DYS/COURSE

News of familial dysautonomia (FD) - Autumn 2013
In memory of Elaine Jamie Lipson, whose love of life will remain forever in our hearts.

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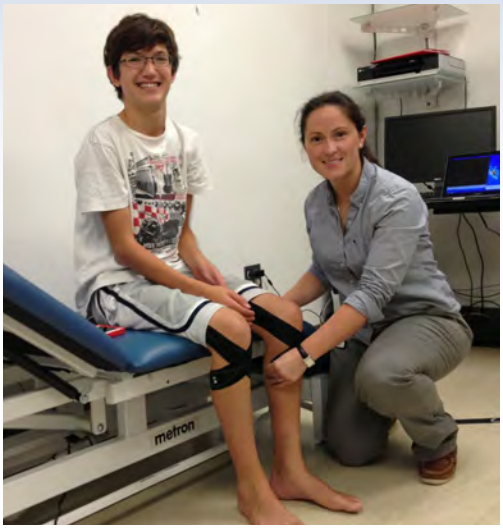
NEW CLINICAL AND BASIC RESEARCH

Researcher Studies Kidneys, Blood Pressure & Gait

Many people with FD face severe kidney problems as they age, and the damage, though mostly a mystery, is likely tied to the dramatic swings in blood pressure their bodies sustain throughout their lives. Niamh Goulding, PhD (pictured right) joined our team in 2012 as a research fellow, hoping that her expertise and interest in renal failure and its relation to blood pressure would benefit the FD population.



Research Fellow Niamh Goulding checks on the progress of a new taping therapy.

Since coming to the Center, Goulding has participated in several important and ground breaking studies related to blood pressure, kidneys and gait. Her work has led to methods to detect kidney damage early on. Such early markers are an essential component of the effort to prevent kidney damage from progressing. Goulding also studied the relationship between drinking large amounts of water and controlling blood pressure in patients with FD. This work has had direct implications on the treatment of the blood pressure swings that are a common and debilitating symptom of FD.

Goulding has gone beyond the study of kidneys and blood pressure to investigate gait and balance issues that are also common in patients with FD. These studies have already influenced treatment and led to the collection of important data that has improved our understanding of this confounding illness. Goulding developed a method to help FD patients with their difficulty balancing, walking and knowing where their limbs are in space. The non-invasive therapy, called taping, has already been shown to improve walking and posture in the FD patient population. "People are walking straighter and posture is better," Goulding said. "This has had a hugely positive impact on their daily lives."

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Stem Cells Help Solve Genetic Mysteries

It is our hope that every Foundation-funded researcher will make great advancements in the understanding of FD. We are even more delighted when a researcher is gripped by FD and continues the investigation of FD throughout his or her career. Furthermore, it is an incredible bonus when a researcher cultivates the interest of others in FD, and, in doing so, expands the pool of experts focusing on understanding this confounding disease.

Professor El Chérif Ibrahim, PhD has fulfilled and exceeded our expectations in all of these areas. Now based in Marseille, France, Ibrahim began his study of the FD gene while collaborating with Sue Slaugenhaupt, PhD, at Harvard University. (An aside - as mentor and mentee, Slaugenhaupt has her own FD research legacy. She began her FD work under Foundation-funded researcher Jim Gusella, PhD, and was part of the team that first discovered the FD gene in 2001).

Prof. Ibrahim and student, Mylène Hervé, label bacteria colonies for FD research.

Ibrahim's work began with testing the effects of the compound kinetin as a treatment for the splicing defect found in FD. His research has since evolved to becoming the principal investigator in his own FD research projects. He has used olfactory stem cells harvested from the nasal passage of FD patients to study cell development and to test the effects of kinetin. Most recently, he has moved onto the intricate study of the effect of messenger RNA (mRNA) on microRNA in FD.

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PRESIDENT'S MESSAGE

Dear Friends:

On June 2, 2013, the Dysautonomia Foundation held its 28th Annual FD Day at the NYU/Langone Medical Center. The results of our support for research over the years were strikingly evident, with more reports on new studies and medical progress than ever before. Our network has expanded to include an increasing number of talented doctors, scientists, and other professionals whose dedication and creativity are essential to the ever-increasing possibilities for people with FD. We also heard the perspectives of a panel of remarkable FD adults who shared their experiences of attending college, as well as their wisdom about to how to live with FD despite its complexities. After formal presentations in the morning, informal afternoon sessions gave everyone a chance to ask questions of a dozen FD experts. As testimony to the impact of these experts and many others working on FD, we have more adults with FD than ever before with greater opportunities to live fulfilling lives.

