with psychotic symptoms in people who did not meet criteria for a psychotic disorder. These findings suggest that the presence of psychotic symptoms in a community is linked to the presence of psychotic disorders, and that the rate of these mental states increases progressively with the level of urbanization. The findings are consistent with a continuous phenotype of psychosis in the population.

Parasite

Dr. E. Fuller Torrey, of the Uniformed Services University of the Health Sciences, presented a review of studies implicating infection with *Toxoplasma gondii*, an intracellular parasite, in schizophrenia. Following on evidence that exposure to house cats in childhood are associated with schizophrenia, Dr. Torrey reported on a series of studies linking antibodies to *Toxoplasma* to schizophrenia. Two studies, in Germany and China, have each demonstrated increases in *Toxoplasma* antibodies among schizophrenic patients. Moreover, increased *Toxoplasma* antibody has also been demonstrated in the brains of patients with schizophrenia. Furthermore, some anti-psychotics have activity against agents such as *Toxoplasma*, further supporting a role for this parasite in schizophrenia. Dr. Torrey received NARSAD's Humanitarian Award in 1999.

Animal Models

Maternal Separation

Dr. Marco Riva, of the University of Milan, Italy and a recipient of a NARSAD Young Investigator award in 2001, presented findings on the effects of maternal separation early in development. Animals exposed to separation from their mothers at day 9 of life were found to have a number of brain abnormalities consistent with findings in schizophrenia.

In particular, there was a reduced content of brain-derived neurotrophic factor (BDNF) in the hippocampus, and the modulation of BDNF in response to acute restraint stress and to stress hormones was altered, suggesting a persistent functional impairment in the regulation of BDNF. This substance plays a critical role in the maturation and regulation of nerve cells. In addition, animals exposed early to maternal separation had reduced pre-pulse inhibition, an electrophysiologic abnormality found in schizophrenia. These findings support the theory that early adverse brain events can result in permanent structural and functional abnormalities, increasing the vulnerability to schizophrenia.

Brain Insult

Dr. John Csernansky, of Washington University School of Medicine, presented findings on the effects of early developmental exposure to the excitotoxin kainic acid on limbic-cortical neurons. Rats that were administered kainic acid on day 9 of life had evidence of neuronal loss in the hippocampus as early as 14 days of life and continuing until 40 days of life. Throughout this period, evidence of a process called apoptosis (programmed cell death) was present

in the hippocampus. These findings suggest that an early developmental brain insult can result in progressive neuronal loss, possibly due to an increase in apoptosis. These findings might be relevant to neurodevelopmental models of schizophrenia.

Cell Division

Dr. Holly Moore, of the University of Pittsburgh and a 1996 NARSAD Young Investigator, presented work on the effects of early developmental administration of methylazoxymethanol acetate (MAM) to rats. This chemical disrupts the ability of nerve cells to divide.

MAM caused several abnormalities found in patients with schizophrenia, including decreased hippocampal thickness, an increase in neuron density in the prefrontal cortex, diminished function of the frontal cortex, and diminished pre-pulse inhibition, an electrophysiological problem found in patients with schizophrenia. One of the most striking findings was selective dysfunction of limbic-related brain structures. These neurons showed abnormal electrical impulses and were hyper-responsive to inputs from the amygdala, while being significantly less responsive to inputs from the prefrontal cortex. Taken together, these findings suggest that disrupting cell division in early life can lead to abnormal gating of the brain circuits to prefrontal cortex and limbic structures.

Prenatal Stress

Dr. J. Koenig, of Maryland Psychiatric Research Center, discussed results of a study in which rats are exposed to variable prenatal stress and examined in adulthood for brain function. Exposed rats evidenced several findings

M O M E N T U M

NARSAD's Annual Gala Awards Dinner to Honor Three Nobel Prize Winners and Award Research Achievement Prizes

NARSAD's Annual Gala Awards Dinner will take place on Friday, October 12th at The Pierre Hotel in New York City. This special celebration will honor NARSAD's Nobel Prize Winners and the recipients of the NARSAD 2001 Research Achievement Prizes—The Lieber Prize for Outstanding Research in Schizophrenia, The Nola Maddox Falcone Prize for Outstanding Research in Affective Disorders, and The Ruane Prize for Outstanding Research in Childhood and Adolescent Psychiatry.

NARSAD's 13th Annual Scientific Symposium

The cornerstone of NARSAD's educational efforts, its Annual Scientific Symposium, will take place on Friday, October 12th, and Saturday, October 13th, 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.

**If you have not received your Save-the-Date card for our
Gala Awards Dinner and Scientific Symposium
please call the NARSAD office at
516-829-0091 or
1-800-829-8289**

Staglin Family Music Festival for Mental Health

Saturday, September 15, 2001 is the date of the 7th Annual Staglin Family Vineyard Music Festival in Rutherford, CA. Hosts Shari (NARSAD Board Member) and Garen Staglin are inviting NARSAD supporters and guests to an afternoon concert with maestro Benjamin Zander, Conductor of the Boston Philharmonic Orchestra. The event will feature wine tasting from some of the finest and rarest wineries, followed by an evening gourmet dinner in the gardens of the Staglin home prepared by chef Wayne Nish of March Restaurant in New York City.

