THE BACHMANN-STRAUSS
Dystonia & Parkinson Foundation, Inc.

WINTER 2004

Outlook

Second Dystonia Think Tank Held to Further Progress

An international group of 30 scientists and physicians came together in New York this past November to escalate progress in finding the causes of and cure for dystonia.

From left, Mark Cookson, PhD., senior research fellow, National Institute on Aging with Michael Y. Sherman, PhD., Associate Professor of Biochemistry, Department of Biochemistry, Boston University School of Medicine.

Titled "New Directions in Dystonia Research: DYT1 Dystonia and the Role of TorsinA," this was the second year that we held a think tank to enable scientists working directly on movement disorders to discuss their hypotheses, probe investigations and findings and suggest possible new directions.

The think tank was co-chaired by Warren Olanow, MD, FRCPC, Professor and Chair, Estelle and Daniel Maggin Department of Neurology, Mount Sinai School of Medicine, and Susan Bressman, MD, Chair, Allan and Barbara Mirkin Department of Neurology, Beth Israel Medical Center. The highly interactive two-day scientific meeting provided a vital, current overview of the clinical features of dystonia, an overview of torsinA – the protein that when mutant can cause dystonia – and current dystonia research relevant to torsinA. DYT1, a gene discovered in 1997 that is responsible for one of the most severe types of inherited dystonia, was recently found to encode torsinA.

The think tank provided a forum for noted scientists and young researchers alike to exchange ideas and information. Kim Caldwell, PhD, Adjunct Assistant Professor of Biological Sciences, The University of Alabama, attended the think tank for the first time with her husband and research partner, Guy Caldwell, PhD, Assistant Professor of Biological Sciences at The University of Alabama. "It was wonderful to get a big picture view of the field and to see where we fit in," she said. "Based on what we've heard here, we've been batting around new ideas."

This dystonia research think tank was sponsored by Allergan, Pfizer Inc, Pamela and Arthur Sanders, Jane and Barton Shallat, Emily and Jerry Spiegel, Bonnie and Tom Strauss and Teva Neuroscience, Inc.

WHAT'S INSIDE

SAVE THE DATE

12TH ANNUAL DYSTONIA & PARKINSON'S INVITATIONAL

Monday, June 21, 2004

at the Century Country Club in Purchase, NY

Sign up to play in this Pro-Am golf tournament and join us for dinner as we honor C. Warren Olanow, MD, FRCPC, for ten years of invaluable guidance on our Scientific Advisory Board and our Board of Directors. Janet Reno, Esq., former United States Attorney General, will be our keynote speaker.

YOUNG PROFESSIONALS

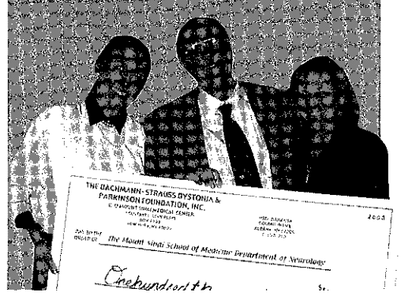
Meet new people, have a great time and help fight dystonia and Parkinson's disease. Cocktail Reception Thursday, March 4, 2004, 7-10 p.m., at Cipriani, 530 West 28th Street, New York City.

To register call 212.241.5614 or email Bachmann.Strauss@mssm.edu

THEATRE BENEFIT "WICKEDLY" SUCCESSFUL

In a terrific show of generosity that will further research at Mount Sinai Medical Center to find a cure for Parkinson's disease, supporters of our fall theatre benefit raised more than $100,000. Two hundred people attended our benefit performance of the Broadway musical *Wicked*.

Our thanks to all those who gave so generously. Special applause goes to all our theatre benefit committee members, to Doris Schecter of "My Most Favorite Dessert" for the "goody" bags' gifts, and to Patti Kenner for providing bus service.



