



DYSTONIA
MEDICAL
RESEARCH
FOUNDATION

Dystonia Dialogue

NEWSLETTER OF THE DYSTONIA MEDICAL RESEARCH FOUNDATION

Summer 2019 | Volume 42 • No. 2

Making Waves in Research

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The Dystonia Medical Research Foundation (DMRF) was founded nearly 45 years ago to make waves, to stir things up. The formation of the organization was a controversial statement for the time: *dystonia is important. People with dystonia are important.* The DMRF had the audacity to demand that dystonia was worthy of scientific investment and that those affected deserved expert medical care. We continue to insist

that dystonia is recognized within neurology, healthcare, social policy, and society at large. We are the voice to pharmaceutical and biotech companies, convincing them to pay attention to dystonia. The DMRF does not shy away from ambitious research goals or high risk, high reward projects when we know they are critical to propelling us closer to a cure. As investigators expand the sphere of what is known about dystonia, DMRF is constantly reaching out to invite new experts and bright young researchers into the field to ensure we continue to make new discoveries into the future.

See page 7 for the latest outstanding research projects underway to advance our understanding of dystonia and bring us closer to a cure.

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The *Dystonia Dialogue* is the magazine of the Dystonia Medical Research Foundation (DMRF). It is published three times a year to provide information to individuals affected by dystonia, family members, and supporters of the DMRF.

The Dystonia Medical Research Foundation (DMRF) is a non-profit, 501c(3) organization founded in 1976. The mission is to advance research for more effective treatments and a cure, to promote awareness and education, and to support the well being of affected individuals and families.

The *Dystonia Dialogue* reports on developments in dystonia research and treatments but does not endorse or recommend any of the therapies discussed. Individuals are urged to consult a physician with questions and concerns about their symptoms and care.

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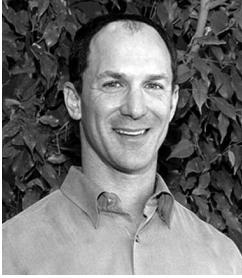
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Research Foundation

Foundation Update



Art Kessler
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Janet L. Hieshetter
Executive Director

The Dystonia Medical Research Foundation (DMRF) was designed from the beginning to do something bold, something that had not been done before. Founders Sam and Fran Belzberg set out to create a better world for their daughter and every individual impacted by this life-changing disorder. Their ambition stimulated dystonia research around the globe and extended a lifeline of resources for patients. This is the spirit in which we continue to rise to the challenge of curing dystonia and, in the meantime, providing patients and families with the information and resources they need to navigate the dystonia experience.

Every day, the DMRF is stretching the boundaries of dystonia science. Your support of DMRF ensures a constant, steady expansion of new discoveries and ongoing outreach to invite experts across medical and scientific disciplines to join us in our mission to cure dystonia. We must stimulate new research discoveries and attract young investigators who will continue making discoveries into the future. See page 8 for interviews with DMRF's new Scientific Director Dr. Joel S. Perlmutter and Scientific Director Emeritus Dr. Mahlon DeLong for more on DMRF's role and impact in research.

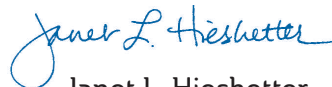
Human connection and collaboration are as vital to living with dystonia as they are to science. While the DMRF is here to provide information to help you and your family cope, we also connect you to the greater dystonia community for invaluable peer support. High rates of social anxiety are just one of the obstacles to feeling connected faced by many individuals with dystonia. Breaking through isolation can dramatically improve quality of life. See page 21 to learn more.

Awareness and advocacy are critical to research progress and bringing visibility to dystonia across sectors of society, from our neighborhoods and government representatives to federal research agencies. Please consider taking action during Dystonia Awareness Month in September to insist that dystonia receives the recognition and consideration afforded to other well-known, and often less common, disorders. Information on how to get involved can be found on page 6.

If you received this issue of the *Dystonia Dialogue* by subscription, it is because you are among the DMRF's generous financial contributors. Thank you for your dedicated support. Your donations make it possible for the Foundation to continue working toward a cure for every person and family impacted by dystonia.



Art Kessler
President



Janet L. Hieshetter
Executive Director

Interested in Volunteering for Research?

Look for opportunities to participate in clinical studies at www.dystonia-foundation.org/news

The Difference YOU Make

Your support of the DMRF immediately powers dystonia research and benefits affected individuals and families. Here are just a few ways your contribution is having an impact this year and beyond.

\$1,500,000+
budgeted for
science in 2019



19 RESEARCH grants,
contracts, fellowships,
and clinical trials
in 2019



28 CLINICIANS trained
to treat patients

1,000+
NEW PEOPLE SEEK HELP
from DMRF each year



100+ MEETINGS
on Capitol Hill
during Dystonia
Advocacy Day



15+ ZOO WALKS and
SPECIAL EVENTS in 2019

FREE EDUCATIONAL MEETINGS
across the country

FREE BROCHURES
and PAMPHLETS
available



50+ local peer
SUPPORT GROUPS
and ONLINE FORUMS



Mobilizing hundreds of
dystonia awareness
VOLUNTEERS

ADMINISTRATIVE
SUPPORT provided for
DYSTONIA COALITION



\$14M for DYSTONIA
INVESTIGATORS awarded from
Department of Defense



GENES DISCOVERED:
DYT1/TOR1A,
DYT6/THAP1,
DYT25/GNAL,
and others

260 INVESTIGATORS
FUNDED since 1976



6th INTERNATIONAL
DYSTONIA
SYMPOSIUM in 2020



**The Global
Dystonia Registry**
5,300 ENROLLED



\$35M invested
in dystonia science
since 1976



★★★★
CHARITY NAVIGATOR
Four Star Charity



THOUSANDS of drug
compounds tested

SAVE THE DATE: DMRF Community Events

DMRF events offer an opportunity for the dystonia community to come together and actively participate in building a better future for everyone impacted by this disorder. Events provide an opportunity to raise awareness, share information, spread the word, and make new friends. Join us!

Visit www.dystonia-foundation.org/events to register for DMRF events in 2019.

Dogs4Dystonia (Cedar Rapids, IA)	August 24	Denver Dystonia Educational Meeting	October 5
St. Louis Dystonia Zoo Walk	August 25	Cincinnati Dystonia Educational Meeting	October 19
Bronx Dystonia Zoo Walk	September 8	Providence Dystonia Educational Meeting	October 26
Cleveland Dystonia Zoo Walk	September 8	Chicago Basket Bash	October 27
Pittsburgh Dystonia Zoo Walk	September 8	Dystonia Day at the Phoenix Zoo	November 2
Providence Dystonia Zoo Walk	September 14	Detroit Dystonia Educational Meeting	November 2
Long Island Dystonia Educational Meeting	September 14	Team DMRF at the TCS NYC Marathon	November 3
Cincinnati Dystonia Zoo Walk	September 21	Los Angeles Dystonia Zoo Walk	November 9
Philadelphia Dystonia Zoo walk	September 22	Atlanta Dystonia Educational Meeting	November 9
Indianapolis Hunt for a Cure	September 29	Omaha Dystonia Educational Meeting	November 22

Runners Go the Distance4Dystonia



There are numerous opportunities throughout the year for runners to lend their support, spirit, and legs to support DMRF, including the 2019 TCS NYC Marathon to be held November 3, 2019. Request an application to join Team DMRF by sending an email to dystonia@dystonia-foundation.org or calling 800-377-3978. If you plan to be in NYC for the marathon, consider joining our cheering section led by local support groups from New York and New Jersey.

Dystonia Coalition Renewed



**DYSTONIA
COALITION**

The Dystonia Coalition is a groundbreaking collaboration of medical researchers and patient advocacy groups focused on accelerating clinical research in the field. Nearly 50 research centers throughout the world are participating, and new investigators and institutions may join at any time. The Dystonia Coalition began in 2009 with a \$6 million, five year grant from the Office of Rare Diseases Research and the National Institute of Neurological Disorders & Stroke. The Coalition was most recently renewed in June 2019 for an additional five years. The Program Director is H. A. Jinnah, MD, PhD, of Emory University School of Medicine. DMRF Scientific Director Joel S. Perlmuter, MD of Washington University in St Louis is Co-Director. DMRF will continue to keep the community informed of updates pertaining to this critical research development.

