United Mitochondrial Disease Foundation

MITOCHONDRIAL NEWS

Volume 8 • Issue 2 • Spring 2003

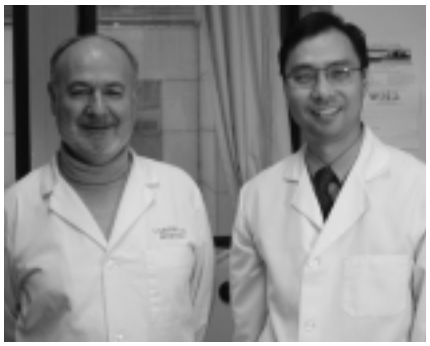
Ask the MitoDoc
See Page 2

Chapters are reaching out to thousands
See Pages 3 & 4

MRS/MMS Meeting UMDF to Participate
See Page 3 & 9

You can make a difference and help give the Energy for LIFE!
See Page 10

We want to hear from you!
See Page 7



MITOCHONDRIAL CAUSES OF PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

Salvatore DiMauro, M.D.
Professor of Neurology
Michio Hirano, M.D.
Associate Professor of Neurology
Columbia University, New York

Progressive external ophthalmoplegia (PEO, or CPEO for "chronic PEO") is an impressive Greek term simply meaning "paralysis of eye movements." PEO is often accompanied by ptosis, another medical term meaning "droopy eyelids." Both PEO and ptosis are among the most common manifestations of mitochondrial dysfunction. In fact, their very presence, in isolation or together with other abnormalities, should alert the astute clinician to the possible diagnosis of mitochondrial disease.

PEO is manifested by severe limitation or total inability to move the eyeballs laterally or vertically. To compensate, patients have to move their whole heads towards the object of their visual interest. Because this limitation affects the muscles of both eyes to the same degree, patients usually do not experience double vision. Drooping of the eyelids is partially compensated by excessive furrowing of the brow or lifting of the head. It is esthetically burdensome, especially to young people, who are considered "sleepy" or "on drugs."

Why should the extraocular muscles, which partially envelop the eyeball, be so vulnerable to the energy shortage of mitochondrial dysfunction? Nobody knows for sure, but there are two possible explanations:

1. Extraocular muscles contain many more mitochondria than limb muscles, an indirect evidence of their high dependence on oxidative metabolism;
2. From the functional point of view, extraocular muscles perform extreme types of tonic and dynamic exercise, such as staring at a fixed point on one hand and following rapid movement on the other, both probably requiring high energy provision from the mitochondria.

Continued on page 5

Adults Corner
Service Dogs Save Energy
See Page 6

Ask the Mito Doc

Living with mitochondrial disease presents many twists and turns - a maze of questions. UMDF is pleased to offer answers to some of those questions. All questions and responses are taken from www.umdf.org -- Ask the Mito Doc. Please note that information contained in Ask the Mito Doc is for informational and educational purposes only. Such information is not intended to replace, and should not be interpreted or relied upon, as professional advice, whether medical or otherwise.

Responders for this issue: Andrea L. Gropman, M.D., Children's Hospital of Washington, D.C., and Richard G. Boles, M.D., Children's Hospital of Los Angeles, CA.

The Question Is:

I am facing the prospect of having a colonscopy in the near future and as a result of severe GI dysmotility, the doctors want to do a three to five day prep. Should any particular precautions be taken during this time given that I have some components of autonomic dysfunction, particularly severe hypoglycemic events? I am fearful of a metabolic crash during this timeframe, but my GI doc seems unconcerned.

Response From:
Richard Boles, M.D.

An intolerance to fasting is seen in many individuals with mitochondrial disease. Although not all mitochondrial patients are sensitive to fasting, it is difficult to predict which ones are and which ones are not. Fasting intolerance can be relatively mild and reversible, such as headache, vomiting or fatigue, or severe and potentially irreversible, such as heart muscle weakness (cardiomyopathy), stroke or sudden death. Hypoglycemia may or may not be present during fasting-induced symptoms. As surgery and other medical procedures are (in general) major stressors that increases energy demand, it is especially important to avoid fasting around the time of procedures. Thus, I strongly recommend that all medical procedures be performed in the absence of fasting in all individuals with proven or suspected mitochondrial disease.