Symposia is Key for Latest Information

This past fall 120 patients, family members and caregivers came together with physicians, researchers and other healthcare professionals at our annual symposia to hear the most up-to-date information about Parkinson's disease and dystonia. Dr. Daniel Moros, Associate Clinical Professor, Department of Neurology, Mount Sinai Medical Center, gave the keynote address on the medical ethics of treating patients with chronic conditions. Followed by a lively Q&A session, the audience was able to ask direct questions of physicians and researchers. Following is an example …

Q: Is there a connection between Parkinson's disease and dystonia?

While scientists know that Parkinson's disease affects a structure within the basal ganglia called the substantia nigra, the exact part of the basal ganglia responsible for dystonia is still unknown. Sometimes, patients with Parkinson's disease exhibit symptoms that look very similar to the hyperkinetic movements that characterize dystonia. These uncontrollable muscle contractions, jerks, or painful cramping in the feet or toes are sometimes caused by certain medications. Conversely, elderly patients with dystonia, who have the genetic form of the disease, may have swallowing difficulties, slowness of movement, and reduced voice volume that is often seen in the late stages of Parkinson's disease. Although researchers have not found a direct link, there is great interest in some of the symptom crossovers and the relationship of these two movement disorders.

For more questions and answers about Parkinson's disease and dystonia, go to www.dystonia-parkinsons.org and click on "Ask Dr. Tse."

Special thanks to Allergan, GlaxoSmithKline, Medtronic, Pfizer Inc, and Teva Neuroscience, Inc. for their sponsorship and help in making these free symposia possible this year.

A Promising New Year

MARGIE J. WALDEN
EXECUTIVE DIRECTOR

BONNIE STRAUSS
FOUNDER AND PRESIDENT

We begin 2004 on the threshold of tremendous possibilities. Dystonia and Parkinson's disease research have made impressive gains in the past year, bringing the promise for translating laboratory science to direct patient help and developing better drug therapies and rehabilitative treatments.

Our Foundation supported more than $1 million in research and educational programs this past year. Our second think tank on dystonia, which again brought together noteworthy scientists and clinicians to expand the knowledge base and foster new collaborative research efforts, was an important key to building on the progress we have made.

There is a lot to look forward to this year. New research grants have been awarded to further the tremendous work that has been done. The result will be expanded information resources for the scientific and medical community and, ultimately, for health care professionals and for patients and their families.

Among our upcoming special events we look forward to paying tribute to C. Warren Olanow, MD, FRPC, this June at our 12th Annual Dystonia and Parkinson's Invitational. We are honored that Janet Reno, Esq., former United States Attorney General, will attend our dinner as the keynote speaker. Events like these make our work possible. Our thanks go to our many, many volunteers and other supporters for making a very real difference.

Best wishes to all for the New Year.

From left: Patti Kenner, theatre benefit committee member, William C. Koller, MD, PhD, Professor and Director of the Movement Disorders Program at Mount Sinai Medical Center and Bonnie Strauss

Nothing Short of a Miracle

Laura Herbert's life has been anything but easy. Hers is a story of medical misdiagnosis, medical success, family determination, and personal resilience. On the downside, her story will be too familiar to many patients and their families. On the upside, it illustrates the significant progress that is finally being made in the awareness of and the treatment of dystonia.

Now 32 years old, Laura first knew something was wrong the summer before she entered sixth grade. One day, her right foot curled inward. She was unable to make it fall flat and unable to put one foot in front of the other. Her father, a physician and a scientist, took her to an orthopedist, who suggested that she might have a hairline fracture or a bone spur. Although nothing showed on the X-rays, her leg was put in a cast to help make walking more comfortable.

