As the holiday season has come and gone and we mark the end of a most productive year for the Stanley Foundation Bipolar Treatment Outcome Network (SFBN), it seems appropriate to highlight the unique contributions of Theodore (Ted) and Vada Stanley to the Network itself, and to the entire field of clinical research in the bipolar illnesses in general.

Through the Stanley Foundation, Ted and Vada were already making major contributions to the field by funding a large series of annual Stanley Foundation grants under the leadership of E. Fuller Torrey and the NAMI Research Institute. These Stanley Grants did much to encourage investigators in new approaches to bipolar illness, particularly when there was an increasing shortfall of funds from traditional NIMH funding sources targeted for bipolar illness.

In 1989 and again in 1994, the NIMH sponsored special meetings on the problem of under-funding of bipolar illness, but appeared unable to move in the recommended directions. Upon hearing both Drs. Post and McElroy speak at a National Depressive and Manic Depressive Association (NDMDA) meeting in Chicago, indicating that there were large numbers of potential new agents and approaches to be assessed for their therapeutic efficacy in bipolar illness, Ted and Vada offered to help jump start the field with a provision of funds for the completion of one of the NIMH’s recommended goals—the creation of a large collaborative network for more rapid investigation of alternatives to lithium in the acute and long-term treatment of bipolar illness. The funding of the Network was prototypical of the Stanley’s unique style and gift of both unceasing generosity and a “Can Do” attitude.

Ted grew up in Pennsylvania where he went to high school and then on to the University of Pennsylvania. After initial successful endeavors as a D.J. and radio announcer, he pursued a business career. Vada grew up in southern Ohio and following graduation from high school went on to Ohio University. She worked as one of the first women executives at Procter and Gamble in Cincinnati, and joined another young executive, Ted Stanley, in a new series of ventures. Ted and Vada moved to Connecticut where Ted founded MBI Incorporated. MBI markets a variety of products by direct mail, and their subsidiaries include Easton Press and the Danbury Mint. MBI is recognized as one of the best managed and most successful businesses of its size. It has the remarkable record in its 28 successive years of existence of increasing sales and profits each year, perhaps very much related to an efficient management style, but also to the use of feedback about what works, so that appropriate changes can be instituted in a rapid fashion.

All of us in the Network are most hopeful that we can emulate these virtues in the management of the Bipolar Treatment Outcome Network, and rapidly acquire new data about the best psychopharmacological agents available for the treatment of bipolar illness, determine what works for each patient, and generate new and creative approaches to treatment.

Ted and Vada have a son who is an attorney, and Vada has two other children by a previous marriage, as well as a huge extended family, primarily in Kentucky and Ohio. Her love and caring for people has been evident, not only in her immediate family but also now in the extended Stanley family of the Stanley Foundation Bipolar Treatment Outcome Network and in her unique encouragement of individuals and group endeavors to better understand and treat the major psychiatric illnesses.

Thus, the entire SFBN family of patients, physicians, clinicians, research assistants, and data analysts, as well as participating industry and advocacy groups, are indebted to the Stanleys for their unique support of this first ever collaborative research Network. The new knowledge emanating from the stud-

(Continued on page 2)
ies of the Network, which stays with patients over the long term to establish what really works, has already helped to make an impact on many people's lives, productivity, and health. We hope we can all live up to the wonderful model and standards that the Stanleys have set for us, combining caring for people with a maximum of efficiency and effectiveness. During this holiday season and the New Year, all in the Network give special thanks to the Stanleys for their generosity and caring.

(Continued from page 1)

NIMH Study Participation
Clinical Center, Bethesda, MD

Depressed patients who wish to participate in a protocol to evaluate repeated transcranial magnetic stimulation (rTMS) of the brain should contact Andy Speer at (301) 402-2293; those wishing to be screened for the Lamictal®/Neurontin® protocol (see Life Chart Highlights) should call (301) 496-6827.

Bipolar Network News

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Life Chart Highlights:
Selective response to the anticonvulsant lamotrigine (Lamictal®), but not gabapentin (Neurontin®), or, previously, carbamazepine (Tegretol®)

Figure 1 illustrates the course of illness and differential clinical response of a patient in the three phases of the NIMH double-blind, randomized, crossover protocol comparing six weeks of lamotrigine, gabapentin, and placebo. This patient illustrates substantial clinical improvement during treatment with lamotrigine; exacerbation of depression on placebo; and some initial improvement in depression, followed by increased cycling with gabapentin.