A scientific symposium will also be held on the topic of "Hormones and the Brain," with Dr. Sam Barondes of the University of California-San Francisco moderating.

**For more details, please contact the Staglin Family Vineyard at:
P.O. Box 680
Rutherford, CA 94573
Phone: 707-944-0477
e-mail: info@staglinfamily.com**

M O M E N T U M

Fifth Annual “Sunshine from Darkness” Sarasota Gala Dinner & Concert

The Sarasota community is once again opening their hearts to hold the Fifth Annual Gala Dinner and Concert to benefit NARSAD on February 8, 2002 at the new Ritz-Carlton, Sarasota. This year’s event will include a program of familiar music performed by the Florida West Coast Symphony, a live auction, and an exhibition of NARSAD Artworks. A research symposium will also be scheduled for the morning of February 17th. It will be held at the Manatee Civic Center to accommodate a larger audience due to the symposium’s growing popularity.

Last year’s event raised over \$350,000, with one Sarasota family underwriting the expenses of the benefit so that all the money raised could go to NARSAD. Lee Peterson (Board member) along with her husband, Bob and with the help of their co-chairs—Bob (Board member) and Diane Roskamp, and Bob and Joyce Tate—have organized the event in the hopes of offering people a powerful educational and cultural experience and to create a dialogue about a subject that has been shrouded in silence (their son was diagnosed with schizophrenia at the age of 18).



Bicycle Ride & Marathon to Benefit NARSAD

To mark his 70th birthday, Thomas B. Coles, Jr., M.D., NARSAD Board member and President of NAMI-Eastside Support Group in Harper Woods, MI, is beginning to train for a 100-mile bicycle ride on October 7th, and a 26.2-mile fast-walk and jog in the Detroit Marathon on October 21st. He has a good reason.

“I think the most important charitable cause in the world is to fund brain disorder research,” says Tom, who has already begun to receive pledges for his efforts in support of NARSAD’s vital research programs.

If you would like to make a donation in honor of Tom’s tremendous dedication to helping to fund the science that will find better treatments and cures for brain disorders, please use the enclosed envelope and indicate that you are behind Tom...*ALL THE WAY!!!*

NARSAD National Leadership Council Members Arrange Upcoming Events in 2002

JANUARY 18 - FEBRUARY 10 MIND MATTERS

A series of events celebrating artists and researchers who explore complexities of the brain and mental illness.

Mind Matters will offer an exhibition of artwork, an educational symposium, and a concert. It will take place at the historic “Great Hall” of The Cooper Union in New York City.

Ellen and Howard Schusterman, NARSAD National Leadership Council Members, are working diligently to make this event a success.

MARCH 6, 2002 BENEFIT CONCERT

NARSAD National Leadership Council Members Roxanne and Guy Lanquetot are arranging a benefit concert to raise funds for NARSAD research programs.

The concert will be held at Weill Recital Hall at Carnegie Hall in New York City, and Richard Kogan, psychiatrist and classical pianist, will speak and perform.

M O M E N T U M

Memorial Tributes January 2001 through June 2001

NARSAD pays tribute to the memory of these victims of the ultimate tragedy of mental illness and pledges our dedication to finding improved treatments and cures which finally will end such losses.

Glenn D. Abarno
Mevalene Adams
Geneva Lacy Allen
Frank J. Ascoli
Aunt Ida
Dara Axelrod
Elliot Badanes
John Bauman
Frank A. Baur
William D. Belter
Elena Berinsein
David J. Bernreuter
Don L. Bernreuter
Stephany L. Bernreuter
Fil Bertucci
Alvin Bienvenu
Michael Bland
Emily Boulton's Grandfather
James R. Brennan
Anna Elizabeth Brown
Bill Bulger
Bruce Burgar
Don Burgar
Janet Burns
William Carasik
N. Peter Cardy
Robert Caver
Frank Cerone
Donald L. Chandler
Sheila Cohen
Olga C. Coles
Willy Cook
Clarence W. Coulter
Harriet Cox
Edward J. Cyryt
Dana
Margaret DeRousie
Louis G. Dickens
Jonathan E. Dixon
Michael Ducate
Larry Esckilsen
Lois Etheridge's Sister