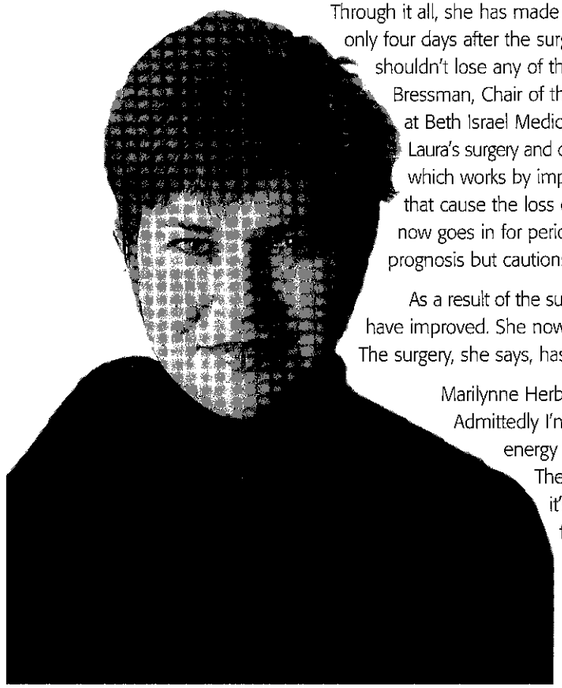
When Laura and her family returned home from spending the summer abroad, she went to see the neurologist who had previously diagnosed her older sister, Alissa, with dystonia. He thought Laura might just be vying for attention, and recommended that she be treated for psychogenic symptoms.

From the sixth grade until her junior year in high school, Laura went to a number of psychiatrists to try and find out what was wrong. All the while the degenerative dystonia was taking its toll. As she recalls, it was "…stealing away my control over body part after body part – toes, feet, leg, fingers, hands, shoulders, torso – until I was completely convinced that I was going mad."

One week after FDA approval, Laura had DBS surgery. She saw it as her last option.

The summer before she was to leave for college, she became "bent at the waist and couldn't straighten up." Her family took her to see another neurologist, Mitchell Brin, MD, who diagnosed early-onset DYT1 dystonia.

From that point forward, Laura tried every treatment she could find, including alternative medicine. In April, 2003 the U.S. Food and Drug Administration approved Deep Brain Stimulation (DBS) as treatment for some dystonia patients. She had heard about it for years and so, one week after FDA approval, Laura had this breakthrough surgery. She saw it as her last option.



Through it all, she has made steady advances. Laura showed signs of improvement only four days after the surgery and, according to Susan Bressman, MD, "she shouldn't lose any of the benefits she has gained from this DBS." Dr. Bressman, Chair of the Allan and Barbara Mirken Department of Neurology at Beth Israel Medical Center in New York, led the team that performed Laura's surgery and continues to monitor her progress. Deep brain stimulation, which works by implanting an electrode into the brain to block the signals that cause the loss of motor control, is similar to a pacemaker and Laura now goes in for periodic adjustments. Dr. Bressman is optimistic about her prognosis but cautions that this is very new and no long term studies exist.

As a result of the surgery, Laura's hand movements, handwriting and walking have improved. She now has the ability to sit still and then to get up and walk. The surgery, she says, has "changed her life."

Marilynne Herbert says of her daughter, "She was never defeated. Admittedly I'm biased, but she is a remarkable person with courage, energy and a sense of humor that's gotten her through this. The DBS was nothing short of a miracle. We know that it's just controlling her symptoms but until a cure is found, Laura's moving on with her life."

Laura Herbert

Grant Awards

New Grants Awarded to Advance Research and Knowledge

The Bachmann-Strauss Dystonia & Parkinson Foundation recently awarded grants of more than $885,000 to advance research to the next level in 2004. These grants include funding for individual researchers at major institutions, as well as to the Dystonia Medical Research Foundation and to The Michael J. Fox Foundation to help them fund additional studies. Grants are made based on recommendations by our Scientific Advisory Board. Following are summaries of some of the studies that will take place as a result of these awards.

PARKINSON'S DISEASE

Environmental Toxins as a Possible Cause of Parkinson's Disease – The proteasome, the primary biochemical machinery responsible for degrading and clearing abnormal proteins within cells, is significantly impaired in the brains of patients with sporadic Parkinson's disease. This suggests that environmental toxins, such as bacteria, fungi, and plants that are widely distributed in the environment, could be responsible for some types of the illness. To explore the hypothesis that exposure to environmental proteasome inhibitors could cause Parkinson's disease, Dr. Kevin McNaught will administer naturally occurring and man-made proteasome inhibitors to rats. They will be examined to determine if they develop movement disorders, and their brains will be studied to see if they have a pattern of neurodegeneration.