None of this could happen without the dedicated fundraising efforts of so many members of our extended FD family. Such work is crucial to our mission. Our extraordinary loved ones are a model for us all; they deal with the considerable liabilities of living with FD with grace, humor and the kind of positive outlook that inspires everyone who meets them to rise above life's challenges. They inspire us to not rest on our accomplishments, but to keep our eyes on what remains to be done.

Faye Ginsburg, President of the Board of Directors

EXECUTIVE DIRECTOR'S MESSAGE

David Brenner

I was recently invited to write an essay for this year's Jewels of Elul, a collection of inspirational messages for each day of the Hebrew month of Elul. This year's theme was "Welcome." We at the Dysautonomia Foundation are well practiced at extending a bittersweet message of welcome to new FD families. Below is my message of welcome, published in the book *Jewels of Elul IX* and online at jewelsofelul.com.

No one would ever choose to join our club. We don't want any new members. We welcome them sadly; they come to us reluctantly. And yet, in the darkness of a horrible storm, we are there, arms open, ready to provide comfort, assistance, and most importantly, hope.

There are common diseases and there are rare diseases; and then there's our disease, an ultra-rare disease called familial dysautonomia, or FD, the most Jewish of the Jewish genetic diseases. Only about 650 people have ever been diagnosed with it; only about 350 are alive with it. A complex dysfunction of the nervous system, FD causes many problems involving the heart, breathing, blood pressure, digestion, orthopedics, vision, kidney failure and the lack of even the most basic functions such as the ability to swallow, feel temperature, or shed tears.

Most cases these days are diagnosed at an early age. The parents of a very sick baby have searched for an explanation of what is wrong with their child. When they get the diagnosis, their momentary relief is followed by a free fall into despair. Their doctor, their rabbi, their family, and their friends have never heard of it. Ahead of them lies a foreboding and lonely horizon.

Then we welcome them into our club, the Dysautonomia Foundation. Finally, there is someone who knows what they go through, someone who understands their pain, their doubts, their fears, not as an outsider with pity or judgment or puzzlement, but as their soul mates with empathy and familiarity. And then, little by little, we help them see a beam of light that turns into a beacon of hope. Here is hope, here is treatment, here is research, and here are others who are ready to help. Welcome.

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The Path to Progress for FD Treatment and Research

By Michael Brownstein, MD, PhD, Scientific Advisory Board Chair & David Brenner, Foundation Executive Director

David Brenner: For decades, the Dysautonomia Foundation has been the world's leader in fostering FD research and treatment. We have achieved remarkable progress, including the discovery of the FD gene, breakthroughs in treatment protocols, advanced understanding of the neurological and genetic mechanisms of the disease, and the use of life-saving surgical interventions. But for anyone who suffers from FD, or has a family member who suffers from FD, progress never comes fast enough.

It's common for me to receive comments that patients are asked to participate in too many clinical research studies, that our doctors should be more aggressive in using new therapies, diets and supplements as soon as there is any suggestion of efficacy, and that we seem to value a conservative approach to research more than a progressive approach to treatment.

Dr. Michael Brownstein, Prof. Adrian Krainer and Dr. Felicia B. Axelrod discuss research with families at FD Day.

I've been questioned about why we insist on peer-reviewed, reproducible and independent confirmation of therapies and research findings before endorsing them. "Why put patients through double-blind and placebo studies," they ask, "when you already have some evidence for the efficacy of a new treatment?"

As the father of an FD patient, I want quick progress and am willing to try any new therapy if there is even the slightest chance of improving my son's quality of life. At the same time, I have to rely on the tried and true methods of medical science to minimize both short-term and long-term risk to my son's, and others' health.