Dear Father
George Ferrans
Bernard Ferry
Chad Forsht
Joseph Glenn
Ella Golbeck
Kathleen Graham
Carolyn Greenbaum
Symcha Grossman
John E. Gunn
Alice M. Gunn
Catherine Halpert-Winn
Mary Harris
Ned Hartung
Rosemary Hassett
Francis Haynie
Richard Hays
Jeanie Heavner's son
Nickie Hedbring
Verne Hendrix
Daniel Hinden
Harry F. Holt
Jean Horowitz
Rita M. Hoskinson
Dolores Howell
Martiel Hoy
Marge Huber's Mother
Rita Ifshin
Mark Ikenson
John C. Jaqua
Linda Javurek
Agnes Kahler
Albert W. Kaplan
Walter S. Katz
Claude R. Kaufman
Arlene Kaye
Sigrun Kebernik
Eric Kertzner
Charlie C. Kimbro
Truman W. King
Janet Klein
Mary Kopelman

Frances Koren
Anne Kotz
Cynthia Kozak
Levia Kwerel
Andrea Landau
Sam Landow
Karen Lapresi
Robert Lauer
Bonnie Leiser
Malcolm Levenson
Brian James Lewin
Hans Lindgren
Judge Buddy Little's Dad
Scott E. Loeffler
Monica C. Loh
Uncle Lou
Lorraine Lovs
William C. Lund
Karen Maizlish
Yetta S. Martin
Ellen Mason
James C. Matthies
Donald F. McCarty
Joseph McEntee III
Helen McStravick
Ronald Michelich
Warren Mindheim
Max Moiseev
Aurelio Narde
Erik Osthus
Mrs. Anne Patten
Murray Pearl
Stephen R. Pellicane
Billie Perry
Michael Pietrzak
Roy Pollard
Mary C. Porter
Finn Posaas
Joanne Owen Pratt
Ramez Qureshi
Jose Ramirez
Patty Riordan

M O M E N T U M

Memorial Tributes *(Continued)*

Helen C. Robinson
Mrs. Irving Rosen
Matthew Rosen
Robert Rossier
Irving Sainer
Jonathan Sandahl
Elizabeth Sanders
Rob Sarkaria
James K. Schaeffer
Florence Schertzer
Norman Schrifter
Norbert Shimek
Alan Siener
Jeffory Sill
I. Philip Sipser
Mrs. Norman Skier
Ann Smith

William Smith
Craig Spengel
Benjamin Stabin
Lois Steffen
John R. Steiner
Mr. Stephens
Sister of Joan Swope
Dr. John Test
Theresa Thomson
Mrs. Thomson
Tighe Tindall
Stanley F. Tomaszewski
Kathy Traynor
Pamela Ann Tusiani
Mrs. Vann
Eleanor Vekovins
Frank Venonsky

David D. Walters
Donald Watrous
Mark Waude
Monica Wertlieb
Robert Weil
Phillip E. Wickstrom
Matthew Wilkey
Rozanne Williams
Mildred Wheeler
Max Winterman
Ann Wolf
Charles R. Wolff
Kathleen M. Wonderly
Russell Woods
Peter W. Zartman
Howard Ziskin
Edward J. Zonsius

Honor Tributes January 2001 through June 2001

Miriam Baron
Judith Baskin
Mr. and Mrs. Terry Brennan
Phil Carter
Dr. and Mrs. Chester Christy
Ellen Cohen
Barbara Duhl
Felix Fertig
Don Frank
Bonnie Freed
Bradford Freer
Gina
Mr. and Mrs. Richard Golden
Mr. and Mrs. Herbert Goldsmith
Frederick K. Goodwin, M.D.
Clare Grisham

Judy Grogins
Helga Guttman
James Heller
Ada Hinden
Mr. and Mrs. William B. Hughes
Marcia S. Kaplan
Mr. and Mrs. Francis Kastenholz
Tom Kowalczyk
Claire Lafer
Mr. and Mrs. Sol Levinson
Mary Rubin and Samuel A.
Lieber
Clair Manson
Scott M. McVadon
Yvonne Meigs
Ruth Michelich

Mr. and Mrs. Donald Moorin
Margaret Moylan
Donald P. Pinkel, M.D.
Nunzio Pomara, M.D.
Jean Reeves
Sally Schneider
Craig Schubert
Judge and Mrs. Ed Scruggs
Lilian Sicular
Mr. and Mrs. Marvin Slomowitz
Philip Thygesen
Donna Tidwell
Edith Tipperman
Dr. and Mrs. Douglas Walck
Betsy Woods
Mary Frances Worley

analogous to those seen in schizophrenia. These include: decreased pre-pulse inhibition, increased responsiveness to amphetamine and PCP ('angel dust'), and decreased expression of NR1, one of the NMDA receptor subunits. Animal models of schizophrenia involving other early developmental insults have demonstrated similar outcomes.

Brain Lesions

Dr. Barbara Lipska, of the National Institute of Mental Health and a NARSAD 1994 Young Investigator, presented findings of studies in which animals receive a toxic substance that destroys part of the hippocampus in early life. These animals had reduced length and density of dendrites (neuronal components that receive electrical inputs) in the prefrontal cortex and limbic regions. In addition, lesioned animals had a reduction in the SNAP-25 protein, which is found in synapses, reduced markers of glutamate neurons in the prefrontal cortex, and diminished connections from other brain regions to the prefrontal cortex. These findings support the theory that an early neurodevelopmental lesion can cause abnormalities of the prefrontal cortex and of limbic regions.