Dr. Mark Frye presented the initial findings from our double-blind, randomized six-week comparison study at the American Psychiatric Association (APA) meeting in May, 1997. He found a 53% response rate to lamotrigine, a 38% response rate to gabapentin, and a 9% response rate to placebo. We have now completed study on 30 patients, with 25 completing evaluable clinical trials. Their overall response rate to lamotrigine was 12 of 25 (48%); gabapentin, 8 of 25 (32%); and placebo, 1 of 19 (5%). Five of 29 (21%) patients responded to both drugs; 11/24 (46%) to neither; 6/24 (25%) to lamotrigine only (such as the patient illustrated in Fig. 1); and 2/24 (8%) to gabapentin only (Frye et al., 1998, in preparation).

The data of Kimbrell and associates (also presented at the APA meeting in 1997) suggest that it is those patients with the greatest deficits in perfusion (blood flow) in the frontal cortex as measured by positron emission tomography (PET) at baseline who are most likely to respond to lamotrigine and gabapentin.

Also at the APA meeting, Dr. Joseph Calabrese and associates reported on an open series of patients, wherein lamotrigine was generally used as an adjunctive therapy, showing substantial antidepressant, antimanic, or mood stabilizing effects. These results are convergent with a series of other studies and posters presented at the Second International Conference on Bipolar Disorder in June, 1997 (see BNN, Vol. 3, Issue 3).

How long-lasting the effects of lamotrigine will be and in which subjects it will specifically be effective deserves further clinical investigation. However, these preliminary findings generated in our blind, randomized trial are consistent with open observations of many others, and with improvement in 11 of 17 (65%) patients on lamotrigine when it was added in an open fashion (level 4) in patients in the Network (Suppes et al, 1998, in preparation).

Lamotrigine has an interesting biochemical mechanism of action profile in which it (along with carbamazepine) has the ability to decrease excitatory amino acid release through blockade of sodium channels. However, other effects of the compound must also be important, since lamotrigine appears to be effective in some patients who are inadequate responders to carbamazepine, such as the patient illustrated in Figure 1. In addition to this blockade of excitatory amino acid release, lamotrigine is reported to be active at serotonin type-3 receptors (5-HT3) and also to block serotonin reuptake at clinically relevant doses in a manner not entirely dissimilar from the classical antidepressants and serotonin-selective reuptake inhibitors (SSRIs). Thus, it is possible that the preliminary evidence of a useful antidepressant profile of lamotrigine could, in part, be related to its ability, like many other antidepressant modalities, to facilitate serotonin transmission via blockade of reuptake (i.e., the normal mechanism that inactivates serotonin).

In contrast, gabapentin is thought to work primarily by enhancing the effects of inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA). The effects of gabapentin (Neurontin®) in this respect are thought to be, in part, similar to those of valproate, which also increases GABA levels in brain and cerebrospinal fluid. As discussed in a previous issue of the BNN (Vol. 2, Issue 2), it is possible that some patients will need the inhibition of excitatory amino acids (such as glutamate) while others will need enhancement of inhibitory processes, such as those mediated via GABA, for effective antidepressant and mood stabilizing effects.

While selective clinical and neurobiological markers of response to these agents have
not been delineated, the current Life Chart Methodology (LCM) illustration of a clear response to lamotrigine in the absence of a clinically relevant response to gabapentin reinforces the concept (originally seen with carbamazepine and valproate) that lack of response to one mood stabilizing anticonvulsant is not necessarily predictive of lack of response to another. Thus, we have seen some patients respond to carbamazepine and not valproate (and vice versa), and now individual and selective responsivity with the new putative mood stabilizing anticonvulsants lamotrigine and gabapentin.

The Network looks forward to better delineation of the acute and long-term efficacy of lamotrigine, as well as the identification of possible predictors of positive clinical response.

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Figure 1: Selective response to the anticonvulsant lamotrigine (Lamictal), but not gabapentin (Neurontin), which was associated with increased cycling and dysphoric mania. Mild, moderate, and severe dysfunction from depression (below midline) or mania (above midline) are rated daily on the NIMH-Life Chart Method (NIMH-LCM™) by a nurse (top row) or the patient, both of whom are blind to medication status (bottom two rows). The middle row is the patient’s daily mood analogue rating of severity of depression (toward 0) or mania (toward 100).