September is Dystonia Awareness Month

You can promote dystonia awareness by joining Dystonia Moves Me, the DMRF's annual awareness campaign. Dystonia Moves Me empowers volunteers to promote dystonia awareness locally and in social media.

There are several ways to take action for dystonia awareness:

- ✓ **Share what you know.** Throughout September, look for posts about dystonia from DMRF on Facebook, Twitter, and Instagram. Share on social media.
- ✓ **Show your support by showing up.** DMRF events and educational meetings are happening throughout the country. Check for events in your area on page 5. If you're unable to attend an event, consider making a donation to support awareness efforts: www.dystonia-foundation.org/donate
- ✓ **Make an awareness moment.** Keep wallet-sized information cards and stickers on hand to promote dystonia among the people you see on a daily basis. You can order here: www.dystonia-foundation.org/cards-stickers
- ✓ **Start a Facebook fundraiser for a cure.** All donations raised for DMRF through Facebook's fundraiser tools in 2019 will be matched dollar for dollar. Go to www.facebook.com/fundraisers to get started and be sure to notify DMRF of your fundraiser to have your donations matched
- ✓ **Make news.** Contact a local newspaper, TV news program, or blogger and ask them to do a story about dystonia. A media kit and press release template are available here: www.dystonia-foundation.org/dystonia-moves-me
- ✓ **Educate your Congressional leaders.** The Dystonia Advocacy Network provides tips on reaching out to your US Senators and Representatives to share your story and advocate for dystonia: www.dystonia-advocacy.org/getinvolved/

Throughout Dystonia Awareness Month, stay informed about activities and highlights from the Dystonia Moves Me campaign by connecting on the website, Facebook, Twitter, and Instagram.



Let us know how you are promoting dystonia awareness by sharing your photos/videos:

- Upload to www.dystonia-foundation.org/DMM_2019
- Email to awareness@dystonia-foundation.org
- Tag us on Facebook, Instagram, or Twitter (#dystoniamovesme)

Everyone who informs DMRF of their awareness activities will be included in a random drawing for a \$100 gift card. Deadline to enter is October 7, 2019.

Thank you for your support!

Cross-Disciplinary Projects Explore Dystonia Brain Networks to Improve Diagnosis & Treatment

The DMRF and Cure Dystonia Now (CDN) announced the latest grant awards to advance research toward improved dystonia treatment options and ultimately a cure. These awards are part of an ongoing effort to push the envelope of what is known about dystonia by funding innovative research projects with a focus on incentivizing collaborative, cross-disciplinary investigations. Dystonia is not caused by pathology in a specific brain structure, but by dysfunctional circuits of communication between multiple brain areas responsible for coordinating and controlling body movement. This year's grants reflect holistic and modular approaches to exploring dystonia brain networks.

Using Functional Connectivity to Optimize Deep Brain Stimulation in Dystonia

Andrea Kühn, MD, University Medicine Berlin (Germany)

Deep brain stimulation is a neurosurgical therapy that uses an implanted medical device to treat dystonia and other neurological disorders. The medical device delivers electrical stimulation to the areas of the brain responsible for dystonia symptoms. Many dystonia patients respond dramatically to deep brain stimulation therapy, but not all. Dr. Kühn and her team seek to clarify the underlying mechanisms of deep brain stimulation in order to better understand why some patients benefit from this therapy while others do not.

Unraveling Hierarchical Network Loops in Isolated Dystonia

Xin Jin, PhD, The Salk Institute for Biological Studies (USA)

The intricate networks in the human brain responsible for controlling body movement are comprised of many millions of neurons across dozens of brain areas. Dr. Jin and his team are working to understand the network activity that underlies dystonia symptoms, and to possibly prevent symptoms from developing. This grant is focusing on blepharospasm, a focal dystonia of the eyelid and brow muscles, as a model to understand dystonia networks more broadly. Partial support provided by the Benign Essential Blepharospasm Research Foundation.

Investigating Multimodal Neuroimaging for Probing Brain Networks in Cervical Dystonia

Richard Reilly, PhD, Trinity College Dublin (Ireland)

Dr. Reilly and his team are in search of biomarkers in the brain for cervical dystonia, a focal dystonia that causes involuntary head movements and neck postures. To do so, they will use multimodal analysis on a dataset from structural, resting state, and functional MRI (magnetic resonance imaging) in a group of cervical dystonia patients. They will compare results against a group of patients with spasmodic dysphonia, a focal dystonia of the vocal cords muscles. The goal is to advance understanding of the structural and functional brain differences in cervical dystonia.

Interregional Brain Connectivity in a Mouse Model of Cerebellar-Induced Dystonia

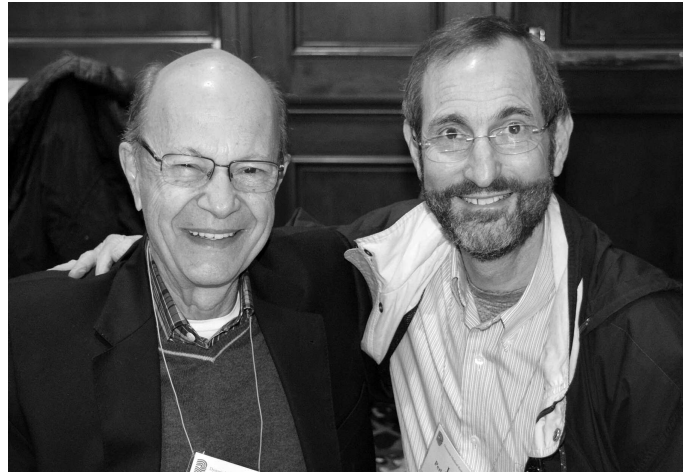
Roy Sillitoe, PhD, Baylor College of Medicine (USA)

This project uses a unique genetic mouse model of dystonia and diffusor tensor imaging, a type of magnetic resonance imaging (MRI), to define how specific brain network changes lead to dystonia symptoms. This work also seeks to better understand developmental aspects of dystonia, namely why and how dystonia progresses over time. Dr. Sillitoe and team are ultimately seeking to define the functional brain network of dystonia as a way to better target therapies such as oral medications and deep brain stimulation.

DMRF's Top Medical & Scientific Advisors Reflect on Dystonia Research Field

The annual meeting of the Medical & Scientific Advisory Council (MSAC) earlier this year in San Antonio, Texas was notable not only for the outstanding caliber of presentations and investigators who attended but also a change in MSAC leadership. Mahlon R. DeLong, MD has retired after 25 years of exceptional service to DMRF as Scientific Director. Dr. DeLong will remain involved with the DMRF as Scientific Director Emeritus and Lifetime Honorary Board Member. Joel S. Perlmutter, MD, Elliot Stein Family Professor of Neurology and Head of the Movement Disorders Program at Washington University in St. Louis, now serves as DMRF Scientific Director. Dr. Perlmutter is a long-time MSAC member and Co-Director of the Dystonia Coalition. As Scientific Director, Dr. Perlmutter will work closely with DMRF Chief Scientific Advisor Jan Teller, MA, PhD and DMRF Vice President of Science Richard Lewis, MD in planning and evaluating the Foundation's scientific efforts. He will also serve as the Chairperson of the MSAC and offer guidance to the Board of Directors on dystonia research.

DMRF was pleased to catch up with Drs. DeLong and Perlmutter for their thoughts on dystonia research and DMRF's role in the field. For video of Drs. DeLong and Perlmutter discussing dystonia research, visit: www.youtube.com/FacesofDystonia



Dr. Mahlon R. DeLong (L) is transitioning to Scientific Director Emeritus and Dr. Joel S. Perlmutter (R) is DMRF's new Scientific Director.

INTERVIEW WITH MAHLON R. DELONG, Scientific Director Emeritus

Mahlon R. DeLong, MD, is a neurologist and professor recently retired from Emory University School of Medicine in Atlanta. His research has advanced the understanding and treatment of Parkinson's disease, dystonia, tremor, and other neurological movement disorders. His pioneering discoveries contributed greatly to the resurgence of functional stereotaxic brain surgery, which has transformed the lives of thousands of patients affected by these debilitating disorders. Dr. DeLong was honored, among other awards, in 2014 with the Breakthrough Prize in Life Sciences and the Lasker-DeBakey Clinical Medical Research Award. His longtime leadership as Scientific Director at the DMRF transformed the Foundation's science program and inspired many investigators and clinicians in the dystonia field. To honor Dr. DeLong's lifetime achievements and service, the DMRF established The Mahlon DeLong Young Investigator Award.