In the majority of cases, fasting and fasting-induced complications can be avoided simply by the placement of an IV in the early morning with the delivery of D10 (10% sugar solution) at a standard (maintenance) rate. The D10 should run during the anesthesia induction, procedure, and afterwards until the patient is able to tolerate a meal. Usually, this does not necessitate an additional night in the hospital beyond that customarily required for the procedure, and outpatient surgery is often appropriate. Individuals requiring continuous or frequent drip feedings, with severe disease, or receiving complicated procedures are potential exceptions.

In your individual case, a history of hypoglycemia (obviously) likely indicates fasting intolerance. The dysautonomic/dysmotility manifestations may also be a sign of fasting intolerance, in my experience. Three to five days is a long time, and if you are unable to take in adequate calories by mouth in any form (i.e. liquids) during that time, then you should discuss IV alimentation (feeding) with your physicians.

The Question Is:

I am a 44 year old woman and have recently been diagnosed with Mitochondrial Myopathy, with a heteroplasmic mutation (A10750G) in the ND4L gene.

Is it wise to "save" energy by using a wheelchair or to continue, though my body hurts a lot and gets tired sooner, without the wheelchair? Is it possible for patients with mitochondrial disease to "build up" their condition? Would it be helpful to go swimming or other sports in the hope that I can push my pain limit further and feel fatigue later? Is fatigue always the first symptom of mito disease?

Response From:
Andrea L. Gropman, M.D.

That is an interesting question. In general, patients with wasting conditions who can participate in a proper exercise program gain muscle protein mass, strength and endurance, and, in some cases, are more capable of performing the activities of daily living. Both resistance and endurance exercise training have been shown to have positive effects in patients with mitochondrial disease, although several questions remain to be answered. Lastly, a good diet, including adequate vitamin intake and the avoidance of obesity are important. Since fasting increases demand on mitochondria, regular meals are recommended. Excessive exertion should be avoided. What level of physical activity you should engage in depends on how severely your muscle is affected, but for those able to exercise, this will improve well being and in some cases lead to improved muscle function.

Chapter Activities

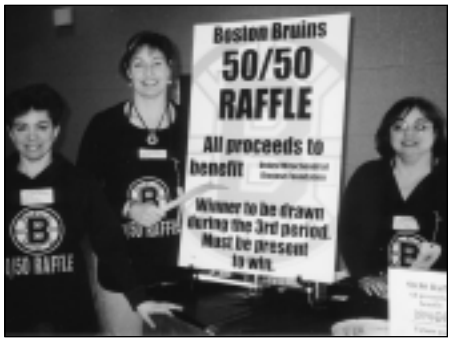
ARIZONA CHAPTER

Arizona Chapter, Phoenix, AZ
President: Karen Lipps
Phone: 623-694-5151
Email: AZChapter@umdf.org

The Arizona Chapter is a member of the Albertson's Community Partners Program. This is an easy way to help raise funds for our chapter. The chapter will receive a contribution check each quarter from Albertsons. The cards are free! Give them to all your friends, family, neighbors, teachers, etc. To get your card or to receive more information, contact the chapter.

The chapter continues to sell "Radiance" The UMDF Energy Bear. For more information, contact the chapter or visit www.umdf.org.

Arizona Chapter has a complete schedule of all their meetings, including speakers and topics on the UMDF web site.



Another Successful Raffle - More than $4,000 raised

New England Chapter volunteers Linda Zollo, Eileen Mitchell and Patty Mastro sold 50/50 tickets to benefit UMDF during Bruins games.

NEW ENGLAND CHAPTER

New England Chapter, Boston, MA
President: Justine Fargo
Phone: 781-396-4286
Email: NEngChapter@umdf.org

Mark Your Calendars NOW for the 4th Annual Mito-What? 5K Walk/Run to benefit UMDF

Sunday, October 5, 2003 in Longmeadow, MA, at Baypath College on Route 5

For more Walk/Run info, please contact: Jackie Tyler at 413-567-5435 or via email at jacknjohn11@aol.com.

DELAWARE VALLEY CHAPTER

Delaware Valley Chapter
President: Maripat Shelly
Phone: 215-256-0273
Email: DelValChapter@umdf.org

Mark your Calendars!

DelVal Chapter's 4th Annual Shelly's Heroes 5K Run 1 Mile Walk and the Blosky Blast-off Family Fun Day is set for **Saturday, May 10, 2003** at St. Maria Goretti Church in Hatfield, PA.