Neurochemistry

Role of Glutamate

Dr. Amanda Law, of the University of Manchester, reported on findings involving the glutamate system in autopsied brains of patients with schizophrenia, depression, and bipolar disorder. Expression of the NR1 subunit, a specific component of the NMDA receptor, which binds glutamate, was examined. In all groups, a

decrease in levels of the NR1 receptor was found in a region of the hippocampus called the dentate gyrus. In patients with schizophrenia, the decrease was more marked on the left side. These findings suggest that glutamate dysfunction in the hippocampus is not specific to schizophrenia, although there may be specificity of the finding to the left hippocampus in schizophrenia.

Dr. P. C. Williamson, of the University of Western Ontario, presented data from magnetic resonance spectroscopy (MRS) studies of the anterior cingulate and thalamus of never-medicated patients with schizophrenia. MRS permits the study of brain neurochemicals in the living human. An increase in a chemical called glutamine, which derives from glutamate, was found in the anterior cingulate. Interestingly, levels of glutamine decreased during treatment with antipsychotic medication. Although more studies are needed, these findings suggest that antipsychotics may act in part by affecting glutamate function in schizophrenia.

NMDA Receptor

Dr. Daniel Javitt, of Nathan Kline Institute and a recipient of a NARSAD Independent Investigator award in 1995, discussed findings from studies on the role of NMDA receptor dysfunction in schizophrenia. This receptor appears to be important in the pathophysiology of schizophrenia, but the precise mechanism is unclear. Dr. Javitt treated rodents with PCP, which antagonizes NMDA receptors, and found significant enhancement of dopamine release in the striatum and frontal cortex following treatment with amphetamine. When the rodents were given glycine, an am-

ino acid which enhances NMDA receptor function, these effects of PCP were prevented. These findings suggest that abnormalities of NMDA receptor function may underlie the increased dopamine response associated with schizophrenia, and that glycine or related chemicals may reverse this response.

Dr. Larry Kegeles, of Columbia University and a recipient of a NARSAD Young Investigator award both in 1995 and 1997, examined the effects of ketamine on the release of dopamine in healthy volunteers. Ketamine blocks the NMDA receptor, which plays a key role in the activity of dopamine through its effects on the neurotransmitter glutamate. When ketamine was administered, followed by amphetamine, there was a marked increase in dopamine release, compared to subjects who received only amphetamine. These findings may mimic the excessive dopamine release found in patients with schizophrenia, and suggest that abnormal regulation of dopamine in schizophrenia might result from a failure of NMDA circuits that limit dopamine release after excessive stimulation.

Neuropathology

Brain Protein

Dr. C. Pesold, of the Psychiatric Institute, University of Illinois at Chicago, discussed recent findings on a protein called reelin, a brain protein with important structural and functional significance. Levels of reelin protein were decreased by about 50% in several brain regions among autopsied specimens of patients with schizophrenia and bipolar disorder with psychosis, but not in bipolar patients without psy-

chosis or unipolar depressed patients. The number of reelin-positive cells did not correlate with duration of treatment with antipsychotic medications. Interestingly, mice with reduced amounts of the reelin protein displayed abnormalities found in patients with schizophrenia, including evidence of disturbed neuronal migration and an increase in neuronal density in the frontal cortex.

Dr. C. Beasley, of the Institute of Psychiatry, London, reported on post-mortem studies of proteins involved in the Wnt signalling pathway. These proteins play an important role in brain development. In an initial study in the frontal cortex, patients with schizophrenia had a decrease in one of these proteins, GSK-3-beta, compared to controls. There were no differences in the other Wnt proteins. A second study, however, did not replicate these initial findings—no differences in any of the proteins were found between patients with schizophrenia, bipolar disorder, unipolar depression, or normal controls.

Genetics

Brain Abnormalities

Dr. R. Walter Heinrichs, of York University, Canada, reviewed extensive data on strategies for genetic investigations of schizophrenia that use endophenotypes for schizophrenia (i.e. biological abnormalities believed to be more closely related to a genetic mutation than the clinical disorder). A review of the biological literature revealed that the most robust findings included several electrophysiological abnormalities (including the P50 evoked potential), and neuropsychological disturbances, such as verbal memory. Studies of brain imaging and postmortem investigations have not revealed as strong

or consistent associations. Thus, it appears that when the brain performs a task, the differences between schizophrenia cases and controls become much more apparent, suggesting that these types of tasks may serve as better endophenotypes for schizophrenia.