You devoted more than 20 years to serving as Scientific Director, and will continue as Scientific Director Emeritus. What keeps you interested in dystonia?

MD: Dystonia is a most interesting and unusual disorder because of its complexity, both clinically and medically.

Historically, it took a long time to clinically characterize dystonia. Physicians were confused in part because it had so many different presentations. It was even unclear at times whether it was a neurologic or a psychiatric disorder. In children, the generalized forms were easier to recognize. What was hard to understand was how dystonia could affect children, teenagers and adults—and multiple, individual parts of the body: the voice or the eyes or the limbs, swallowing, chewing. So putting these pieces together, realizing that it's all dystonia, was a major accomplishment. David Marsden was one of the people who brought that together, realizing the focal and generalized forms belonged under the same umbrella. Also what has emerged are the multiple genotypes and complex genetics of these disorders. Then there are the cases that are not genetic but look very much the same—the secondary dystonias, as we call them. The very complexity of dystonia is a challenge and makes it particularly interesting.

“This is a more complex and richer field than I ever imagined, and one that keeps budding new flowers. We understand more and more now, and that understanding can be translated into more successful treatments.”

~ Mahlon R. DeLong, MD

Also, the patients themselves are a major factor. This is a chronic illness for most patients, often a lifelong problem, which they've adapted to and live with. Offering care and hope is one of the things you do as a physician. It's one of those disorders where your involvement as a physician is critical. There are so many things that have kept me interested. It's also all the people working in the field. A major factor has been the DMRF in bringing together the scientists, the clinician scientists, the young researchers who are entering the field, and the clinicians. The DMRF has been a point of focus for that community of physicians and researchers and trainees along with the DMRF Board of Directors, which plays a highly active role. So, the complex nature of dystonia, the progress in understanding and characterizing it, treating it, and the patients themselves and the community, in particular the DMRF—all of these are important factors.

What are you most proud of, or impressed by, regarding what DMRF's science efforts have accomplished during your time as Scientific Director?

MD: When I first contacted the DMRF, it was as a grant appli-

cant. I received research support from the DMRF and it was a very important time in my career. Later I served on the Medical & Scientific Advisory Council. They asked me to come on because I had some expertise in this emerging area of micro-electrode recording and mapping in trying to understand the functions of the basal ganglia, which play a major role in dystonia. Charlie Markham was Scientific Director before me, and I had a wonderful time and interactions with him. I was really honored to be asked to serve and also very intrigued because it was such a wonderful organization and an opportune time to be involved with so much progress being made. I think the number one breakthrough would have to be the discovery of the DYT1 gene by Laurie Ozelius and Xandra Breakefield. That discovery triggered an enormous amount of hope and expectations that we would get to the bottom of this. Of course, we now fully recognize that finding the gene is not the final answer. It's the beginning of a long, arduous process to understand the nature of the disturbance. Dozens of other genes have been discovered, and other causes, that have made it even richer in a way, but more complex.

One of the major advances relates to the work that our group did in trying to understand the circuits in the basal ganglia and their role in movement disorders. This played a role in opening up surgical approaches for treating movement disorders, particularly Parkinson's disease, but that spilled rapidly into dystonia. Surgical approaches for dystonia had been done in the 1950s and 60s, but were abandoned, and this was part of that revival and success in treating Parkinson's with surgery. In terms of the direct therapeutic advances, I think probably the most important is the deep brain stimulation (DBS) targeting the globus pallidus (GPI) for dystonia. That has brought the most remarkable benefit to patients, restoring function particularly for the DYT1 and the generalized forms of dystonia, but also for the focal and to some extent the secondary forms. Thousands of patients with dystonia have had enormous benefit from DBS and seen their lives turned around, because of the surgeries. Some more than others, certainly. The results are really quite astounding.

DMRF became a home base for dystonia research. Annual meetings brought people together nationally and internationally. We were reviewing grants, but also discussing progress and strategizing, thinking collectively in the field. The DMRF was the center of that activity, and brought together an enormous diversity of expertise.

Continued on page 10

I also want to highlight the importance of the Dystonia Coalition and the important role of the DMRF in its formation and support. Because of concern that research groups were not collaborating or interacting as effectively as possible, we thought let's try to bring together different groups under this larger organization that would have federal funding and support. It was a 'build it and they will come' approach. And, by all measures, it was a success. Buz Jinnah became Director. Joel Perlmutter played a major role in taking responsibility for one of the studies and the biorepository. The Dystonia Coalition brought together centers and research groups worldwide, particularly in Europe and Asia. And the DMRF has played a major role in the organizing.

I also want to mention the role and importance of Jan Teller. Jan has played a crucial, most remarkable role as Chief Scientific Advisor. I give him enormous credit for his keen insights and direction as well as the heavy lifting and hard work and sustaining DMRF's progress in science. It goes without saying for me, but what has made the Foundation so effective has been the staff. All of those who often work behind the scenes to make it all happen. That is an integral part of the success.

What have been some of the most important things we have learned about dystonia since you began working on the basal ganglia, especially in terms of helping to improve quality of life for patients?

MD: We've made a lot of progress at better characterizing and defining dystonia. Every five or 10 years the clinical description gets better and more complete. There's been remarkable progress in understanding and treating dystonia over the past three decades. Botox® was one of the real advances, in the late 1980s. What a godsend that was. It brought so many people out of the woods who had not been diagnosed, or treated. It was a real step forward and an important part of progress.

The basal ganglia were known to be important structures for Parkinson's and dystonia and related movement disorders, and also psychiatric and cognitive behavioral disorders. What we [Dr. DeLong's research group] did that helped the field was to provide a road map for basal ganglia, to show how they interacted with the cortex and brainstem and thalamus. We began to realize that these disorders, and particularly dystonia, was a network or circuit disorder. It wasn't a basal ganglia disorder specifically. This was a network that involved the basal ganglia and we could target the network. And the

networks were separate for motor, cognitive or executive functions, emotional and reward functions. They are laid out in brain pathways that are anatomically separate and functionally separate. So it was possible to identify those networks and target them specifically with either lesioning or stimulation. I think the work of a number of colleagues, Peter Strick and others, is showing that these networks are more complex than we even thought. This is a more complex and richer field than I ever imagined, and one that keeps budding new flowers. We understand more and more now, and that understanding can be translated into more successful treatments. And the technology for delivering stimulation and modifying brain activity is progressing so rapidly. New approaches are less invasive, more targeted, effective, and more efficient. We're turning a corner there as well. Lots of hope.

You have often praised the close relationship between the DMRF Board of Directors and the Medical & Scientific Advisory Council. Can you talk about the benefits of investigators and clinicians and patients working together to advance research and to bring greater visibility to dystonia?

MD: The DMRF is a model foundation—I've always believed that. Most people who know the Foundation appreciate the benefit of putting together researchers, basic and clinical, board members, advocates, and patients along with the research trainees and being able to interact on a regular basis and create that sense of a community. DMRF plays a vital role in patient support and awareness as well as advocacy which turned out to be a very important piece in terms of NIH [National Institutes of Health] funding and research funding from other institutions such as DOD [Department of Defense]. And it's not just the formal socializing at DMRF meetings that is meaningful. It's also the informal times people spend together after the meetings, in between the meetings, that makes it all work and why it's a great formula. It's the people that make the Foundation and the community what it is. It is impossible to give recognition to all the individual staff who are part of the DMRF, but it is no secret that it is Janet Hieshetter, the Executive Director, who is the public face, engine, and coordinator of all things of the DMRF. I would require a separate page, not a paragraph, to do any justice to this.

Any kind words for Joel Perlmutter as DMRF's new Scientific Director?

MD: Joel has also played an enormous role in the DMRF. I'm so pleased that he accepted the challenge. Joel has been one of the pillars of DMRF and, like me, came in through

grant support and served many rotations on the MSAC. He took on a major component of the Dystonia Coalition. He himself has made enormous research contributions. I'm so delighted Joel has accepted that position, and know he will do a great job.