Looking ahead:

- 6th Annual You Go Girl Golf Outing, October 8, 2003
- 2nd Annual Fashioning Hope for UMDF, November 8, 2003

The 5th Annual Holiday Party was once again a grand success. The Delaware Valley Chapter would like to thank the Merion Tribute House for providing such a beautiful setting!

San Diego REGIONAL Mitochondria 2003 Family Meeting

Hosted by California and Arizona Chapters of UMDF

Hyatt Regency Islandia, Mission Bay

Saturday, June 14, 2003
9:45 a.m. to 4:30 p.m.

Program

Speakers include Drs. Doug Wallace, Annette Feigenbaum, and David Whiteman. Topics will address genetics, diagnostic issues, metabolic pathways, therapies, and patient management -- issues for all patients, both children and adults.

The cost to UMDF members registering before May 20 is $50 ($65 for non-members). After the 20th, cost is $65.

Please contact the UMDF Office at 412-793-8077 or via email at info@umdf.org for a registration form or for more information regarding the meeting.

Chapter Activities

NEW YORK METRO CHAPTER

New York Metro Chapter
President: Joe Rice
Phone: 631-862-8975
Email:NYMetroChapter@umdf.org

The New York chapter sponsored a Mito-What? Ceramic party at Diane's Ceramics, in Hamden, CT.

Lingerie Party

On January 25, 2003, the NYMetro Chapter held a lingerie party. Milicie, a company that imports Italian lingerie donated 20% of the proceeds to UMDF and more than $400 was raised. Anyone in the tri-state area wishing to hold a similar party can contact Beatrice at 1-877-645-4079. *(Please don't forget to mention that you would like to have the party as a fundraiser for UMDF.)*

SOUTHERN CALIFORNIA CHAPTER

Southern California Chapter
President: Sharon Shaw
Phone: 562-634-4855
Email: SCalChapter@umdf.org

Plans are already underway for the chapter's 2nd Annual Golf Outing. The date is set for **October 4, 2003** at Lakewood Country Club. The Chapter is looking for volunteers to sign up for the golf committee. **If you (or someone you know) would like to help, please contact Linda Cooper at 714-921-2272**.

The chapter continues with its "on-going" fundraisers - MRM Vitamins, North Bath and Body Shop, Albertson's Community Partners Cards, United Way and Hearts Full Of Hope Cookbook Sales.

Check out all of the upcoming events for the chapter nearest you at www.umdf.org and help spread the word about mitochondrial disease in your community!

OHIO CHAPTER

Ohio Chapter
President: Jennifer Lyman
Phone: 330-929-4430
Email: OHChapter@umdf.org

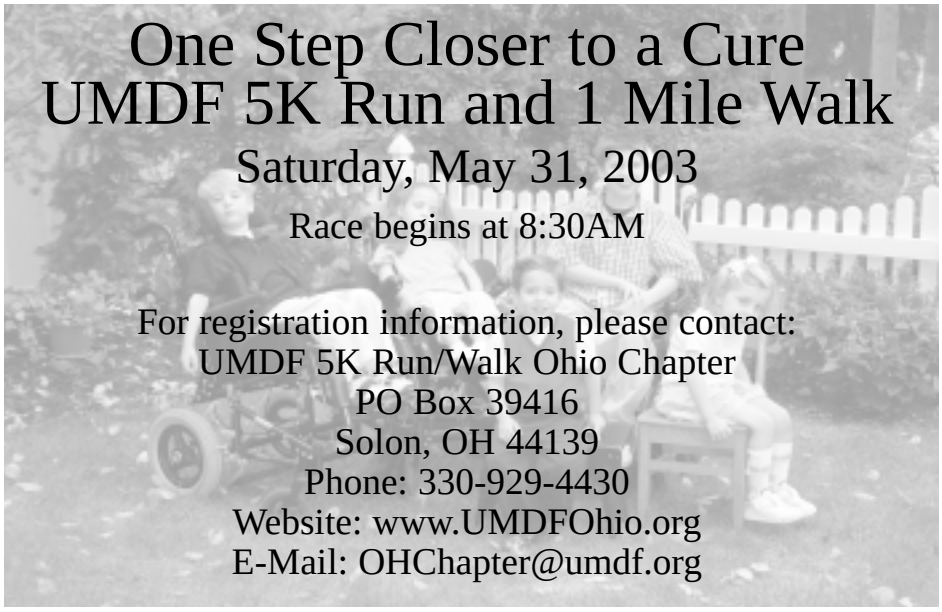
Ohio Chapter's Amazing Youth Fundraisers

Samantha and Alexandria Stahler, cousins to Bobby Arnold of the Ohio Chapter, raised money once again this year making holiday cookies. Thanks for raising $280, girls!