Predictors

Dr. L. Erlenmeyer-Kimling, of Columbia University and a 1996 NARSAD Distinguished Investigator, reviewed findings from her New York High Risk Project, a pioneering study of early antecedents of schizophrenia. Subjects were required to have at least one parent with schizophrenia, or with an affective disorder, and were assessed on multiple measures, including attention, verbal memory, and motor ability in childhood, and followed up for schizophrenia and affective disorders in adulthood. This permitted the examination of childhood developmental abnormalities among a genetically high-risk sample of subjects.

Among many findings to derive from this study, Dr. Erlenmeyer-Kimling found that impaired attention, verbal memory, and motor skills were the strongest predictors of schizophrenia, with verbal memory impairment being the strongest predictor.

Dr. Daniel Weinberger, of the National Institute of Mental Health, presented recent findings on a study of a mutation in the gene for catecholomethyltransferase (COMT) and working memory. The COMT gene is involved in the breakdown of dopamine. In this study, Weinberger and colleagues demonstrated that individuals with a mutation of this gene, which decreased activity of COMT, thereby increasing dopamine levels, had better performance on the Wisconsin Card Sorting Test, a common test of work-

ing memory. This finding was demonstrated for both patients with schizophrenia and controls. Dr. Weinberger is a recipient of NARSAD's Distinguished Investigator award in 1990 and 2000 and a NARSAD Scientific Council member.

Susceptibility Genes

Dr. Hans W. Moises, of the University of Kiel, Germany, reviewed molecular genetic studies of schizophrenia. The talk included findings of linkage on chromosomes 1, 2, 6, 8, 13, and 22. Regarding specific genes that have been strongly associated with schizophrenia in association studies, three studies support the notch 4 gene, which may play an important role in brain development; this gene is found on chromosome 6. In addition, other studies have shown that the following may be susceptibility genes for schizophrenia: a calcium-activated potassium channel gene on chromosome 1, the DISC (Disrupted in schizophrenia) 1 and DISC 2 genes on chromosome 1, a cholinergic receptor gene (CHRNA7), and a gene called WKL 1 on chromosome 22.

Gene Expression

Dr. Arturas Petronis, of the University of Toronto, Canada and a recipient of NARSAD's Young Investigator award both in 1998 and 2001, discussed the topic of epigenetics, the study of the regulation of gene expression. Most genetic linkage and association studies examine DNA; however, the amount of expression of that DNA to messenger RNA is also critically important to the production of the encoded proteins. Gene expression can be influenced by environmental factors and chance events, as demonstrated in studies of identical twins, who, although share all of

their genes, show many differences in gene expression. The hormonal changes that occur during adolescence may help to explain the onset of schizophrenia in later adolescence and early adulthood, as hormones are known to affect gene expression.

Brain Imaging

Disturbed Connectivity

Dr. Monte Buchsbaum, of Mount Sinai School of Medicine and a 1990 NARSAD Distinguished Investigator, presented work using positron emission tomographic (PET) scanning and magnetic resonance imaging in antipsychotic-free schizophrenia patients, schizotypal personality disorder patients, and controls. Lower glucose metabolism (which reflects brain activity) was found in parts of the medial area of the cortex, in some but not all of the prefrontal cortex, and in areas of the superior temporal gyrus. Decreases were demonstrated in the correlations within the dorsolateral prefrontal and superior temporal regions, and between these brain regions. These findings support disturbed connectivity between the prefrontal and superior temporal regions of the brain in schizophrenia.

Frontal and Temporal Lobes

Dr. M. M. Picchioni, of the Institute of Psychiatry, London, re-

ported on a functional magnetic resonance imaging (fMRI) study of schizophrenia in identical twins. Discordant twins (i.e. those in which only one member of a pair had schizophrenia) were compared with one another and with healthy controls on brain activation changes during a verbal fluency test. It was found that within twins discordant for schizophrenia, the affected twin had lower activation in several brain regions, including the right inferior frontal, temporal, and medial cortex. Compared to control twins, the healthy member of the identical twin pairs demonstrated lower activation in the left inferior frontal and temporal cortex and the cingulate gyrus. These results suggest that functional abnormalities of the frontal and temporal lobes in schizophrenia are more severe even when controlling for genetic background, and these abnormalities are also present in those at high genetic risk of the disorder.

Facial Emotion Processing

Dr. Raquel E. Gur, of the University of Pennsylvania and recipient of a NARSAD Distinguished Investigator award in 1999, presented findings on facial emotion processing in schizophrenia using fMRI. Schizophrenic patients and healthy controls were tested with fMRI while viewing photographs of faces displaying different emotions. For emotion discrimination,

patients activated the right amygdala and right inferior frontal gyrus. In contrast, during this task, controls activated the left amygdala and bilateral inferior frontal gyrus. These studies suggest that the activation of these brain regions by facial emotion processing differs by hemisphere (i.e. side of the brain) in patients versus controls.

