THE BACHMANN-STRAUSS
Dystonia & Parkinson Foundation, Inc.

Outlook

FALL 2002

Of Mice and Men:

On the Road to Finding the Cause of Dystonia

Dr. P. Shashidharan is one of the first to admit that right now there are more questions than answers. He and his research team know that with dystonia there is no apparent damage to the brain and they know one of the genes responsible for the disease. However, that is not enough. They need to find the molecular mechanisms that bring on the disorder.

Daniela Sandu, Research Coordinator, with Dr. Shashidharan

"It appears that there's a problem in the communication between certain cells," Dr. Shashidharan says. "The brain looks normal in people with dystonia, so what's going wrong?"

His search for answers is conducted at the end of a long grey steel table in a lab in the Mount Sinai Medical Center. Shelves above are lined with vials and bottles of chemical solutions. Cell cultures from mice enable his team to look at the function of the protein TorsinA and biopsies allow biochemical and genotype analyses. Data is categorized and tests are repeated over and over to see if there is a pattern.

Called "Shashi" by his colleagues, this scientist's progress is impressive. Thanks to a series of grants from The Bachmann-Strauss Dystonia & Parkinson Foundation, he and his research team at the Department of Neurology, Mount Sinai Medical Center in New York, began to develop an animal model with the human DYT1 gene, which is prevalent in childhood onset dystonia and is responsible for one of the most severe types of inherited dystonia. His results were so promising that he applied for funding to the National Institutes of Health (NIH) and, in April of this year, was awarded a coveted five-year grant. Now Shashi is moving full steam ahead to the next level and toward the ultimate goal – finding the root causes of dystonia in children.

Schooled in Southern India at the Osmania University, Dr. Shashidharan came to the states as a fellow of molecular biology with the University of Medicine and Dentistry of New Jersey. In 1988, he welcomed the chance to join the Neurology Department at Mount Sinai Medical Center, and has been researching the causes of neurological diseases ever since.

continued on next page

WHAT'S INSIDE

THE PRESIDENT'S VIEW

This summer marked an important benchmark – the tenth anniversary of our golf invitational. It also marked a decade of generosity, which has made it possible to continue to fund research to help find better treatments and cures. My husband, Tom, and I were very touched and proud to be chosen as honorees this year, and we are so grateful for such a tremendous show of support for our work.

Steadily but surely, we are making scientific headway in the inquiry of dystonia and Parkinson's disease. We are at such a pivotal point. There is more information than ever before about Parkinson's disease, and medical and scientific inroads are being made in dystonia research. Importantly, reports about dystonia and its treatment are making their way into popular health and science stories. Most recently, on July 31, Dr. Max Gomez, Health and Science Editor of NewsChannel 4 in New York City, did a terrific report on the use of Botox in treating dystonia. Our thanks to Dr. Gomez and to NBC for bringing this information to millions of people.

To those who persist in their investigative research and to those who help make this research possible, I extend my sincere admiration and appreciation.

BONNIE STRAUSS
FOUNDER AND PRESIDENT

continued from page 1

On the Road to Finding the Cause of Dystonia

Under the direction of Dr. Mitchell Brin, former director of movement disorders, Dr. Shashidharan's focus shifted from studying Lou Gehrig's disease to Parkinson's and then on to dystonia. Like many scientists, he suspects a link between dystonia and Parkinson's disease, but it is yet to be confirmed. "In Parkinson's disease, cells producing dopamine, which signals movement, degenerate. In dystonia we know that dopamine is implicated but we don't know how. We know there's a disturbance somewhere in the dopamine system but we don't know where the defect is," he says.

So far, 14 different types of dystonia associated with genetic factors have been identified. Although only one copy of the abnormal DYT1 gene is sufficient to produce the symptoms of the disorder, only 30-40 percent of people with the abnormal gene develop the disorder. Because of this, Dr. Shashidharan suspects that the onset of dystonia may be influenced by other genetic factors or by environment or trauma.

Surprisingly, there is a strong parallel in mice. Only 30-40 percent of mice with the abnormal DYT1 gene show dystonia symptoms, and their onset also occurs during the maturation stage equivalent to human childhood and adolescence.

Through the NIH project, Dr. Shashidhran and his team are looking to see what happens when they make a mutant protein in the mouse model. So far, they believe that the hyperkinetic movements in this animal model are similar to what they are seeing in humans, although the "architecture" of the mouse brain is entirely different.

Using a colony of mice bred to carry the mutant gene of DYT1 dystonia, he is now able to further explore how TorsinA affects the molecular connectivity. "In biology, proteins are highly regulated," he explains. "We're looking at this protein and its interactions and asking who are the close and distant partners. With the animal model, we can begin to categorize and analyze any difference in connectivity between the transgenic mouse and a normal mouse. If there's a mutation in the protein TorsinA, we must find out what's going on.