Jordan Birdson (age 10), Alyssa Hill (age 9), Chase Birdsong (age 7), Leigh Birdsong (mom), Annie Hill (mom), Ashlyn Hill (age 6), and Gigi Allen (age 9) all worked together to raise $900 to benefit the UMDF. They made jewelry, beaded socks, badge holders and more and sold them at Frito Lay/Pepsico where Jordan's mother works. Cooper Adelstein has quite a fan club!

KFC Franchises Collecting Change to Benefit Ohio Chapter

Thanks to Tom Arnold, grandfather to Bobby Arnold, Premier Restaurant Management Company's Kentucky Fried Chicken franchises will be collecting coins to benefit UMDF. The coin collectors ask patrons to "Donate your change and help UMDF find a CURE for Mitochondrial Disease!" Tom has also connected UMDF with his counterpart in Western PA and through the courtesy of Morgan's Foods, Inc., the coin collectors will arrive in Western PA franchises this spring. Outstanding!!!



MITOCHONDRIAL CAUSES OF PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA

Continued from page 1

Few conditions other than mitochondrial diseases cause PEO and ptosis. Of those that do, the most significant is myasthenia gravis (MG). In MG, however, the eye muscle weakness fluctuates in severity, usually worsening throughout the day, and does not affect both eyes symmetrically, thus resulting in double vision. A second condition characterized by PEO and ptosis is oculopharyngeal muscular dystrophy (OPMD) which differs from mitochondrial myopathies because of late onset (sixth or seventh decade), and severe involvement of swallowing muscle, causing dysphagia (swallowing impairment). The most common form of MG is sporadic (not inherited) whereas OPMD is a genetic disease generally transmitted as an autosomal dominant trait, usually occurring in every generation.

Which mitochondrial diseases are characterized by PEO/ptosis, or usually associated with them? There are many individual clinical entities, most of which have only recently been characterized at the molecular level (see Tables 1 and 2). As with all mitochondrial diseases, those with PEO/ptosis also fall into two broad genetic categories: defects of mitochondrial DNA (mtDNA) and defects of nuclear DNA (nDNA). There are further subdivisions within each category.

Mitochondrial DNA (mtDNA)

The most common primary defect of mtDNA causing PEO/ptosis is the "single deletion." By this, we mean the deletion of a segment of mtDNA (or, more appropriately, an"arc", as mtDNA is circular). Although both the length of the deleted portion and the abundance of partially deleted mtDNA molecules vary in different patients, each patient harbors one and only one specific mutation in all affected tissues.

Table 1. Mitochondrial Disorders with PEO

Disorder	Gene Product	Chromosome	Mutation
Autosomal Dominant PEO with multiple mtDNA deletions			
adPEO	Adenine nucleotide translocator 1	4q34-q35	Point mutations
adPEO	Twinkle	10q23.3-24.3	Various
adPEO	Polymerase gamma	15q22-q26	Point mutations
Autosomal Recessive PEO with multiple mtDNA deletions			
MNGIE	Thymidine phosphorylase	22q13.32-qter	Various mutations
PEO	Polymerase gamma	15q22-q26	Point mutations
ARCO	Unknown	Unknown	Unknown
Autosomal Recessive PEO with mtDNA depletion			
Severe myopathy	Thymidine kinase 2	16q22-q23.1	Point mutations
Sporadic PEO			
KSS, PEO, PEO-plus	tRNAs and mitochondrial proteins	mtDNA	Single large-scale deletion of mtDNA

Single mtDNA deletions can cause either a myopathy or a generalized disorder. The myopathy (muscle disease) affects extraocular muscles (PEO), eyelid muscles (ptosis), and proximal limb muscles, characterized by waddling gait, difficulty lifting the arms above the head, and exercise intolerance.

The generalized disorder is Kearns-Sayre Syndrome (KSS), so called because of the two physicians from the Mayo Clinic who first described it. KSS consists of an obligatory triad of signs and symptoms:

1) onset before 20 years of age,
2) PEO,
3) pigmentary degeneration of the retina.