Prefrontal Deficits

Dr. Cameron Carter, of the University of Pittsburgh and recipient of NARSAD's Young Investigator award in both 1994 and 1997, reported on an fMRI study of first-episode psychotic patients. These patients and healthy controls were administered cognitive tests that activated the prefrontal cortex during the fMRI imaging procedure. Compared with healthy controls, patients with schizophrenia showed a specific impairment in the control of attention and working memory. However, a similar pattern of deficits was shown in patients with psychosis who did not have schizophrenia. These results suggest that prefrontal deficits in the ability to control cognitive processes are not specific to schizophrenia. Dr. Carter recently received NARSAD's 2001 Klerman Award for outstanding research. ❖

Visit NARSAD's Website 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.

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.

NEW PSYCHIATRIC MEDICATIONS IN DEVELOPMENT

by Anne B. Brown

Progress continues in the development of new psychiatric medications. New insights are being discovered into the special benefits, as well as the limitations, of currently available drugs.

New applications are also being found for existing drugs. For example, the antidepressant venlafaxine (Effexor) may be an effective treatment for hot flashes in breast cancer survivors. Topiramate (Topamax), an anticonvulsant, can be used to treat bulimia nervosa, and bupropion (Wellbutrin) is effective in treating Attention-Deficit/Hyperactivity Disorder (ADHD) in adults.

One of the most significant new potential developments is mifepristone, the politically controversial RU-486 birth control pill, for psychotic depression. In a preliminary trial by Dr. Alan Schatzberg at Stanford University, patients with psychotic depression who were treated with mifepristone showed marked improvement within about four days. Moreover, the results have been sustained, with patients then receiving antidepressant monotherapy for continuation treatment, avoiding the need for neuroleptics or electroconvulsive therapy. If confirmed by further studies, the mechanism of action underlying these benefits likely involves the antiglucocorticoid actions of mifepristone, as elevated cortisol levels are associated with numerous psychiatric symptoms, including depression and psychosis. Research over the last 17 years has revealed that cortisol is extremely elevated in psychotically depressed patients.

We have compiled information on compounds starting in Phase II of the drug development process. First, we begin with new drugs being developed for depression, followed by medications for schizophrenia, and finally for disorders such as ADHD and anxiety.

AFFECTIVE DISORDERS

Fluoxetine Weekly Approved

The FDA has approved Eli Lilly's new Prozac Weekly formulation of fluoxetine for the continuation phase of treatment for major depression. The new version might appeal to patients who find taking a daily medicine too stigmatizing. The safety and side-effect profiles for the weekly formulation are the same as the standard form of fluoxetine.

Reboxetine (Vestra)

Reboxetine is a selective norepinephrine reuptake inhibitor (NRI) with low affinity for adrenergic and muscarinic receptors. The FDA did not approve reboxetine as was expected in May 2001, but no safety concerns were raised. The fact that the clinical trials supporting the FDA application were performed outside of the

United States might be a possible concern for the FDA. Reboxetine is already being sold in 50 countries outside the United States.

At the last American College of Neuropsychopharmacology Meeting, British psychiatrists presented data on reboxetine in a subset of patients with severe depression. The investigators concluded that the results indicate that reboxetine is significantly more effective than placebo among a subgroup of patients with severe depression at baseline, indicating that it is at least as effective as fluoxetine (Prozac) and imipramine (Tofranil).

As for its role in the depression armamentarium, reboxetine may be a good alternative to non-responders of selective serotonin reuptake inhibitors (SSRIs), those with melancholic or severe depression, and the elderly who tend to have many complicating illnesses. Also, reboxetine may be

beneficial for treatment-resistant depression when used in combination with an SSRI.

An advisory meeting will be held in the fall of 2001 and Pharmacia hopes to gain the FDA's approval at that time.

Duloxetine

Duloxetine is a dual reuptake inhibitor of serotonin and norepinephrine. Preclinical studies suggest that duloxetine is potent in blocking the serotonin (5-HT) and norepinephrine (NE) reuptake transporters. Unlike the currently marketed dual 5-HT/NE reuptake inhibitor venlafaxine (Effexor), duloxetine may not need titration (determining the concentration of a dissolved substance in terms of the smallest amount required to bring about a given effect) to achieve optimal 5-HT/NE blockade.

In a Phase III clinical study comparing duloxetine versus placebo and paroxetine (Paxil), patients on 80 mg per day of duloxetine experienced statistically significant improvement in depressive symptoms compared to randomized to placebo or 20 mg per day of paroxetine (Note: 20 mg is a very low dose for paroxetine). Adverse side effects of duloxetine include insomnia and loss of energy.

Eli Lilly is currently conducting Phase III clinical trials.

MK-869 Substance P Antagonist

This investigational compound was designed as a highly specific blocker of the substance P receptor, also known as the neurokinin-1 receptor. Because substance P was believed to mediate pain and inflammation, the drug was originally tested for its ability to relieve those symptoms, but without success. Later studies showed that substance P accumulated at brain sites that regulate affective behavior and responses to stress.