Questionnaire on Early Intervention in Childhood Bipolar Illness

The Stanley Foundation Bipolar Network/Early Intervention Initiative (E.I.I.) is seeking information from families interested in bipolar disorder in children. This questionnaire surveys opinions about intervening early with an at-risk child to potentially prevent symptoms from progressing.

In addition, for families with affective illness on both the maternal and paternal sides, the questionnaire asks parents about any symptoms their child or children may be showing already. This information will not only help us identify the symptoms and behaviors associated with bipolar disorder in children, but will also help us design early treatment intervention protocols for this population.

If you are interested in filling out the questionnaire, please call (301) 496-6827 or 1-800-518-SFBN (7326); email us at: stanley@sparky.nimh.nih.gov; or write to: The Stanley Foundation Bipolar Network, 5430 Grosvenor Lane, Suite 200, Bethesda, MD 20814
This special meeting on brain imaging was organized to highlight the latest progress in the area of functional brain imaging:

- Dr. Harry Chugani began the meeting with an introduction to different methodological approaches to positron emission tomography (PET) and single photon emission computed tomography (SPECT), both of which can provide unique insights into the functioning of the developing and adult brain. Dr. Chugani has pioneered studies of changes in metabolism over an individual’s formative years, with the remarkable finding that glucose utilization, i.e. metabolic activity, in many areas of the cortex (and especially the temporal lobe) shows a marked peak between ages four and eight and then a gradual decrement to more adult levels during adolescence. In contrast, brainstem and cerebellar glucose utilization is more level with development.

This information suggests that there is a period in early childhood of markedly expanded nerve terminal sprouting and synaptic density in proportion to glucose utilization, with individuals generating far too many synapses during early development and having to prune these back prepubertally. These changes are also related to age-dependent recovery and reorganization of neuronal function after lesioning, such that recovery from strokes and other brain damage is much easier in childhood than later in adulthood. For example, one of Dr. Chugani’s patients with an entire left hemispherectomy (i.e., the surgical removal of the left cerebral hemisphere) in childhood is now a highly functioning hospital administrator. Dr. Chugani’s studies of Romanian orphans demonstrate bilateral temporal hypometabolism, especially in the anterior portion of the superior temporal gyrus. It is possible that this faulty development based on inadequate environmental input is related to the decreased bonding and social functioning of these highly maternally and socially deprived individuals.

- Diane Chugani, Ph.D., presented new and exciting data on autism based on her technique with alpha-[11C]methyl-L-tryptophan PET imaging to study serotonin turnover. She found that, consistent with diverse literature indicating serotonergic alterations in patients with autism, her patients appeared to have selective alterations in cortical and cerebellar development. In particular, there was decreased serotonin turnover in the right cerebellum and left frontal cortex, perhaps accounting for the deficient language functioning (mediated by the left frontal cortex) in patients with autism.

Dr. D. Chugani et al. have documented these defects in 30 out of 35 autistic males, although a smaller number of females studied (n = 5) showed fewer focal abnormalities. These data are consistent with a postulated defect in the serotonin transporter, which has also now been identified using gene mapping strategies in other groups. Therefore Dr. D. Chugani has begun to study patients with the direct serotonin 5-HT1A agonist buspirone (Buspar®) with promising initial results.

- Dr. Alan Zametkin reported decreases in cortical glucose utilization in adults with attention deficit hyperactivity disorder (ADHD) with metabolism decrements on the left compared with the right hemisphere. Using a new imaging technique, he also reported that patients with Lesch-Nyhan’s syndrome (a syndrome involving mental retardation and profound self-mutilation) have marked decrements in dopamine.

- Dr. Gregory Moore gave an introduction and overview to the functional components of magnetic resonance imaging spectroscopy (MRS), showing how this technique will allow us to assay levels of biochemical substances directly in the brains of psychotic patients. He found, for example, in patients with intractable epilepsy, that decrements in N-acetylaspartate (NAA) are highly correlated with decrements in glucose utilization (r = .64). Patients with schizophrenia (Bertolino et al., 1996, *Am J Psychiatry* 153:1554-1563), and now bipolar illness (Ketter et al, 1997, *AcNP Scientific Abstracts* 236), are reported to have lower NAA in the prefrontal cortex.

Dr. Moore was also able to measure myo-inositol with MRS and found it depleted in proportion to the severity of depression and that it decreased further with acute and chronic lithium administration. These data provide mechanistic support for the recent observations of Belmaker and associates (Benjamin et al., 1995, *Psychopharmacol Bull* 31:167-175) of the potential antidepressant effects of myo-inositol (12-14 gms/day).