In addition, there is at least one of the following: heart conduction defect (heart block), cerebellar brain dysfunction with ataxia (loss of balance, clumsy movements), or markedly increased protein in the cerebrospinal fluid. Other problems may also be present, including hearing loss, diabetes, and declining intellectual abilities.

There is no effective therapy for KSS and the disease progresses relentlessly. Death usually occurs at a young age. However, the timely placement of a pacemaker can be life-saving, surgical correction of ptosis can help at least temporarily, and cardiac transplantation has been successful in a few patients with cardiomyopathy.

Less common causes of mtDNA PEO/ptosis are point mutations, which include the MELAS mutation (A3243G in the $tRNA^{Leu(UUR)}$ gene), as well as mutations in several other tRNA genes. These mutations are usually transmitted by maternal inheritance. Some mutations appear spontaneously, and for these patients (whose cases are sporadic), the family history is negative.

Continued on page 8

Service Dogs Save Energy

By Melissa Lingk and Melissa Nixon-Lingk

Melissa Lingk is a professional service dog trainer; she is herself partnered with Dharma, a two-year-old female Leonberger. Her stepmom Melissa Nixon-Lingk is partnered with Thor, an eight-year-old male Norwegian Elkhound who has been working for six years. Both women are part of our UMDF family. Please address any inquiries to figaro@saber.net.

While the legal definition of a service dog (SD) may vary between countries, essentially a service dog is specially trained to mitigate a person's disability. In the United States, service dogs are protected under the Americans with Disabilities Act. This federal law gives people who qualify for an SD the right to have their fully trained SD in places of public accommodation including stores, movies, trains, taxis, restaurants, and hospitals.

Many times complete strangers have asked whether a service dog could help them, their family member, or perhaps a disabled friend. Since each situation is so different, this is never an easy question to answer. Service dogs

Types of Service Dogs

There are many different types of service dogs, including guide dogs, hearing dogs, seizure and metabolic alert dogs, psychiatric service dogs, and mobility assistance dogs.

- **Guide dogs** are the eyes for a blind person. They will stop at cross walks, lead around obstacles, stop their partner from stepping in front of traffic, get them safely up and down stairs, and take them back to the car after a shopping excursion. Intelligent disobedience (refusing a partner's command if it would lead them into danger) may be part of their training. For example, the dog may see a hole in the sidewalk that is not perceptible to the human partner.
- **Hearing dogs** are the ears for a deaf person. They will tell a partner when the stove timer goes off, when someone is calling on the telephone, when a visitor is at the door, and when the baby is awake from a nap. More importantly, they will alert their partner if the fire alarm is going off. If the human partner drives, the dog may be trained to let them know if there are sirens or honking horns.
- **Seizure alert dogs** are trained to help a person with an uncontrolled seizure disorder. These service dogs have an inborn capacity to sense an impending seizure before the patient or those around them are aware of it. This innate ability is shaped with training so that seizure alert dogs are able to let partners know a seizure is imminent, allowing the partners to reach a safe place prior to onset of the seizure. These particular SD's may accomplish other tasks also. They can be trained to "catch" their partner when they seizure so the partner has a safer fall. They can lie on top of their partner to prevent excessive movement. They can be trained to get help by alert barking. They can even be trained to push a special button on the telephone that dials 911.
- A closely related service dog function is **metabolic alerting**, and this is one of Thor's (Melissa Nixon-Lingk's dog) tasks. He is able to sense if my stepmother is becoming hypoglycemic, hypokalemic, or low on certain medication levels. He is trained to bump his partner incessantly until he sees her take the medication.
- **Psychiatric SD's** partner with people with qualifying mental disabilities. These SD's are trained in a variety of tasks, depending on the partner's individual needs. Psychiatric SD's can alert to upcoming panic attacks. They can be trained to realize the signs of stress in a partner and interrupt a destructive cycle. These service dogs can be trained to take a partner out of a building just as a guide dog would if the partner becomes unable to deal with the situation. PSD's can be taught to stop a partner's anxiety pacing or to help a partner who has been housebound for years slowly venture into life outside their home.
- Last but far from least is the **mobility service dog**. Mobility SD's have great diversity to their training. Dharma can pull a wheelchair, pick up anything I drop, and get the specific grocery item I want off a shelf as indicated by a laser pointer. She wears a special harness and is trained to counter balance my movement so that walking requires much less energy for me. She can carry my groceries from our van to our kitchen and put them on the counter. Dharma also does my laundry. All this saves me a great deal of energy. Thor is also exceptionally good at gait assistance, but when my stepmom is using her scooter or motorized wheelchair, he trots alongside in a modified heel unless specifically told to go ahead or behind her vehicle.

are a great help on many levels, but an SD is not going to miraculously fix a disability. To expect such not only leads to disappointment but sets up a canine partner for failure. An SD should supplement their partner's life and abilities, not replace them.