MK-869 has demonstrated robust antidepressant effect in preliminary clinical testing against paroxetine (Paxil) and placebo. MK-869 appears to cause mild adverse effects and no sexual dysfunction. Merck believes Phase IIa completed studies have confirmed 'proof of principle' for the substance P mechanism of action in depression.

Merck Pharmaceuticals is currently planning Phase IIb large-scale trials for their substance P antagonist.

Topiramate (Topamax)

Already available as adjunctive therapy for seizures, topiramate is

A Selegiline Patch for Depression

The only antidepressant under development for transdermal delivery is selegiline (formerly l-deprenyl), an atypical monoamine oxidase inhibitor (MAOI) originally developed as an adjunctive antiparkinsonian drug. Unlike oral selegiline, which behaves like a conventional MAOI at doses required for antidepressant efficacy, the transdermal patch does not increase tyramine sensitivity, so that dietary restrictions are not required. This patch may be especially beneficial for individuals who need to take an MAOI, have atypical depression, or exhibit psychomotor retardation (slowed motor movement).



The first clinical trial showed that transdermal selegiline was effective for depression after one week of treatment. This delivery system was well-tolerated with only 36% of subjects having local skin irritation compared to 17% with placebo. Treatment compliance was unusually high, with 89% of subjects on active drug completing the trial and nearly 100% of patches used.

Somerset Pharmaceuticals has submitted a New Drug Application for the selegiline transdermal system and hopes to gain approval in 2002.

NARSAD first reported on this skin patch in the Winter 1998 Newsletter.

being studied for monotherapy and add-on therapy of bipolar disorder. Topiramate is a GABA modulator and facilitates the inhibition of AMPA/kainate glutamate transmission, modulation of sodium and neuronal calcium channels, and inhibition of carbonic anhydrase.

Side effects of topamax include weight loss, nausea, headaches, psychomotor slowing, drowsiness, and numbness or tingling. Because topiramate has been shown to reduce appetite and cause weight loss, researchers are also testing its efficacy and safety in binge-eating disorder.

R.W. Johnson Pharmaceutical Research Institute is conducting Phase II clinical trials for topiramate.

PSYCHOTIC DISORDERS

Aripiprazole (Abilimat)

Aripiprazole is an antagonist at postsynaptic D2A receptors, and an agonist at presynaptic dopamine autoreceptors. Studies of aripiprazole show a reduction in psychotic symptoms with a favorable extrapyramidal side effect (EPS) profile. The drug appears to have less potential to cause side effects because of the relative lack of upregulation of D2 receptors in the striatum. Aripiprazole appears to have no statistically significant rise in QT prolongation, no increase in prolactin, and only a small percentage of patients experience significant weight gain.

Aripiprazole is currently being tested in Phase III clinical trials with Bristol-Myers Squibb hoping to submit the drug to the FDA in the fourth quarter of 2001.

Nontoxic Clozapine Under Development

Researchers at Harvard Medical School have teamed with a privately held pharmaceutical company to chemically modify the atypical antipsychotic clozapine. Early results of preclinical studies on animals show the new drug DHA-clozapine (Clozaprexin) to be nearly 10 times as potent, much longer acting, and significantly safer than the existing medication.

Protarga Inc. has patented its technology for developing what it calls ‘targaceuticals—joining a known pharmaceutical agent to a fatty acid lipid vector that is taken up by the cells being targeted for treatment. The result is directed delivery of the pharmaceutical agent, which should provide greater therapeutic effectiveness and a better safety profile.

Protarga is preparing to submit an Investigational New Drug Application with the FDA to allow clinical trials in humans.

DU-127090

This atypical antipsychotic has dopamine D2, D3, and D4 agonist/antagonist and serotonergic properties.

Solvay pharmaceuticals is currently conducting Phase II clinical trials for DU-127090.

ORG 5222

The novel antipsychotic, ORG 5222, combines dopamine D1 and D2 antagonist properties and binds to the 5-HT_{2A} serotonin receptor.

Organon is continuing its Phase II clinical trials.

THE DRUG DEVELOPMENT AND APPROVAL PROCESS

Although the drug development process appears long, important new treatments do eventually become available. It takes approximately 12-15 years for an experimental drug to travel from lab to medicine chest at a cost of \$359 million (based on 1993 figures from the Congressional Office of Technology Assessment). Only 5 in 5,000 compounds that enter preclinical testing make it to human testing. Only one of these five tested in people is approved.

Regulatory Review: Investigational New Drug (IND) Application (30 days)

This is an application filed with the FDA prior to human testing. The IND application is a compilation of all known information about the compound. It also includes a description of the clinical research plan for the product and the specific protocol for Phase I study.

Phase I (average 1.5 years) studies involve the first testing of a new compound in 20-80 healthy human subjects. Information is gathered on dosages and safety.