"Levels of the protein TorsinA, which is present in every neuron in the brain, normally go up in mice in the development stage, which means it is being commissioned to work. With dystonia, we think some situation may occur that gets in the way of the function. We need to see what's causing this disruption to know what happens in children with dystonia."

Research Highlights

Among the range of scientific investigation funded by The Bachmann-Strauss Dystonia & Parkinson Foundation are these two key studies:

PARKINSON'S DISEASE

"A Rat Model of Parkinson's Disease that Shows Dopaminergic Neuronal Death with Lewy Body-like Inclusions."

This project at Mount Sinai Medical Center examined the effects of blocking proteasomes in rats to see if Parkinson's disease symptoms and pathology found in humans could be recreated. Proteasomes are enzyme complexes that clear unwanted, damaged or mutant proteins. In the study, a chemical compound known to block proteasomes was infused into the brains of rats. These animals were studied three weeks later to see if they had developed Parkinson's disease-like features. Results were in three key areas. Behavioral tests showed the development of movement disorders. Pathological examination of the brains revealed that dopamine-containing cells died in the same way that they do in humans. Lastly, it was evident that only dopamine cells degenerated, consistent with the findings in humans.

One of the most important aspects of the study was to determine whether Lewy bodies – massive clumps of protein within cells – could be detected within dopamine neurons. When the brain tissue of the treated rats was examined microscopically, Lewy body-like structures were found. This was important because Lewy bodies are a prominent observation in Parkinson's patients.

This is one of the first studies to produce an animal model for Parkinson's disease which shows Lewy body-like inclusions in addition to behavioral abnormalities and dopamine cell death. According to Kevin McNaught, PhD, of Mount Sinai (shown left), "This provides strong evidence to suggest that impairment of proteasomes is responsible for cell death and the clinical disorder of Parkinson's."

DYSTONIA

"Prevalence and Clinicopathologic Correlations in Dystonia and Other Hyperkinetic Movement Disorders in the Elderly."

The first systematic study aimed at uncovering the prevalence of dystonia in the elderly is expected to get underway this year. Conducted at the Jewish Home and Hospital, a major nursing home in New York City, the study will evaluate older adults for any signs of dystonia and will, for the first time, enable the type and severity of the disease to be documented and correlated with changes in the brain after death. To date, for example, facial involvement appears to be the most common among this age group. The study will help to verify this observation and will examine the correlation between different medications and how they impact the disease.

Ruth Walker, MD (shown above), principal investigator of the study, said, "Very little is actually known about changes that occur in the brains of people with dystonia. This study is particularly important to help us broaden our understanding. As more people donate their brains for research, it will be particularly important to future treatment and cures."

CHARTING NEW DIRECTIONS IN DYSTONIA RESEARCH

Leading experts in the study of movement disorders, genetics, molecular chemistry and biology will come together in October in New York City to discuss the future of dystonia research. The Roundtable brings together scientists and clinicians from the nation's top medical centers to review existing data and set directions for the next ten years of study. Sponsored by The Bachmann-Strauss Dystonia & Parkinson Foundation and co-chaired by Susan Bressman, MD, Chair, Department of Neurology, Beth Israel Hospital and C. Warren Olanow, MD, FRCPC, Professor and Chair, Department of Neurology, Mount Sinai Medical Center, findings will be featured in the winter issue of "Outlook".

Message from the Executive Director

For a non-profit organization like ours, the implementation of a business plan is pretty challenging these days. It also presents opportunities to find and tap new revenue streams to ensure we continue to get answers for dystonia and Parkinson's patients.

What has proven invaluable to our efforts are the people who volunteer their time and talent to help make our organization's events fun and, above all, successful. We sincerely thank the 15 men and women who helped run our golf event this summer and the Bloomberg staff for their generosity in helping us to produce an exceptional journal. Our thanks also go to the Young Professionals Committee, which organized and ran an event that will make a true difference in helping us fund medical research.

As the summer comes to an end, we are looking forward to continuing our exploration of new strategic alliances between government, corporations and foundations that will help increase research funding for and awareness of dystonia. In addition, we are looking forward to reviewing new grant proposals for 2003 from researchers who apply to us for funding to help beat dystonia and Parkinson's disease.

MARGIE J. WALDEN
EXECUTIVE DIRECTOR

Young Professionals Set the Pace

A top group of cool, sophisticated and caring New Yorkers turned out in force on Tuesday, July 16th for our fifth annual Young Professionals event. Held at the club Light, the theme of the evening was "Make a Difference" and they did just that by raising nearly $40,300. Co-chaired by Felicia Hoffenberg and Edward Olanow (pictured below) and joined by a great benefit committee, it was an evening of dancing and competing for nearly 50 raffle prizes. Above all, it was an evening that will go a long way to help fight dystonia and Parkinson's disease.

If you are between 25-35 years old and would like to join our Young Professionals, please contact 212. 241.5614 or Bachmann.Strauss@mssm.edu.