INTERVIEW WITH JOEL S. PERLMUTTER, Scientific Director

Joel S. Perlmutter, MD is the Elliot Stein Family Professor of Neurology, Professor of Radiology, Neuroscience, Occupational Therapy and Physical Therapy. He is Head of Movement Disorders at Washington University and the NeuroClinical Research Unit. His research interests include development of biomarkers for Parkinson disease, investigations of pathophysiology of Parkinson disease and dystonia, investigations of dementia in Parkinson disease, studies of deep brain stimulation and development of new neuroimaging methods. His research spans animal models and patient-oriented research. He is Co-Director of the Dystonia Coalition, a collaboration of medical researchers and patient advocacy groups working to advance the pace of clinical and translational research in the dystonias to find better treatments. He has been a longtime advisor to the DMRF, serving intermittently on the Medical & Scientific Advisory Council (MSAC) for over 20 years, and an active partner in DMRF patient educational programs and awareness efforts.

What do we understand about dystonia now compared to when you met your first dystonia patient?

JP: I saw my first dystonia patient more than 40 years ago, and the differences are incredible. First of all, we know a lot more about the manifestations of dystonia, how it appears, what is dystonia, what's not dystonia. I remember when a person with cervical dystonia came into the hospital while I was a junior resident and the person had pain in his neck. And so the attending 'expert' physician said, that's not dystonia because it hurts. Well, that was wrong. We understand much more about what's going on in the brain. We understand much more about treatment. I remember early on treating people with neck dystonia or blepharospasm. I would say 15% of people would get modest benefit with substantial side effects from medicines by mouth and now in cervical dystonia, 90% of people get substantial benefit with minimal side effects with botulinum toxin.

Finding genetic causes of certain types of dystonia is very helpful. Even though the genetic causes that we know about so far are relatively rare, each of those genetic causes gives

us an opportunity to find out in the brain what that genetic abnormality does, what biochemical pathway it affects, and then to determine what additional genetic abnormalities do and where these different pathways intersect, because that may be important for everybody with dystonia, whether they have the genetic defect or not. The secondary causes of dystonia are also very important for trying to understand the pathophysiology. If we look at different kinds of secondary causes and see what's in common in the brain pathophysiology, that intersection is exactly the same way that genetic etiologies can be informative.

Is there a specific unresolved question about dystonia that you would especially like to see answered, that could dramatically accelerate improved treatments and/or a cure?

JP: It's probably just not one single thing for all forms of dystonia. Now, there may be common mechanisms, whether dystonia affects the face or the hand, and that could be a critical discovery if we can figure out that common mechanism. So, if we could find the precise dysfunction in brain pathways that lead to dystonia that could be terrific, but my guess is there's not just one spot. But it could be one spot as part of a network of brain regions that are working together, and dysfunction at any point in the network could lead to dystonia.

The latest big controversy is whether dystonia arises from dysfunction in networks involving striatal-basal ganglia region or from dysfunction in the cerebellum? I'm not so sure these notions are mutually exclusive, because basal ganglia and cerebellum are functionally connected. They work together for many functions including movement and probably learning as well. And so the culprit is not necessarily just one brain area versus another. These different regions may contribute to common brain networks, and dysfunction of these networks could produce the same outward manifestations of dystonia, no matter which specific brain region instigates the network dysfunction. Mahlon DeLong really stuck me with this deep interest in dystonia. He infected me with his enthusiasm. I was on the Scientific Advisory Board [now MSAC] for the Dystonia Medical Research Foundation back in the 1980s, and we would have meetings at Emory. I recall giving a talk about basal ganglia dysfunction that could lead to dystonia and Mahlon would say wait a second, he would run to his lab and get a slide to show how he disagreed with my points. We would have back and forth discussions about key issues. These types of interactions are and remain very important

Continued on page 12

as they stimulate critical thinking for complex issues such as which regions of brain and which networks are critical. That is how research and discovery move forward.

Which brings me to Mahlon DeLong. I'm going to blame him for why I'm where I am now. He's kept me interested in dystonia over the many years that we've known each other. For example, he pushed me into my role in the Dystonia Coalition. I remember when the idea first developed with the DMRF and Mahlon. I think we were on a bench in an airport somewhere with several people around trying to decide whether we should apply for one of these rare disease consortia [under National Institutes of Health]. Buz Jinnah was there and I said, Buz, this is a great opportunity. Mahlon was there and he said, Joel, you need to be involved as well. The bottom line is that Buz took it forward and did a fabulous job with it. But Mahlon was a primary instigator. The mentorship that he's provided to people throughout the world and to the Foundation, the direction and guidance have been incredible. He's a wonderful, kind-hearted man who's extremely bright and has such a good big picture view. He has always been helpful to everybody he meets. It's a pleasure to have been working with him for these many years and also a bit daunting to try to take over as Scientific Director. It's a good thing he's staying around so that I can continue to lean on his shoulders.

What role does DMRF have in continuing to stimulate research progress?

JP: The DMRF is responsible for almost all the dystonia research that's done today, and I don't say that lightly. The reason I say that is they've had several roles. Role one is advocacy and I'll give a quick example. Back in the 1980s, I wrote an RO1 research grant application to NIH [National Institutes of Health] about neuroimaging of dystonia. It was reviewed and it was thought to be scientifically outstanding yet it received almost the worst percentile rating possible because the main and only criticism was that dystonia is not an important disease. That was the entire criticism. Then the DMRF began advocating at NIH. I resubmitted that grant and, all of a sudden, I was funded. But let's go back a few steps. I would have never submitted an RO1 if I had not attended the second DMRF scientific symposium. Before that meeting, as a resident I had seen people with dystonia and I had written a neuroimaging paper about dystonia that was published, but I was pretty much in isolation. I had spent some time with David Marsden, which was absolutely

fabulous, but I didn't know a lot of people beyond that group who did research in this area. And when we had that symposium supported by the DMRF, it was incredible. It brought people together, and we all wanted to understand dystonia better and treat people with this condition to make sure they were diagnosed properly. Not only that, there were people from the DMRF Board of Directors at the symposium. It was an eye-opening experience, really inspirational and invigorating.

So, the DMRF has brought together investigators, patient advocacy groups, and people with dystonia, which is incredibly important. It's provided the support for collecting preliminary data that's led to multiple researchers obtaining federally funded grants. It has provided the initial support to help train people, to start them as clinician-scientists studying dystonia. One of my junior colleagues, Dr. Scott Norris, started with a clinical DMRF fellowship and he is absolutely stuck on doing dystonia research and providing care to people with dystonia. That's his baby because of that first grant. DMRF also brings together research groups to collaborate and share data with other people who make new discoveries. The Dystonia Coalition is an example of that, where patient advocacy groups have come together, primarily with the leadership of the DMRF. It's brought together recruiting sites and collaborative sites. It has brought us together to collect and share data. There have been over a 100 publications from those data—new understanding and improved dissemination of information, including new genetic discoveries. In addition to research, we have trained many new clinicians and scientists, all now doing dystonia research because of these efforts. DMRF provides an incredible engine to jumpstart research and promote training and promote collaboration. DMRF support has provided seed grants to support collection of preliminary data that subsequently makes larger NIH grant applications viable. Yet, the most important thing I do this year isn't a new discovery, it's to train a new person who can continue to make additional discoveries. Each discovery is important but each discovery will be superseded by new discoveries in the future. But training new investigators produces wide ranging effects, like ripples in a pond. If you throw a seed grant in there and you get one person working on dystonia, then they train other people to do more projects and to help more people and to treat more people. Research and patient care are tied together very closely.

What keeps you dedicated to dystonia?

JP: Dystonia is mysterious. And yet I can listen to a person's story and hear what their family and significant others tell me. Then I can examine that person and determine the type of movement disorder that they have or what specific type of dystonia. The next challenge is to determine what occurs in the brain that causes the dystonia. Then we try to intervene to alleviate the symptoms and hopefully at some point cure the problem. Over the years, I have seen tremendous progress in each of these steps. When I was starting out, somebody with generalized dystonia—what we call now TORIA or DYT1—most of them would have substantial problems, and the best treatment we had for them was high dose anticholinergics which helps some but with lots of potential side effects. Now we see these people walking around doing great with deep brain stimulation. It's amazing, and we have Mahlon DeLong to thank for much of that progress. Or some of these people turned out to have dopa-responsive dystonia—just give them a little levodopa and they do much better. Not only is dystonia intellectually challenging and interesting, but we can really make a difference for people. We have come a long way, yet, we still need to do much better.