Phase II (average 2 years) studies are controlled clinical trials of a compound’s potential usefulness and short-term risks. The study involves a relatively small number of patients, usually no more than several hundred subjects.

Phase III (average 3.5 years) studies gather precise information on the drug’s effectiveness for specific indications, determine whether the drug produces a broader range of adverse effects than those exhibited in the small study populations of Phase I and II studies, and identify the best way of administering and using the drug for the purpose intended. If the drug is approved, this information forms the basis for deciding the content of the product label. Phase III studies can involve several hundred to several thousand subjects.

Regulatory Review: New Drug Application (NDA) (average 1.5 years)

The NDA is an application to the FDA for approval to market a new drug. All information about the drug gathered during the drug discovery and development process is assembled in the NDA. During the review period, the FDA may ask the company for additional information about the product or seek clarification of the data contained in the application.

Post-Approval Research

Clinical trials conducted after a drug is marketed (referred to as Phase IV studies) are an important source of information on as yet undetected adverse outcomes, especially in populations that may not have been involved in the premarketing trials (i.e. children, the elderly, pregnant women) and the drug’s long-term morbidity and mortality profile.

Iloperidone (Zomaril)

Iloperidone has antagonistic activity on a wide spectrum of receptors for dopamine and serotonin, with preferential affinity for 5-HT_{2A} serotonin receptors. It appears to exhibit efficacy in both positive and negative symptoms of schizophrenia and schizoaffective disorder.

Novartis Pharmaceuticals is currently conducting Phase III clinical trials.

Injectable Atypical Antipsychotics Soon to be Approved

Intramuscular (IM), immediate-release formulations of the atypical antipsychotics olanzapine (Zyprexa IM) and ziprasidone (Geodon IM) were recommended for approval by an FDA advisory committee for treatment of agitation in patients with schizophrenia. Ziprasidone was also recommended for agitation in schizoaffective disorder, and olanzapine was recommended for agitation associated with bipolar mania and dementia. Agitation for a wide variety of illnesses was chosen by the manufacturers for the FDA filing probably because of its larger potential market and the fact that the effectiveness for agitation could be demonstrated more easily with short-term evaluations than would have been required for schizophrenia. The IM ziprasidone does need to carry the cautionary labeling approved for the oral dosage form.

OTHER DISORDERS

ADD/ADHD

Atomoxetine

The letter 'A' was added to the former medication, tomoxetine, to lessen the possible confusion over the breast cancer drug, tamoxifen. Atomoxetine is a non-stimulant norepinephrine enhancer that affects attention and inappropriate behaviors. Studies in children as young as seven and in adults have found the medication to be superior to placebo. As a non-stimulant medication, atomoxetine is not expected to be a classified drug. Possible adverse effects of atomoxetine include headache and runny nose. Unlike methylphenidate (Ritalin), atomoxetine does not appear to be associated with insomnia. Atomoxetine may be beneficial for treating children with ADHD along with other comorbidities, such as anxiety disorder.

Eli Lilly is finishing up Phase III clinical trials of atomoxetine and expects to file a New Drug Application by the end of 2001.

ANXIETY DISORDERS

Pagoclone

This drug is a novel member of the cyclopyrrolone class of compounds, which acts as a gamma amino butyric acid (GABA) receptor modulator. Pagoclone is believed to mimic the action of GABA, which reduces excessive neuron activity thought to be responsible for the symptoms of anxiety and panic disorder. To date, Phase III clinical trials suggest that pagoclone may avoid some of the troubling side effects commonly seen in other drugs

MANY NEW COMPOUNDS IN PIPELINE

Sanofi-Synthelabo, a French pharmaceutical company, has many compounds in its pipeline for psychiatric disorders:

- **SR 58611 B3 Adrenergic Receptor Agonist**
Phase IIb clinical trials are being conducted for the study of severe depression.
- **SR 142801 NK3 Receptor Antagonist**
Phase IIb clinical trials are being performed for major depression, anxiety disorders, and schizophrenia.
- **SL 91.1077 Amisulpride**
Phase III clinical trials are only being conducted in Europe for possible treatment of schizophrenia.
- **SR 48692**
Phase IIa clinical trials are being conducted for schizophrenia.
- **SR 141716 Cannabinoid Receptor (CBI) Antagonist**
Phase III clinical trials are starting soon for schizophrenia, dementia, obesity, and substance abuse.

currently used to treat anxiety disorders.

This drug was licensed by Interneuron Pharmaceuticals to Warner-Lambert Company (now Pfizer). Pfizer is currently conducting Phase III trials. ❖

NARSAD Scientific Council

The keystone of NARSAD's structure is its Scientific Council, which today consists of 64 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
- Managing the Side Effects of Antipsychotic Medications
- 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)
- Preventing Relapses in Schizophrenia (\$10)
- 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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**The National Alliance for
Research on Schizophrenia
and Depression** - represents the

united 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 \$112.4 million to fund 2,543 grants to 1,344 scientists at 172 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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