- Dr. J. Giedd reported progression in the size of the ventricle in childhood onset schizophrenia as well as a decrement in thalamic volume assessed by magnetic resonance imaging (MRI). He noted Dr. Sue Swedo’s recent finding that Sydenham’s chorea is associated with group A β-hemolytic streptococcal infections and that this may be associated with increases in the size of the caudate and putamen in association with the development of prepubertal chorea and obsessive-compulsive disorder (Swedo et al., 1997, *Am J Psychiatry* 154:110-112).

- Dr. Perry Renshaw reported increases in monophosphodiesterases in mania compared with controls. Deficient choline in the caudate nucleus of depressed patients was associated with prediction of good antidepressant response to fluoxetine (Prozac®). He also reported that bipolar patients had decreased choline to creatinine ratios in their temporal lobes, particularly on the left side. He found that patients who relapsed and were rehospitalized had lower choline/creatine ratios compared with those who did not. These data provide mechanistic support for the preliminary observations of Sachs et al (Stoll et al., 1996, *Biol Psychiatry* 40:382-388) that supplements of large doses of choline may help stabilize mood in treatment refractory rapid cyclers.

- Dr. Scott Rauch presented evidence of frontal cortical and striatal alterations in patients with obsessive-compulsive disorder.

- Dr. Steven Yager summarized a series of exciting findings in the anxiety disorders, and

- Dr. Robert Post summarized the promising effects of repeated transcranial magnetic stimulation (rTMS) of the brain for the treatment of depression, as highlighted in a previous *BNN* (Vol. 2, Issue 3).
JOIN NAMI TODAY!

As a member of NAMI you join forces with parents, spouses, siblings, friends, and people who have been diagnosed with a brain disorder. You can join NAMI today by filling out the membership form below and sending it back to us. We need your voice alongside our 160,000 members to work effectively for improved treatment of and more research into these no-fault brain disorders and a better quality of life for those who suffer from them. Become a member today to start making a difference!

Benefits of membership (for all membership categories):

- Subscription to NAMI's bimonthly newsletter, the Advocate, which features cutting edge articles about the latest research, treatments, and medications for brain disorders; the status of major policy and legislation at the federal, state, and local levels; and provocative editorials and columns.

- Discounts on books, brochures, and fact sheets with the most current information on brain disorders, medications, and related issues.

- A 30-percent discount on the registration fee for the annual NAMI convention.

- Literature from your state organization with specific information about services, grassroots advocacy, and educational activities in your area.

- The availability of NAMI's toll-free Helpline, which responds with science-based information about brain disorders and aspects of living with them.

NAMI MEMBERSHIP OPTIONS:

INDIVIDUAL/FAMILY MEMBERSHIP
Individuals and/or families may join NAMI and receive all the benefits of membership listed above.

LOW-INCOME CONSUMER MEMBERSHIP
Individuals with a mental illness may join NAMI at a reduced membership rate and receive all of the membership benefits listed above.

PROFESSIONAL ASSOCIATE MEMBERSHIP
Mental illness service providers are encouraged to join NAMI and receive all the benefits of membership listed above in addition to: Subscription to NAMI's science newsletter, Decade of the Brain, Professional Membership certificate, 50 NAMI brochures with display stand.

AGENCY MEMBERSHIP
 Hospitals, schools, state agencies, and CMHC's are encouraged to join NAMI and receive all the benefits of membership listed above in addition to: four (4) additional subscriptions to the Advocate, Professional Membership certificate, 100 NAMI brochures with display stand, Mental Illness Awareness Week Kit.

I want to become an associate member of NAMI in one of the following categories:

☐ INDIVIDUAL/FAMILY MEMBERSHIP
$25.00 annual membership fee.

☐ LOW-INCOME CONSUMER MEMBERSHIP
$___ (Consumers on limited income are invited to join NAMI at a membership rate of their choosing, while still receiving all of the membership benefits).

Your name and a portion of your membership dues will be shared with your state's NAMI organization to provide local support for our efforts.

☐ PROFESSIONAL ASSOCIATE MEMBERSHIP
$40.00 annual membership fee.

☐ AGENCY MEMBERSHIP
$100.00 annual membership fee.

☐ I want to make a TAX-DEDUCTIBLE DONATION to NAMI. My check/money order for $______ is enclosed.

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