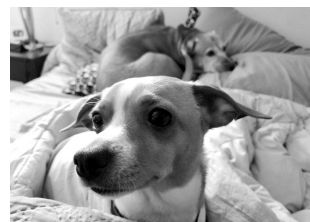
What is important for dystonia patients and family members to understand about what's happening in dystonia research and the work of the DMRF?

JP: The first thing, the most important, is there are investigators around the world interested in dystonia and working hard for you. And the reason there are so many people working hard for you is the DMRF helped seed their labs, helped seed their new ideas, so they can grow and train new people. We're all in this together. What I would caution against is expecting one thing that's going to solve the whole problem. It's not just neuroimaging. It's not just genetics. Not just one grand slam, but a lot of singles and doubles that produce runs.

The DMRF isn't "The DMRF"—it's all the people: the Belzbergs who started the organization, the Kesslers [Board Members], John Menkes [DMRF's first Scientific Director], the staff, everyone right from the beginning. It's been an incredible organization of patients and families, and now we have a President of the DMRF, Art Kessler, who is benefiting tremendously by the research that's been supported by the DMRF. We're all committed and we're working together, and that's a pleasure. That's what makes this organization very special.

Good Dog!

Dogs for Dystonia Raise Awareness & Research Funds



Dogs for Dystonia is an annual campaign to raise awareness while celebrating the special bond between people and their dogs. Each February, dog lovers unite in a Virtual Dog Walk to raise visibility of dystonia and the urgent need for research toward a cure.

In 2019, the following dogs and owners raised more than \$500!

- Ginny Bryan & Snoopy
- Melissa Greenberg & Petey
- Laura Herbert & Gigi & Lola
- Joanna Manusov & Nicki & Princess
- Janet Hieshetter & Coolidge & McKinley

The DMRF wishes to thank all the generous dogs and people who participated in this important and fun campaign.

Advocates Gather on Capitol Hill to Push for Increased Research Funding and Patient Protections in Healthcare

The Dystonia Advocacy Network (DAN) hosted Advocacy Day, March 26–27, 2019, in Washington, DC to speak out on behalf of individuals with dystonia and encourage Members of Congress to support the DAN's legislative priorities. More than 90 advocates from across the country gathered on Capitol Hill for legislative training and meetings in Congressional offices.



(L-R) Jeff Shair, Amy Yurchision, and Raman Patel were among the advocates from Pennsylvania.

The DAN is a coalition of patient organizations focused on issues relevant to the dystonia community. These issues are anchored in advocating for support of federal research funding and for accessible, affordable treatment.

The DAN's victories include increased funding for the National Institutes of Health, new dystonia funding



Dystonia Advocacy Network

DMRF is proud to provide staff support for the DAN.
Member organizations include:

Benign Essential Blepharospasm
Research Foundation (BEBRF)

Dystonia Medical Research
Foundation (DMRF)

National Spasmodic
Dysphonia Association (NSDA)

National Spasmodic
Torticollis Association (NSTA)



(L-R) Melissa Alvarado, Sam Ashkenas, Serina Griffin, Amy Yurchision, and Haseeb Khawaja were recognized with Douglas Kramer Young Advocate Awards.

released through the Department of Defense, the first-ever Congressional Briefing on Dystonia, protecting access to deep brain stimulation and botulinum neurotoxin therapies, and safeguards for new biologic therapies.

The DMRF was proud to welcome this year's Douglas Kramer Young Advocate Award recipients to Advocacy Day: Melissa Alvarado of Florida, Sam Ashkenas of Virginia, Haseeb Khawaja of Texas, Serina Griffin of Oregon, and Amy Yurchision of Pennsylvania. The DMRF will work with these outstanding advocates on legislative and policy matters throughout the year. The annual Douglas Kramer Young Advocate Award recognizes exceptional volunteers who are giving voice to dystonia through advocacy. The award was created by the late Florence Kramer in memory of her son Douglas.

“The initial orientation on the first day in DC actually brought me to tears because for the first time I was in a room with people who understood what I was going through. The chance to tell legislators my personal story, and for my husband to be able to share his side of what dystonia is, to bring awareness and request funding for research, was an honor. All of the attendees and the DMRF team were very kind and welcoming. This experience helped me with my path to acceptance, and my drive to fight!”

~ Melissa Alvarado, Douglas Kramer Young Advocate Awardee

“I loved participating in Dystonia Advocacy Day,” said Kramer Award recipient Serina Griffin, who attended for the first time.



Senator Todd C. Young (center) met with advocates Darrick and Sunshine Fox.

becoming a dystonia advocate, visit www.dystonia-advocacy.org/contact

“It was a great privilege to see our elected officials at work, to engage with them, and to promote awareness about such an important issue alongside such a wonderful group of advocates and new friends.” Serina has lived with dystonia for 13 years and recently underwent successful deep brain stimulation surgery.

For information about joining the DAN and

Clinical Fellowships Train Young Movement Disorder Specialists

Evaluation by a movement disorder specialist can have a dramatic impact on quickening dystonia diagnosis time, increasing treatment options, and maximizing benefit from treatment. Many individuals with dystonia must travel significant distance and endure long waits for appointment openings to access a physician with the necessary qualifications to diagnose and treat dystonia. In response to the urgent need for additional clinical experts, the DMRF sponsors one-year clinical fellowships to train second-year fellow physicians in the diagnosis and treatment of movement disorders with special competence in dystonia. The fellowships focus on training in both the clinical evaluation and care of patients with dystonia and clinical research. The training is patient-oriented and includes hands-on experience in clinics as well as participation in professional meetings and workshops.

Congratulations to our 2019 DMRF Clinical Fellow and mentor:

Abhimanyu Mahajan, MD, MHS

University of Cincinnati

Mentor: Alberto J. Espay, MD, MSc

Research Project: “Cerebellar Degeneration in Tremor-Dominant Cervical Dystonia: Clinical and Neuroimaging Cohort Study”

Past DMRF clinical fellows have earned positions in movement disorder programs at prestigious institutions and are filling gaps in communities previously without movement disorder experts. Clinical fellows remain engaged with the DMRF as reviewers for educational materials, speakers at support group meetings, participants at dystonia awareness events, and medical experts for news stories about dystonia.

The Clinical Fellowship Training Program is made possible by grants from Merz Pharmaceuticals and The Allergan Foundation.

People on the Move

The DMRF is grateful for the grassroots volunteers across the country working to improve dystonia awareness in their communities. Every volunteer makes a difference!



Jonathan Boone of House Plan Zone has partnered with DMRF Board Member **Jon Davis** of Architectural Designs to raise funds for the DMRF. House Plan Zone created a modern farmhouse design plan that is available for purchase through both companies and 100% of proceeds go to the DMRF. Visit Architectural Designs to check out or purchase the plan at <https://bit.ly/2Xcb4zG>

Eric Slaasted created a fundraiser in memory of **Nini Del Rosario**, who lived with dystonia symptoms for years before being properly diagnosed. Learn more about Nini and this year-long campaign at: <https://dystonia-foundation.org/friends/ndr-fund/>



Jirome De Castro traveled 7,000+ miles from his home in the Philippines to compete in the Orange County Marathon in California to support DMRF and raise awareness. He will be back in the USA to run the Chicago Marathon in October. Donations in support of his campaign can be made at <https://www.dystonia-foundation.org/jirome-de-castro>

Gill Hall Elementary School in Pennsylvania hosted a fundraiser in honor of student **Braden Sorley**, raising \$2,100 in support of the DMRF. Braden's parents, **Tara and Chris Sorley**, lead "Braden's Brigade," a team at the annual Pittsburgh Dystonia Zoo Walk.

Jeff Dyer is embarking on a multi-year mission to ride every mile of Michigan's Rail to Trail system to raise awareness and money for research towards a cure for dystonia. Follow his Facebook page "Triking to Defeat Dystonia" for updates. He is collecting donations to support \$5Cure4Dystonia (<https://5dollar cure.com/>), a campaign started by **Mike Delise** and **Jason Dunn** to support urgently-needed dystonia research.