While for many partners the SD is a social facilitator, this is not always the case. Some people just do not see service dogs as doing important jobs. These same people may try to make you and your SD (known as a team) leave a public place. This is, of course, illegal in the U.S. and other countries, yet it still happens. If a qualified service dog partner is not willing to defend her right to have her qualified service dog in public, then perhaps a service dog is not the right answer for her. If a team allows an ignorant person to take their rights away, they have made the path instantly more difficult for every other working team.

SD's require prompt high quality veterinary care to make sure they stay in great working health. Of course, this costs money, and, while some veterinarians offer significant discounts to service dog teams, there will always be out-of-pocket expenses for a service dog's partner. A few programs for disabled people offer a nominal monthly stipend, but it is very important to look into any assistance programs before acquiring a partner, as funds are not available in all areas.

A service dog's partner must either be capable of giving the dog daily exercise and playtime or be willing to have an ongoing arrangement for someone else to help with such necessities. An hour of playing fetch can relieve stress nicely for a dog after a hard day at work. SD's need a healthy social life.

If the balance of pros and cons of partnering with a service dog tips in favor, the task of finding a dog begins. There are two basic training options: program-trained dogs and owner-trained dogs.

Program SD's are fully trained before the partners are introduced; the team shares only a brief training period together under professional guidance. Since the costs of raising and training the dog are often covered by nonprofit entities, the cost of a program dog is often nominal to the disabled partner. However, the wait to be partnered with a dog can last for years.

While disabled partners can train their own dogs, I recommend assistance from a professional trainer. The extensive costs are generally the sole responsibility of the human partner, and there is often the necessity to try several dogs before finding the special individual capable of qualifying as a working SD. However, the wait is much shorter, and some of us feel the rewards are even greater.

NEWSLETTER FEEDBACK FORM

Mitochondrial News contains the following sections in every issue. Please rate your interests in these sections, 5 = high interest and 1 = least interest (Circle one for each).

Sections	**Rating**				
Lead Medical Article	1	2	3	4	5
Ask the Mito Docs	1	2	3	4	5
Chapter Activities	1	2	3	4	5
Adult Corner	1	2	3	4	5
Secondary Article	1	2	3	4	5
(Research Updates, UMDF Development, Various Topics of Interest)					
Fundraisers	1	2	3	4	5
Chairman's Report	1	2	3	4	5
Donor Acknowledgements	1	2	3	4	5
(from past issues-NOT IN THIS ISSUE)					

Please provide topics of interest to you and your family:

_____

_____

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Don't Forget to Mark your Calendar for the 2004 UMDF Conference in Pittsburgh, September 16-19, 2004. Visit www.umdf.org for more info.

We want to hear from you!

Please take time to complete the **Newsletter Feedback Form** and submit in the enclosed envelope.

Continued from page 5

Nuclear DNA (nDNA)

Mutations in nDNA cause PEO/ptosis that is inherited by traditional mendelian genetics, usually by autosomal dominant and more rarely by autosomal recessive transmission. These disorders are defects of intergenomic signaling, meaning that the normal communication between nuclear DNA and mitochondrial DNA gets garbled. Put another way, primary mutations in nuclear DNA result in alterations in mtDNA. In turn, the mtDNA alterations can be qualitative or quantitative.

Qualitative alterations are multiple mtDNA deletions. Tissues from these patients harbor several different deletions in their mtDNA instead of the single deletion seen in muscle from the sporadic patients with PEO and myopathy described previously, or in tissues from patients with KSS.

Patients with multiple mtDNA deletions have a variety of symptoms and signs besides PEO/ptosis, including exercise intolerance (premature fatigue), cataracts (clouding of the lens), peripheral neuropathy (with loss of sensation, tingling, or limb weakness), or psychiatric problems (depression alternating with euphoria). Although these are generalized disorders, they are less severe than KSS and are often compatible with a normal lifespan.

In the past two years, mutations have been described in three nuclear genes associated with multiple mtDNA deletions. The three genes encode adenine nucleotide translocator 1 (ANT1), polymerase gamma (POLG), and a helicase (Twinkle). However, many patients do not have mutations in any of these three genes, indicating that mutations in other nuclear genes remain to be identified.