Can Cells Be Protected Against Damage? – Oxidative stress may be at least partially responsible for the slow and progressive neuronal degeneration observed in Parkinson's disease. It can damage various cell components or can adversely activate specific physiological signaling pathways. Dr. Venugopalan Nair hypothesizes that an early transcription factor named egr1 acts as a regulator to protect cells against oxidative damage. His lab will study the egr1 response to various neurotoxins. The results will identify potential signaling components responsible for cell survival and provide additional targets for the development of new treatment strategies.

DYSTONIA

Metabolic Profiling to Develop a Biomarker for Dystonia – Utilizing analytic biochemical techniques, Drs. M. Flint Beal and Susan Bressman hope to identify small molecules that are uniquely found in the blood of dystonia patients and compare them with normal controls and with patients who have Parkinson's disease and ALS. The discovery of such a marker would accelerate current efforts to map and identify dystonia genes and may also shed light on disease symptoms, helping to direct better treatment strategies.

Analyzing the Roundworm to Find Clues for the Function of Proteins – Quality control systems within cells promote accurate protein folding and prevent damage over time. A breakdown in these systems can result in aberrant protein aggregation and cell death – a hallmark of a variety of neurological disorders. This study is designed to advance understanding of how torsin proteins function in cells by utilizing the nematode roundworm, C elegans, to examine torsin activity. Drs. Guy Caldwell and Kim Caldwell hope to shed light on the naturally protective functions of torsins and help resolve the subtle cellular deficits that result when their proper action is absent.

The Role of TorsinA in the Nuclear Structure – To understand the cause of dystonia, this study explores a possible role for torsinA at the nuclear envelope membranes, which separates a cell's nucleus from its cytoplasm. Working under the hypothesis that torsinA operates by modifying proteins of the nuclear envelope, Dr. Phyllis Hanson will carry out live-cell imaging studies. Researchers will use cultured cells to compare behavior of normal and mutant torsinA in the nuclear envelope to the rest of the endoplasmic reticulum (ER). The ER is a microscopic organelle within cells which produces and distributes proteins.

Investigating Molecular Mechanisms in DYT1 Dystonia – Dr. Thomas Warner has created cell models to determine the normal function of torsinA, how the mutant affects this function, and whether this alters dopaminergic neurotransmission. TorsinA is normally part of the endoplasmic reticulum (ER), a complex involved in protein processing. Abnormal torsinA forms inclusions within the cytoplasm that do not associate with the ER but with another protein called VMAT2, which is vital for dopamine release. Abnormal dopaminergic neurotransmission is believed to play a key role in producing dystonic movements. Dopamine is a chemical responsible for transmitting signals across nerve pathways to produce smooth, purposeful muscle activity. Dr. Warner will study these cell models to determine if the mutant torsinA alters dopaminergic neurotransmission.

Investigating the Cause of Neurodegeneration – Dr. Kevin McNaught is working under the hypothesis that the mutation in DYT1 torsinA causes neurodegeneration in the thalamus, leading to alterations in the brain's basal ganglia, which in turn results in patients' motor dysfunction. To test this, he is looking at identifying markers of various neurons to determine which cell type and to what extent they are lost in various areas of the brain. His team will use highly specific and very sensitive antibodies to ubiquitin-protein conjugates, torsinA, and other proteins to determine which components accumulate to form protein clumps that are toxic to cells because they can't be cleared properly.