\$5Cure4Dystonia started a Facebook group dedicated to raising funds for dystonia research toward a cure. Campaign creator and group admin **Mike Delise** is inviting members of the dystonia community to join the group as a pledge to donate \$5 to the campaign during Dystonia Awareness Month in September. Find the group by logging into Facebook and searching "5Cure4Dystonia." Donations can be made at <https://5dollarcure.com/>.

Co-Leader of the Minnesota Dystonia Support Group **Brad Schmitt** was invited by University of Minnesota postdoctoral researcher **Rebekah Summers, PT, DPT** to speak to a group of future physical therapists about dystonia and promote the Twin Cities Dystonia Zoo Walk.

To celebrate legendary Seattle blues musician **Little Bill Engelhart's** 80th birthday, fellow musician **Randy Oxford** organized an all-star show in March. Bill Engelhart's son **Anthony Starr** is diagnosed with dystonia. Randy and friends previously produced a tribute concert for Little Bill to benefit DMRF on his 70th and 75th birthdays.



Congratulations and thanks to event organizer **Mandi Sleeper** and her 100+ supporters who participated in the Nashua Dystonia4Dystonia Walk in New Hampshire on May 5 to support the DMRF. The event was covered by local news media, bringing much-needed awareness to the community. The event raised \$5,000.



Shanna and Brad Schmitt, Billy McLaughlin, and members of the **Minnesota Dystonia Support Group** organized the 4th Twin Cities Dystonia Zoo Walk on June 22.

The **6th Annual Detroit Dystonia Zoo Walk** took place July 14. The event was organized by DMRF Community Leadership Council Member **Rosemary Young** in honor of her son **Kavin**, who has dystonia.

The **4th Portland Dystonia Zoo Walk** was organized by Dee Linde and members of the Portland, Oregon & Southwest Washington Dystonia Support Group. The event took place July 20.

Facebook Fundraisers Matched in 2019



Thanks to a very generous anonymous donor, all donations

raised for DMRF through Facebook fundraisers are eligible to be matched dollar for dollar throughout 2019. This generous challenge will help us continue to collect support for dystonia research towards a cure. If you or a family member are raising donations for DMRF via Facebook, you must notify us by emailing events@dystonia-foundation.org or inviting us to participate in your fundraiser to qualify for the match. Facebook does not notify DMRF of these fundraisers, and we wish to acknowledge the generosity of all our supporters. For more information, please email events@dystonia-foundation.org. Thank you to our Facebook friends for participating in this exciting challenge.

Longtime Letter-Writing Campaign Honors Granddaughter



"I didn't know what dystonia was when Maddie was diagnosed," explains Kay Cooksey of Florida, whose granddaughter Maddie Paolero was diagnosed with generalized dystonia in kindergarten, about 20 years ago. "Everything I know about dystonia I learned from DMRF and Maddie." Maddie resides in Rhode Island with parents Beth and Tony.

Kay and her late husband James started an annual letter-writing campaign to support DMRF in Maddie's honor. "I knew friends and family would want to help. It was easy to continue each year because friends wanted to know how Maddie was doing." Even in today's digital age of email and social media, Kay's personalized letters continue to be successful. She has raised nearly \$40,000. "I appreciate every dollar given to fight dystonia."

Kay's full name is Madaline Kay Cooksey. Granddaughter Maddie is her namesake. Recently the two women discovered something else they have in common. Kay was diagnosed with cervical and cranial dystonia in 2015.

"Dystonia has impacted our whole family. Maddie is so brave, and Tony and Beth are so supportive every day. You do not know unless you live with a chronic illness how it effects everything! Maddie recently graduated from Rhode Island Community College. It has been a long, hard drag of bus rides, special tests, homework, professors who don't understand, special equipment, hours and hours of study. Everything was complicated by not being able to walk or talk or write."

The extended Cooksey/Paolero family generously supports DMRF's mission to find a cure. Maddie and her parents are frequent presenters at DMRF events, have attended multiple Dystonia Advocacy Days on Capitol Hill, and lead a team at the annual Providence Dystonia Zoo Walk. Beth is also on the Zoo Walk organizing committee. In 2018 Maddie and Beth presented U.S. Senator Jack Reed with a distinguished service award on behalf of the Dystonia Advocacy Network. Maddie's brother A.J. and uncle Jimmie Cooksey are also dedicated DMRF supporters.

"If you want to help with fundraising, jump in wherever you're comfortable," says Kay. "I think with everyone pulling together, we will find a cure to help Maddie and her fellow sufferers in her lifetime."

There are many ways to support DMRF. Visit <https://dystonia-foundation.org> or call 800-377-3978 to find out what option is best for you.

30 Years Later Botulinum Neurotoxin Remains Unique Dystonia Therapy

Botox® became a household name in the dystonia community long before its use to correct wrinkles made it famous to the rest of the world.

As of 2019, botulinum neurotoxin has been available for commercial use in the USA for three decades. “It’s remarkable that there’s a drug on the market for 30 years and we’re still developing it for new indications. I am not sure there are any other drugs out there like that, where the potential benefits of the drug haven’t been totally explored,” says Mitchell Brin, MD, Senior Vice President of Global Drug Development & Chief Scientific Officer for Botox® & Neurotoxins at Allergan.

In the mid-1980s, Dr. Brin was a Movement Disorders Fellow training with Stanley Fahn, MD at Columbia University. The Neurological Institute had received funding from the Dystonia Medical Research Foundation (DMRF) to explore the cause of dystonia and identify effective treatments. As Program Coordinator for the Institute’s Dystonia Clinical Research Center, Dr. Brin began treating dystonia patients using a research preparation of botulinum neurotoxin developed by ophthalmologist Alan Scott, MD under the purview of the grant.

“One memorable patient was our first patient,” recalls Dr. Brin. “This patient had blepharospasm and was functionally blind because of the severity of her eye closure. She was unable to navigate as she walked. After treatment she was more functional and could do house work and all the activities she previously

ARTICLE AT A GLANCE

- Botulinum neurotoxin injections have been FDA-approved since 1989.
- Botulinum neurotoxin is a unique therapy with advantages over oral drugs.
- Researchers and pharma companies continue to improve upon this therapy.

could not accomplish.” She reported back to her doctors that she had walked from 168th Street all the way down to the bottom of Manhattan, a distance of about 10 miles. “And when asked why she took that long walk, she reported ‘because now I can!’...because she could see.”

...

In 1989, therapeutic botulinum neurotoxin type A, under the brand name Oculinum®, received marketing approval by the US Food & Drug Administration (FDA) for the treatment of strabismus (“crossed eyes”) and blepharospasm (focal dystonia of the eyelids). Allergan acquired Oculinum® and changed the product’s name to Botox® (onabotulinumtoxinA). Botox® was additionally FDA-approved for cervical dystonia in 2000 and is used off-label in the treatment of other focal dystonias.

Ben Beach was an accomplished runner for more than 30 years when he devel-

oped focal leg dystonia. It caused his left hamstring to contract when it should have been extending for a stride, and his left foot often struck his right ankle, causing pain. After four years seeking an accurate diagnosis of his problem, he began quarterly off-label botulinum neurotoxin injections into his hamstring muscles at the National Institutes of Health (NIH). “The Botox® has made a big difference for me,” he says. “Of course, my gait is still awkward, and my pace is much slower. When dystonia entered my life, I thought my running days were over, but 17 years later I’m very grateful that I’m still on the roads.” In April, Ben completed his 52nd consecutive Boston Marathon, breaking his own world record.

“There are certain drugs or therapies that the increment in benefit is minor and so it may take a long time for it to really get into clinical use, but if you have a major benefit like botulinum toxin has, everybody wanted it right away,” recalls Mark Hallett, MD, Senior Investigator in the Human Motor Control Section at the National Institute of Neurological Disorders & Stroke at NIH. Dr. Hallett’s group was among the first to use botulinum neurotoxin for the treatment of focal hand dystonia.

...