An especially severe form of generalized mitochondrial disease with PEO/ptosis has received the unpronounceable acronym MNGIE, which stands for **M**itochondrial **N**euro-**G**astro**I**ntestinal **E**ncephalomyopathy. As the acronym suggests, gastrointestinal problems characterize this disorder. Symptoms include chronic diarrhea and altered intestinal motility, leading to severe weight loss.

MNGIE is transmitted as an autosomal recessive trait and is due to mutations in a gene encoded as thymidine phosphorylase (TP). One consequence of TP mutations is massive accumulation of thymidine in body fluids. We have hypothesized that the excess thymidine alters the pool of nucleotides required as building blocks for mtDNA. We hope that lowering the levels of thymidine in patients may be a first approach to therapy for this crippling disease.

Quantitative alterations of mtDNA cause a spectrum of clinical conditions, generically called mtDNA Depletion Syndromes (MDS). Some of these are confined to a single tissue, most commonly muscle or liver. Others affect multiple tissues. Patients with the myopathic variant of MDS often have PEO/ptosis.

Mutations in two genes have been associated with the myopathic and the hepatopathic variants of MDS: thymidine kinase 2 (TK2) and deoxyguanosine kinase (dGK). Like TP, TK2 and dGK also control the concentration of nucleotides in the mitochondrion, and nucleotides are indispensable building blocks for the synthesis of DNA.

In conclusion, the best approach to the correct diagnosis of diseases characterized by PEO/ptosis is family history, as shown in the tables. These tables are simplified versions of one published by the authors of this article in a Neurology editorial (Neurology 2001;57:2163-2165). Readers can refer to this article for more detailed information.

Table 2. Maternally Inherited PEO

Disorder	Gene Product	Chromosome	Mutation
PEO/PEO-plus	$tRNA^{LEU(UUR)}$	mtDNA	A3243G
PEO-plus	*$tRNA^{LEU(UUR)}$	mtDNA	A3251G
PEO-plus	$tRNA^{LEU(UUR)}$	mtDNA	C3256T
PEO-plus	$tRNA^{LEU(UUR)}$	mtDNA	T3264C
PEO-plus	$tRNA^{LEU(UUR)}$	mtDNA	T3273C
PEO-plus	$tRNA^{LEU(UUR)}$	mtDNA	G3255A
PEO	*$tRNA^{Ile}$	mtDNA	T4274C
PEO	$tRNA^{Ile}$	mtDNA	T4285C
PEO-plus	*$tRNA^{Ile}$	mtDNA	G4298A
PEO	*$tRNA^{Ile}$	mtDNA	G4309A
PEO-plus	$tRNA^{Ala}$	mtDNA	T5628C
PEO-plus	*$tRNA^{Tyr}$	mtDNA	Δ5885T
PEO	$tRNA^{Asn}$	mtDNA	A5692G
PEO	$tRNA^{Asn}$	mtDNA	G5703A
PEO-plus	$tRNA^{Lys}$	mtDNA	G8342A
PEO	$tRNA^{Leu(CUN)}$	mtDNA	T12311C
PEO	$tRNA^{Leu(CUN)}$	mtDNA	G12315A

*possibly sporadic

Fundraisers

Vacation Toward a Cure with AmericanAirlines

Plans are underway for the 2nd Annual ***Vacation Toward a Cure*** raffle. Through the efforts of Joe Rice of the New York Metro Chapter, UMDF will once again raffle off a vacation -- this time in the Caribbean!

American Airlines has generously donated round trip air transportation to the winners.

Tickets are $5 each or a book of 6 for $25. If you would like to purchase or sell tickets to help UMDF Redefine Hope, please contact the office at 412-793-8077 or info@umdf.org.

3rd annual Richie Classic Golf Tournament raises $25,150 to benefit UMDF

The Richie Foundation in collaboration with the Metropolitan Health Administrators' Association hosted the event. Special thanks goes to Phyllis Yezzo and the board of MHAA (Metropolitan Health Administrators' Association) for choosing UMDF as this years beneficiary. Pictured above from left to right, UMDF Chairman Chuck Mohan, Phyllis Yezzo, Michael and Rhonda Friedberg. The Friedbergs, parents of Zachary Friedberg, were instrumental in making the event a success.