Studying Proteins as a Possible Cause of Dystonia – Dr. Stuart Sealfon believes that improved dystonia treatment will result from understanding how hereditary gene defects lead to the expression of dystonic symptoms. A seminal milestone towards this objective was the discovery that myoclonus dystonia is caused by a variety of mutations that disrupt the function of a protein called ε-sarcoglycan. Dr. Sealfon's group recently demonstrated that in the brainstem of a mouse the protein is highly expressed in dopamine neurons. In order to understand how mutations of ε-sarcoglycan lead to dystonia, he will establish a mouse model to provide the foundation for basic advances into the causes and treatment of dystonia.

DYT1 Gene Regulation in Mice and in Humans – While great progress has been made by identifying the gene for childhood onset dystonia (DYT1), the role of torsinA's cellular function is still not known. Although the DYT1 gene was identified in 1997 no information is available on the gene promoter or its transcriptional regulatory elements, which are specific DNA fingerprints present on the gene. In this study, Dr. Shashidharan will clone, characterize and identify these elements of both the mouse and the human DYT1 gene. He will make the mouse model that carries the human mutant torsinA gene to further understand torsinA's cellular function.

DeMartino and Hardy Join Scientific Advisory Board

George DeMartino, PhD John A. Hardy, PhD

We are honored to include two new members to our Scientific Advisory Board. George DeMartino, PhD, is the Robert W. Lackey Professor of Physiology, University of Texas, Southwestern Medical Center, in Dallas. He specializes in the function of the ubiquitin-proteasome system with regard to cellular protein degradation. John A. Hardy, PhD, is Chief, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health. A specialist in neurodegenerative diseases, Dr. Hardy has received numerous awards for his research into Alzheimer's disease and has extensively studied the genetics and molecular biology of Parkinson's disease and dystonia.

The Scientific Advisory Board, which reviews all grants awarded by our Foundation, guides our scientific direction.

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The Bachmann-Strauss Dystonia & Parkinson Foundation, Inc., was established in 1995 to find better treatments and cures for the movement disorders dystonia and Parkinson's disease, and to provide medical and patient information. An independent, nonprofit, 501(c)3 organization, its funding is made possible through the generosity of individual and corporate contributors.

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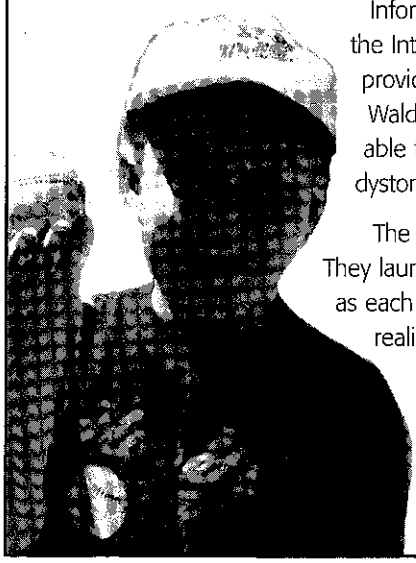
An Outpouring of Support to Boost Research

An initiative by the parents of an 8-year old boy, who was recently diagnosed with dystonia, has generated an added boost for research funding.

It was just last year that Linda and Greg Spielberg were on the difficult search to find help for their son, Jacob, who began having acute involuntary spasms in his arm and his leg. In June, when Jacob was diagnosed with early onset childhood dystonia, they began researching the disease to find the best help possible.



Information was scarce in their Kentucky hometown and so the family began searching the Internet. "The Spielberg's contacted us for help and I'm pleased that we were able to provide them with the most up-to-date information," said Executive Director Margie Walden. "When we found out they have family in New York and in Houston, we were able to connect them to some of the best doctors there, who are working in the field of dystonia today."

The Spielberg's quickly learned that the causes of and cure for dystonia are still elusive. They launched a personal letter writing campaign to friends and family, telling them, "... as each day goes by and we learn more and more about this disease, we have come to realize that our only way of helping Jacob is to help find a cure as quickly as possible."

The end-of-year fundraising campaign, conducted in cooperation with our Foundation, generated more than $90,000. The research grant made in Jacob's honor is "...so youngsters like Jacob can have a chance to live a normal life like so many other children his age."