Numerous studies have demonstrated that botulinum neurotoxin is the primary therapy for reducing focal dystonia symptoms. Botulinum neurotoxin is

Botulinum Neurotoxin Products Available in USA:

Brand Name	Medical Name	Manufacturer	Initial FDA Approval
Botox®	OnabotulinumtoxinA	Allergan	1989
Dysport®	AbobotulinumtoxinA	Ipsen	2009
Myobloc®	RimabotulinumtoxinB	US WorldMeds	2000
Xeomin®	IncobotulinumtoxinA	Merz Pharmaceuticals	2010

injected directly into muscle, where it blocks signals from the nerves that make the muscle contract. When the signals are blocked, dystonic muscle contractions are reduced and the muscle relaxes. The effects are temporary and injections are repeated every three to six months. Side effects can include temporary muscle weakness, flu-like symptoms, pain or bruising at the injection site, dry mouth, and additional side effects depending on the area of the body treated. The FDA requires a black box label on botulinum neurotoxin products warning of a rare but potentially life-threatening complication when the effects of the neurotoxin spread far beyond the injection site.

The qualities that made botulinum neurotoxin a unique therapy when it first became available continue to make it stand out as a primary therapy for many individuals with dystonia. For one, it is not a man-made, chemical drug, but a purified biological product derived from live bacteria.

"It was unique because we were able to treat the symptoms directly," explains Dr. Brin, "and you could start at a low dose and gradually increase the dose. If a patient had a strong reaction to a dose and the goal was less muscle relaxation, then the effect wore off and you could re-adjust for the next treatment and change your treatment paradigm over time." Because it is a local therapy, botulinum neurotoxin does not cause the systemic side effects—for example,

drowsiness or memory problems—that can occur with oral medications.

Botulinum neurotoxin injections are a highly skilled therapy that must be customized to the needs of each patient. Physicians must assess what dose is appropriate, what muscles to inject, where in the muscle to inject, and how to access the appropriate target within the muscle. It requires expert understanding of anatomy in some of the most complex parts of the body: neck, voice box, face, hand. Physicians must be attuned to their patients' expectations, lifestyle, and response to treatment over time.

Linda Davis of New York began receiving botulinum toxin neurotoxin injections every three months in 2010, shortly after being diagnosed with cervical dystonia. It took about a year to fine-tune the appropriate dosing and injection sites for her specific needs. "Keep in mind, that is only four treatments," she notes. "While it is most definitely not a cure, along with my meds, I'm able to continue living my life as close to 'normal' as you can get."

Linda's symptoms have changed over the years and her physician has adjusted the therapy accordingly. "While it is not the most pleasant experience getting the injections, it is something I look forward to. I know it will help alleviate the pulling and the tremors. It is something I cannot go without."

"The patients teach you a lot, and from that perspective, it is a partnership," says Dr. Brin. "If you listen to the patient carefully they help you better understand their symptoms and, particularly for complex conditions like cervical dystonia, how to develop a treatment program."

• • •

While the utility of botulinum neurotoxin to reduce the excessive muscle spasms associated with dystonia became apparent rather quickly, over time clinicians discovered there were additional unexpected benefits.

"In the beginning there was the relatively simple-minded view that the benefit was entirely because of weakening of the muscle spasm," explains Dr. Hallett. "But it became clear relatively early that there were secondary effects in addition to the muscle weakness that were important also. For example, a certain amount of the benefit comes from weakening of the motor fibers that go to the muscle spindles in the muscle, which changes the sensory information from the muscle and that influences the motor system in a positive way." Botulinum neurotoxin influences motor pathways in the brain, even though it does not treat the brain.

"The other thing that was somewhat of a surprise in the beginning," said Dr. Hallett, "particularly in cervical dystonia, is that pain was benefited even if the muscle spasm wasn't

Continued on page 20

benefited so much, and eventually that led to the understanding that botulinum toxin has a role in pain relief as well as in muscle relief. So that has led to it being a lot more useful than people originally thought it might be.”

Four botulinum neurotoxin products are marketed in the USA by four manufacturers. Each neurotoxin has unique biological qualities, which means they are not interchangeable. Chronic migraine, chronic pain, spasticity, and overactive bladder are just a few of the medical conditions treated with specific botulinum neurotoxin products. Research is underway for use in wound healing and depression. A qualified physician can recommend what product may be appropriate for a given patient.

• • •

Investigators and pharmaceutical companies continue to work on making botulinum neurotoxin therapy more effective, including for those individuals who currently do not respond well to this treatment. “In my role both in academia and in my role at the pharmaceutical company,” says Dr. Brin, “the focus is how to make a drug available to patients to improve their lives, and that’s not just a tagline. In R&D [research and development] at Allergan, there’s a total focus on examining an effective dose, understanding safety, the benefit/risk profile, and developing a treatment paradigm that will translate into benefits for patients.”

“This is the type of treatment that is going to be around for a long time,” assures Dr. Hallett.

For more information about botulinum neurotoxin therapy for dystonia, visit: <https://dystonia-foundation.org/living-dystonia/botulinum-toxin-injections/>

Ongoing Research in Botulinum Neurotoxin Therapy

- **New botulinum neurotoxins.** New toxins and types of toxin are in the development pipeline.
- **Perfecting injection technique.** Clinicians continue to refine the science of customizing muscle selection and dosing for each patient.
- **Decreasing injection pain.** This includes experimenting with how the botulinum neurotoxin solution is reconstituted to adjust the pH and lessen discomfort in the muscle.
- **Appreciating the role of mental health.** Untreated depression may sabotage quality of life even in individuals who have positive results from botulinum neurotoxin therapy. Individuals experiencing depression may require supportive mental health therapy to feel and function better.
- **Cost savings.** Most botulinum neurotoxin products are stored as powders. After reconstitution with saline, the shelf life is reduced from years to hours. The ability to safely store reconstituted botulinum neurotoxin solution could reduce cost by minimizing waste.
- **Muscle targeting.** Electromyography (EMG) and ultrasound guided injections assist the physician in targeting the intended muscle and improve accuracy.
- **Flexible treatment schedules.** Injections are typically repeated on a strict schedule of 12-16 weeks. Researchers are carefully exploring injecting select patients more frequently.
- **Higher dosing.** Researchers are carefully exploring using botulinum neurotoxin at a higher total-body dose, to treat more widespread and severe symptoms.
- **Listening to people.** In a survey of individuals with cervical dystonia, the top suggestions to improve satisfaction with botulinum neurotoxin therapy included:
 - Better administration of medical appointments
 - Shorter waiting times
 - More time with the doctor
 - Fewer changes among medical staff
 - More written information about dystonia, treatment options, and living with dystonia

How Can a ‘Toxin’ be a Medical Treatment?

Botulinum neurotoxin is a biological substance derived from *Clostridium botulinum*, the bacteria responsible for causing botulism (food poisoning). Complex purification manufacturing processes transform botulinum neurotoxin into a therapeutic agent. The doses used to treat dystonia are far less than the amount that would typically be expected to make a person feel sick from botulism. Botulinum neurotoxin injections have decades of research and clinical experience demonstrating that they are a safe and effective therapy when used according to recommendations. This is a highly specialized therapy that should be administered only by expertly trained physicians.

Eyes on Me

Dystonia & Social Anxiety

Moments of social awkwardness are a common human experience. We may feel anxious or uncomfortable when meeting new people, public speaking, or in other situations where we are the focus of attention. For some of us, the anxiety becomes severe and permeates social interactions of any and all kinds.

“Some people have social anxiety disorder, or social phobia, which is an intense fear of being judged or negatively evaluated in social situations,” explains Bryan Bernard, PhD, a neuropsychologist with expertise in movement disorders at Rush University Medical Center. “The individual is concerned that they will say or do something that will result in embarrassment or humiliation.” This fear can affect work, school, relationships, and daily life. “People with social anxiety disorder tend to avoid social situations, and when the situation cannot be avoided, they experience significant physiological symptoms of anxiety such as increased heart rate, nausea, or hyperventilation.”

Estimates suggest 7% of the general population has social anxiety disorder. For individuals with dystonia, the percentage may be as much as 10 times higher. “Of the non-motor symptoms that we see in dystonia,” says movement disorder specialist Brian Berman, MD, MS of University of Colorado Movement Disorder Center, “the psychiatric disorders are of specific interest because of how common they are and because of how often they can be disabling, even more disabling than the motor symptoms, and have a greater impact on quality of life.”