Save the Date

A theater benefit for Parkinson's disease research

Join us for dinner
and the Broadway performance of
Man of La Mancha
starring Brian Stokes Mitchell

Thursday, November 21, 2002

Martin Beck Theater, 302 West 45th Street,
between 8th and 9th Avenues

Dinner at 6 p.m. and Theater at 8 p.m.

For reservations and more information contact 212. 241.5614 or email Bachmann.Strauss@mssm.edu

10th Annual Dystonia Invitational Scores Top Results

The early summer weather threatened rain, but the skies cleared just in time for our 10th Annual Dystonia Invitational. The turnout was strong for the Hedi Kravis Ruger Memorial Tournament. In all, 225 golfers and 56 pros played at the Century Country Club in Purchase, New York. The event raised more than $1.3 million in support of movement disorder research, and honored Bonnie and Tom Strauss for their tremendous work on behalf of people with dystonia.

Co-chaired by Gedale Horowitz, Loren Katzovitz and Louis Susman, the day's event was capped off by dinner and an auction. With prizes including a travel package to St. Barthelemy, dinner with author Tom Wolfe, and tickets to the US Open, the auction raised $88,000.

Errata–*Jeanmaire and Will Weinstein, who so generously supported our 10th Annual Dystonia Invitational, were inadvertently left out of our Journal. Our thanks to them both.*

Key Information for Patients and Families

THURSDAY, OCTOBER 17, 2002

- **Dystonia Symposium 2002, 11 a.m. – 1 p.m.**
- **Parkinson's Disease Symposium 2002, 2 – 4 p.m.**

Hatch Auditorium, Guggenheim Pavilion, Mount Sinai Medical Center,
Fifth Avenue and 100th Street, New York City

Save the Date

Held annually, these free symposia are developed to bring patients, families and caregivers up-to-date on the latest research breakthroughs. Presented jointly by The Bachmann-Strauss Dystonia & Parkinson Foundation and the Mount Sinai Medical Center Department of Neurology, Movement Disorders Program, the symposia will feature the latest scientific and medical advances, as well as new drug therapies.

For more information or to register, please call 212. 241.5614 or email Bachmann.Strauss@mssm.edu.

Outlook is published by

THE BACHMANN-STRAUSS
Dystonia & Parkinson Foundation, Inc.

Mount Sinai Medical Center
One Gustave L. Levy Place, Box 1490
New York, NY 10029
Phone: 212. 241.5614
Fax: 212. 987.0662
www.dystonia-parkinsons.org

The Bachmann-Strauss Dystonia & Parkinson Foundation, Inc. was established in 1995 to find better treatment 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.

THE BACHMANN-STRAUSS
Dystonia & Parkinson Foundation, Inc.

Mount Sinai Medical Center
One Gustave L. Levy Place, Box 1490
New York, NY 10029

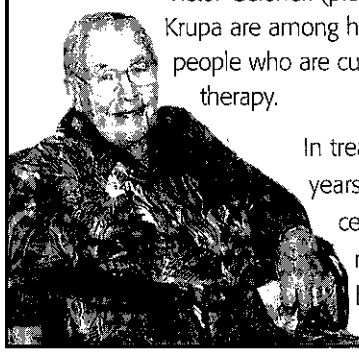
Phone: 212. 241.5614
Fax: 212. 987.0662
www.dystonia-parkinsons.org

Botox Spells Relief for Dystonia Patients

Mention of the name Botox now spells promise for thousands of people looking for a wrinkle-free appearance. For people with dystonia, it often provides relief from highly painful muscle spasms.

A toxin produced by the bacterium that causes botulism, Botox, manufactured by Allergan, was originally developed to treat dystonia. It initially received FDA approval for treating blepharospasm – the form of dystonia involving excessive eye blinking, and for spasmodic torticollis – muscle spasms of the neck.

Victor Gershek (pictured below) and Ellen Krupa are among hundreds of thousands of people who are currently getting this new therapy.



In treatment for the past two years for spasmodic torticollis or cervical dystonia, Ms. Krupa receives injections in the back and front of her neck because her neck involuntarily "wants to pull to the left". Mr. Gershek is being treated for generalized dystonia.

Suffering for ten years, Ms. Krupa tells the all too familiar story of fruitless visits to chiropractors, osteopaths, acupuncturists, and a range of others to find out why she had these spasms. Then, three years ago, she saw a piece on TV that highlighted the research being done to help dystonia patients. She knew she had found her answer.

Retired from her job in an accounting office of a computer company, Ms. Krupa has received Botox treatments for the past two years at Mount Sinai Medical Center. When she does, the needles are wired to electrodes to measure the activity of the muscle spasms so the drug can be injected into the exact place to ease the pain.

"If you had dystonia, you'd go through anything to help", she says. "I don't mind the needles. It's a miracle for me. Without it, I'm lost."