I recently asked the chairman of our Scientific Advisory Board, Michael Brownstein, MD PhD, to help us explain to our FD families and our supporters how we select research projects, why treatment progress sometimes seems slow, and why we are so insistent that our doctors rely on rigorous clinical studies before adopting new therapies for FD treatment. The following was his reply.

Michael Brownstein: Rene Descartes, the Renaissance philosopher and mathematician, believed that nerves were hollow tubes connecting the brain to the muscles. He suggested that when you want to move a limb, fluid flows from your brain into appropriate muscles, inflating and contracting them. It never occurred to Descartes to test this idea experimentally. If he had done so, he would have discovered that the volume of a muscle does not change when it contracts. It does not "inflate."

Ideas about how the body works, what goes wrong when it functions improperly, and how to fix it aren't always right - no matter how pretty they are and how enthusiastically they are championed by those who give birth to them. Medicine moved forward in the last century because scientists, clinicians, and patients were willing to subject hypotheses to rigorous tests. If this isn't done - if we base our decisions on hopes and rumors - we may not help patients; we may even hurt them. This can have the unintended effect of preventing people from using other safer or more efficacious remedies too. So as anxious as I am to find new treatments for dysautonomia, I am also eager to be sure that we offer the best and safest possible therapeutic options to kids and adults with FD.

One thing that will help us do this is an animal (mouse) model that faithfully reproduces the biochemical and physical changes that are seen in FD. Thanks to the efforts of Sue Slaugenhaupt, PhD and Ioannis Dragatsis, PhD, we now appear to have animals like this, and we should be able to use them to discover whether specific treatments (alone or in combination) affect the development/progression of FD, and the doses of drugs that are required for efficacy. Results of the studies in mice can be "translated" into treatment strategies for patients and they should give us confidence that our drug development program is moving in the right direction.

As we look for drugs that will increase production of the FD gene product (IKAP), we will continue to work to improve patient care - symptom by symptom. This is why it is so important for patients to participate in the studies going on at the Dysautonomia Center. Careful clinical studies have shown us that crisis can be better managed, blood pressure swings can be minimized, and blood carbon dioxide levels can be reduced. The discovery that retinal problems are associated with FD has allowed us to think about sight-saving interventions; and the observation that FD patients lose their ability to detect the positions of their joints suggested that taping joints, which allows you to use skin touch sensors to determine their position in space, improves gait (see the photo on the first page).

In short, we are moving forward with as much speed as pos-

Path to Progress

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sible. I understand how crucial it is to improve the quality and duration of the lives of FD patients. We cannot sacrifice rigor to speed however. As Hippocrates said, "above all do no harm."

You may be wondering how we find scientists and physicians to help us, or how they find us. And how we select people to support. Felicia Axelrod, MD and Horacio Kaufmann, MD at the FD Center have found many excellent collaborators. This is one of the many reasons the Center is so valuable to us. Others hear about us from friends or colleagues, or read about work supported by the Foundation in the scientific literature. Regardless of the nature of their introductions, the process for obtaining a grant is the same: they write proposals that consist of a statement of their specific aims, the background information upon which they base their ideas, the experiments they want to do, and a budget section. Some may have come to one of the conferences sponsored by the Foundation. If so, they know we are not interested in supporting an open-ended search for truth. I urge them instead to conceive of projects that will have concrete benefits for those with FD - both short- and long-term. The projects that they outline are reviewed by a panel of excellent scientists and clinicians who judge their merit and relevance to us. This peer-review process has allowed us to create the best possible research portfolio, and it is seen by applicants as tough, but fair.

We encourage the people we support to write papers about the studies they do and publish them in excellent peer-reviewed journals. This helps us recruit additional researchers, and gives us a way to measure the quality and reproducibility of what they have done. Some findings are hard to publish, however, especially those which are negative. Even so, it is just as important for us to know what has failed as what has worked, so we encourage our grantees to share such information with us and with one another.

You may wonder how a drug's safety and efficacy can be tested. Ordinarily, the Food and Drug Administration would require a placebo-controlled, double-blind study. That is, some patients would get the drug that is being tested and others would get tablets or capsules that look the same, but contain something inactive and innocuous like sugar. Patients are assigned treatments randomly, and what they are receiving is unknown to them and to the doctors who treat them and evaluate their responses. Placebo responses are often seen when you try to detect changes in behavior. For example, 30-40 percent of patients in the placebo arm of depression trials have symptomatic improvement. Perhaps this is a result of hope on the patients' part and encouragement on the part of their physicians. It seems likely that some improvement in crisis symptoms could arise from placebo effects. How great these are and how long they are sustained is unknown.