Untangling Dystonia & Anxiety

Researchers are working to understand the complex relationship between dystonia and anxiety.

“Some studies support the premise that the dystonia leads to increased anxiety and social anxiety, but then there are equally other studies that provide evidence that these disorders can occur before someone has the motor symptoms of dystonia, suggesting that it’s part of a clinical spectrum rather than just a reaction to the motor symptoms,” explains Dr. Berman.



Social anxiety often begins in childhood or adolescence. Social anxiety disorder is sometimes confused with shyness, which is a tendency to feel awkward or tense during social encounters but does not necessarily include the fear of scrutiny or embarrassment that is a hallmark of social anxiety disorder.

Donna Russow, LCSW, ACSW is a Certified Life Coach and Licensed Therapist. She was diagnosed with cervical dystonia in 2009. “A lot of people with dystonia do have a physical difference and that itself can make you feel embarrassed or make you wonder what somebody’s going to think about you,” she explains.

The physical symptoms of dystonia can alter posture, body language, facial expressions, eye contact, and voice quality—all of which are at play when interacting with other people. Furthermore, dystonia symptoms are known to worsen in social situations and can be exacerbated by stress, which heighten the physical and emotional discomfort of social interactions.

Ms. Russow elaborates: “The other thing is, when we have dystonia, you might be home alone a lot, you’re unable to work or do a lot of the things you used to do that could provide the normal social interaction most people take for granted.

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So the isolation is greatly increased. And, because people do feel different, they begin intentionally to avoid situations where they may feel embarrassed or humiliated because of the disorder.”

Who is Most at Risk?

It might be natural to assume that individuals with the most severe dystonia symptoms are more prone to social anxiety, but this does not necessarily seem to be the case. “Patients with dystonia and social anxiety disorder may have feelings of low self-esteem and disturbed body image,” explains Dr. Bernard.

In a study comparing rates of social anxiety among adults with cervical dystonia, essential tremor, and hemifacial spasm, the frequency of social anxiety disorder and impact on quality of life were similar across these disorders. The patients who experienced the most severe social anxiety tended to be younger and had co-occurring depression. The severity of social anxiety correlated to the patient’s perception of physical disfigurement and negative body image. It was not the individuals who had the most severe movement symptoms, or who had lived with a movement disorder the longest, who were prone to social anxiety disorder. Individuals who were depressed and self-critical about the physical appearance of the motor symptoms had the most severe social anxiety.

Similarly, in a large study of cervical dystonia patients, a high prevalence of social anxiety disorder was associated with depression rooted in negative body image. The prevalence of social anxiety disorder was more than 50%, and in most cases (80%) the individuals reported that onset followed the cervical dystonia.

Dr. Berman led a large international study of adults with focal dystonia which revealed that high levels of depression, anxiety, and social anxiety occurred across all types of focal dystonia. However, the severity of anxiety and social anxiety varied by the type of dystonia and body parts affected.

Common Social Anxiety Triggers

- Meeting new people
- Going somewhere new
- Speaking on the phone
- Eating or drinking in front of other people
- Speaking to a group of people
- Talking to strangers
- Dating
- Job interviews
- Going to work, school, or appointments
- Making eye contact
- Using public restrooms

“We found that 45% overall of the adult onset focal dystonia patients—those with blepharospasm, cervical dystonia, cranial dystonia, laryngeal dystonia, limb dystonia—had clinically significant social anxiety, but then we also found that the rates vary quite a bit. It ranged from 32% in those with limb dystonia up to 73% of those with laryngeal dystonia, so there may be a wide variation in social anxiety symptoms amongst those with different focal expressions of dystonia.” Dr. Berman and his team found that, “at least in laryngeal dystonia, there was a strong link between the motor symptoms and the severity of social anxiety, but in the other forms of dystonia it was less evident that there was that relationship.” The study did not conclude why higher rates of social anxiety were seen in individuals with laryngeal dystonia but suggested it could be related to the

unique role speaking plays in social interaction. Laryngeal dystonia, also referred to as spasmodic dysphonia, is a focal dystonia that affects the voice box and impairs speech.

Seeking Help

Social anxiety becomes a problem when it happens frequently, intensely, and to the extent that individuals have difficulty functioning in their lives. Relationships may be strained. “Anxiety can affect quality of life by limiting social interactions, which are generally positive, and thereby limit the potential emotional support we can receive from other people,” explains Dr. Bernard. Job performance or career trajectory may be suffering. “Social anxiety can lead people to avoid possible promotions at work or going on job interviews or turning down opportunities they know otherwise could benefit them,” says Ms. Russow.

Social anxiety generally does not go away without treatment. Evaluating for and addressing anxiety is an essential part of a comprehensive dystonia treatment plan. “Even if you find that you’re making progress on the motor symptoms, there could be persistent psychiatric disorders that are impairing quality of life,” explains Dr. Berman.

45% of adults with focal dystonia may experience significant social anxiety

There is a growing wealth of evidence that social connection is vital to good physical and mental health. “We are healed through social connection,” says Ms. Russow. “In healthy social interactions, we learn to trust, we discover parts of ourselves that we didn’t know about. When we’re not able to be in social connection, or we choose not to be, because of social anxiety, it can be damaging. But the good news is there is hope and ways to deal with that.”

Cognitive behavioral therapy (CBT) provided by a certified professional is typically the most effective type of psychotherapy for social anxiety disorder. CBT may be used in combination with oral medications, depending on the needs of the individual. Relaxation techniques, such as meditation and deep-breathing exercises, can reduce the physiological symptoms of anxiety. In most cases, treatment can dramatically reduce or eliminate social anxiety disorder symptoms, and the benefits are long lasting.

Breaking through Isolation

Social connection is not always about venturing outward. “On my really bad days,” says Ms. Russow, “when my friends would call and say, *How are you doing? Can we bring you some soup?* My first thought would be no, I just want to be alone. But then I would say, no, I don’t want to isolate. So, they would come over and it was a great distraction. By the time they left, I felt not just mentally but physically better. It’s not all about going out. It’s also about inviting people in.”

“The clinical spectrum of dystonia is expanding,” explains Dr. Berman, “and these psychiatric symptoms as well as pain and other non-motor symptoms may be linked. I want to encourage patients to not feel shame and to feel free to bring these symptoms up with their movement disorder specialist or other medical practitioners and seek help because the benefit can be drastic. We know that if we if we can improve the psychiatric disorders that we improve quality of life.”

“The dystonia doesn’t have to define you,” says Ms. Russow, “you can break through the isolation.”

Time to Ask for Help?

It may be time to talk to a mental health professional if:

- Your anxiety feels overwhelming.
- You can’t do the things you need to do or like to do.
- Friends and family have expressed concern about you.
- You feel out of control of your emotions.
- You feel like you need help.

To locate a mental health professional, ask your doctor, health insurance provider, or a professional organization such as the Anxiety and Depression Association (<https://adaa.org>). Or ask for recommendations from family and friends.

Individuals who experience heart racing, shortness of breath, nausea, or sweating may consider consulting a primary care doctor to assess for any physical or metabolic problems contributing to the symptoms, in advance of contacting a mental health professional.

Social Anxiety Disorder: Signs & Symptoms

When faced with situations that require interacting with other people, individuals with social anxiety disorder may:

- Flush, tremble, sweat, feel a rapid heart rate, or feel their ‘mind going blank’
- Feel nauseated or sick to their stomach
- Have a rigid body posture, make little eye contact, or speak very softly
- Find it scary and difficult to be with other people, especially those they don’t know
- Have a hard time talking to people even though they wish they could
- Be very self-conscious in front of other people and feel embarrassed and awkward
- Be very afraid that other people will judge them
- Stay away from places where there are other people
- Drink too much or abuse drugs

Dystonia Dialogue

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Contribute to Research by Registering as a Brain Donor



You can make an important contribution to dystonia research by registering in advance as a brain donor.

The DMRF works in partnership with the Harvard Brain Tissue Resource Center at McLean Hospital to maintain a private collection of brain tissue from individuals with all forms of dystonia. Donated tissue is available to researchers for dystonia-related studies.

For more information on brain donation or to begin the registration process, visit www.dystonia-foundation.org/brain or contact the DMRF at 800-377-3978 or brainbank@dystonia-foundation.org.