While it may be impractical to do studies of the sort that I described above in FD patients, it is important to study the effects of new treatments carefully. Insisting on objective (biochemical and clinical) evaluations of efficacy as opposed to subjective impressions is essential. We need data, not anecdotes.

As I said earlier, establishing the safety of new treatments in the FD population is very important. We cannot assume that a drug that has been given safely to other patients is necessarily benign in kids and young adults with FD. It has been suggested recently that cardiac glycosides like digoxin might be used to improve splicing of the FD primary transcript (i.e., the RNA product of the FD gene). Frankly, this scares me. Digoxin is used to treat heart failure much less than it once was. Partly, this is because it is so toxic. It was common to see "heart block" in patients who were given the drug, and both blood levels and cardiac function (EKGs) had to be monitored carefully. When I taught pharmacology many years ago, I stressed the importance of recognizing toxicity in patients who were receiving cardiac glycosides. Whether they affect splicing or not, I think that we have to offer FD patients safer drugs than these.

It makes me sad to think that we already have safe treatments - ones that could even be life-saving - that are under-utilized. An example is the interventions for sleep apnea (CPAP or BiPAP). These offer FD patients a better night's sleep and also prevent carbon dioxide from building up in the blood and causing disturbances in the rhythm of the heart. While the masks are a bit uncomfortable to wear, many people can ultimately adapt to them if they are well-fitted or use nasal pillows, and I recommend such therapy with enthusiasm.

We have come a long way in the twelve years that have elapsed since the FD gene was discovered. New cases of FD already seem to be much rarer than they once were, and treatments that we devise for dysautonomia must mainly target the people who already suffer from the disease. I am convinced that we can improve the quality and duration of their lives. It is urgently important that we stay focused on these goals.

Kidneys, Blood Pressure & Gait

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Goulding said she loves working with FD patients not only because the disease presents so many challenges to her as a researcher, but also because the patients are such "troopers." "Never in my life have I come across patients who have so many things wrong, but who walk around happier than I have ever been," she said.

Stem Cells Solve Mysteries

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Why use stem cells?

While several Foundation-funded researchers are using or developing mouse models to test the efficacy of compounds that affect splicing, nothing can get closer to the characteristics of FD than the study of real, human cells. Together, these techniques provide greater insight than either could on its own. The olfactory cells Ibrahim is using can express the variability found in a cross-section of patients with FD, while a mouse model is limited to reproducing the same expression of symptoms in every mouse from that model. At the same time, a mouse model is exceedingly helpful when assessing therapeutic activity throughout the entire body, whereas stem cells from a specific part of the body only show what is happening in that one part of the body. As such, both research models complement each other, Ibrahim explained.

With these cells, Ibrahim confirmed that kinetin does increase IKAP protein levels, which are in short supply for people with FD due to the splicing defect caused by their genetic mutation. This is encouraging work, confirming that the ongoing kinetin clinical trial is truly worthwhile.

The difference between mRNA and microRNA

The human genome is still very much a mystery, but building on recent developments in the general understanding of gene behavior and consequent advances in other disease research, Ibrahim is testing a hypothesis that messenger RNA (mRNA), along with RNA and microRNA, could play a role in the amount and production of proteins in the body. RNA regulates gene expression, microRNA, or small RNA, is involved in functions ranging from cell migration to cell death, and mRNA, or messenger RNA, conveys genetic information. The theory is that knowing more about how these components function and interact will lead to a new way to regulate IKAP levels in FD patients.

Continuing the legacy

We are delighted that, beyond his own interest in FD, Ibrahim has been able to attract future scientists to FD with his ambitious and exciting research. One of Ibrahim's students, Mylène Hervé, has been granted a fellowship at Aix-Marseille Université to continue her study of FD while she earns her PhD starting in October. We are excited to see where this team of researchers will lead us!

Gear Up: 10th Tour de Foliage

It's our 10th anniversary! The 10th Annual Tour de Foliage, FD Cycle Tour celebrates a decade of wonderful rides on Sunday, **September 22, 2013**. The event has raised more than $1.6 million since its inception. Co-Chairs, Lisa and Jeff Newman, Lisa Rudley and Melissa Slive are working to make this cycle tour truly the best ever. To see what's new, register to ride, sponsor the event or sponsor a rider, visit us at www.fdcycletour.org.

If you have always wanted to ride, but date, location or skill level have made it impossible, this year you can participate as a Virtual Rider with all of the same fundraising incentives and rewards! Sign up, and then on race day, take to your own course or spin bike! Details on our website.

FD Author Completes Trilogy

Alexia de Gunzburg has published the final installment of her FD trilogy on gaining independence while facing the world with a disability. *Steps of Life: Exceeding Boundaries* offers inspiration for people of all abilities, to live to their full potential. Alexia's other books, *Steps of Courage: Traveling with Confidence* and *Steps of Progress: My Years in London*, are all available for purchase, with a portion of proceeds going to the Dysautonomia Foundation. Please contact the Foundation if you would like to obtain a copy.

Meet our New Nurse

Leila Percival, BSN joined the Dysautonomia Center team this summer. She graduated from NYU College of Nursing in 2008 and has previously worked in the departments of cardiology and emergency. Additionally, Leila has worked as a paramedic in the New York City 911 system and holds a Master's degree in forensic psychology from John Jay College of Criminal Justice. "As FD affects multiple facets of patients' physiology, as well as their experience of daily life, I hope to incorporate my knowledge of cardiology, emergency medicine and psychology in providing care to the FD population," she said. Leila grew up in New England and currently lives in Brooklyn.

28th Annual FD Day

Our 28th Annual FD Day Conference included featured speakers (pictured right) who presented updates on their work on FD research and treatment. The presentations were followed by an inspiring panel of FD adults discussing their achievements and challenges in college. Alexia de Gunzburg, Lindsay Ross, Nathaniel Sharir and Zoe Schvan provided poignant and humorous accounts of FD life after high school.

In the afternoon, a panel of FD experts met with FD families in small groups to answer questions and give more detailed accounts of their work. Additionally, the 5th Annual FD Photo Competition, the entertainment of Illusionist Elliot Zimet, the exotic animal show and an appearance by "No Tears: Life with FD" comic artist, Mindy indy, all combined to make FD Day a truly special event.

Abstracts from the presentations are available on our website and pictures of the event, along with the winners from the photo competition, are available on our Facebook page. Plans are already in the works for next year, so mark your calendars for Sunday, **June 8, 2014**.

Left: Elliot Zimet pulls doves from thin air. Right: Children meet an alligator.

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Below: Morning Speakers, Horacio Kaufmann, Lucy Norcliffe-Kaufmann, Faye Ginsburg, Adrian Krainer, Sue Slaugenhaupt, Felicia Axelrod and David Brenner.

Left: Golfer plays the Long Island Course. Right: Gregg and Laura Meyers with their children Zach and Sophie.

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Below: The course at Glen Oaks Country Club.

Golf Outings: 17th Annual Long Island 10th Annual Chicago

The annual golf outings in Long Island and Chicago on May 13 and July 29 were both wonderful successes thanks to the hard work of organizers **Paul Wexler**, **Steve Fass**, **Adam Posnack** and **Paul Sunderland**, for Long Island, which marked its 17th year, and **Gregg** and **Laura Meyers**, for Chicago, which marked its 10th year. Combined, 300 golfers turned out to play the courses and show their support for our cause. In addition to golf, the Chicago outing had a "Ladies Lunch and Play" mahjongg and card tournament that attracted over 200 participants. Together, the events raised over $300,000.

Join our Volunteer Roster!

Looking for an opportunity to volunteer? Our events happen largely thanks to the dedication of our wonderful friends and family who share their talents with us. Our volunteers look after children; they sell raffle tickets; they swipe credit cards; they take pictures; and they breakdown an event after the fun is over.

We are looking to build our reserves of people we can call on when in need. If you have a few hours of your time to share throughout the year and a special talent you would like to provide, please email us at info@famdys.org and request to be put on our "volunteer roster."