Donor Acknowledgements

Since the very first issue of *Mitochondrial News*, UMDF has diligently thanked our many donors by listing each and every donor of $50 or more. In 2003, we have moved to a quarterly newsletter.

We would like to print one huge THANK YOU publication at the end of the year so that we can list ALL of our donors - from $5 to $500,000. This new publication will be coupled with our Annual Report.

The quarterly newsletter is intended to inform our members about mitochondrial disease, upcoming conferences, chapter events and activities, fundraisers and annoucements. It is our sincere hope that this transition will be well received by our supporters.

Research Update

By Mark Fleming
UMDF Vice-Chairman, Research Coordinator and SAB Liaison

The UMDF is pleased to fund this year's Research Grant Program to the tune of half a million dollars. We have received 29 grant applications -- more than we have ever received in a single year. The grants are currently under review and we will announce the results this coming June.

We are looking forward to a successful joint UMDF/Mitochondrial Medicine Society (MMS) / Mitochondrial Research Society (MRS) Symposium, June 11-14, 2003, in San Diego. The meeting will focus on the research and clinical aspects of mitochondrial medicine. The UMDF will fund several of its previous grantees to present their results at the conference. For more information about the conference go to the MMS website at www.mitosoc.org/mito2003.

The last day of the conference will feature a one-day regional patient/family meeting on Saturday, June 14, hosted by the Southern California and Arizona Chapters of the UMDF (see Page 3). For more information, call 412-793-8077 or visit www.umdf.org.

SAB Update

Our veteran SAB members have been busy: Dr. Robert Naviaux (Mitochondria and Metabolic Disease Center, San Diego, CA) recently received the National Leadership Award from the National Congressional Committee for his work in mitochondrial medicine and the ongoing development of diagnostic standards. He has also been appointed the California Chair for the US government's Business Advisory Counsel to represent children's health issues and innovative biotechnologies.

Dr. Gerard Berry was recently appointed as the Dean of Research at Thomas Jefferson University in Philadelphia. Dr. Keshav Singh has joined the staff of the Roswell Park Memorial Institute in Buffalo, NY. Doug Wallace now heads the Center for Molecular and Mitochondrial Medicine and Genetics at the University of California, Irvine.

Our SAB provides a valuable service to the UMDF by advising the board on many aspects of mitochondrial disease. We appreciate their assistance and wish each of them success in their endeavors.

Fundraiser

Special Thanks to . . .

Tierney Holiday Golf Tournament raised $1,798 in January

The Haddad Family collected more than $2,000 in memory of Samya Haddad's 9th Birthday

The Mott Family pulled in $440 at the Balentine Elementary School Fall Carnival

McKinsi Faye Thompson had friends and family donate $200 in lieu of birthday presents for her 8th birthday

Florida Rays of Hope held a bowl-a-thon and raised $500

Sherry Prince, Avon Representative (District 4338 in Ohio), hosted an Avon fundraiser and donated $225

Joseph Adam Langer donated $3,628.50 to UMDF, 50% of his Bar Mitzvah money, in memory of his sister Sarah Elizabeth Langer

The Hefferon Family hosted a Post-Holiday Gift Recycling Party and raised $2,317.50 to benefit UMDF.

2nd Annual Wiffle Ball Tournament in honor of Austin Manz of Finleyville, PA, raised $850 to benefit UMDF

St. Bernadette Catholic School, Monroeville, PA, raised $1,000 during the 2nd Annual *Coins for a Cure* in memory of Gina Marie Mohan

Tomato Face Foods continues to roll across the U.S. Barbara Bruck and Allan Segal took the meatless spaghetti sauce to a sampling in Indianapolis this winter and we hope that the Kroger stores will embrace this new product -- REMEMBER, ten percent of the proceeds from the sales go to UMDF. Keep up the great work!!!

Chairman's Report

"I'm sorry, but there's nothing more we can do. There is no cure, there is no hope and there is nothing more you can do."

These words have been and will continue to be spoken. People actually believe there is nothing they can do. They need to understand that we can take action and that there is always hope, even when there is no cure!

Many of our members re-define hope by being proactive, getting involved in fundraising, or UMDF Chapters and support groups. Money is important, but sometime talents and actions can have just as much impact.

I recently received an email that deserves repeating. It tells the story of a father at a fundraiser dinner. After extolling the school and its dedicated staff, he offered a question. "I was taught to believe that everything God does is done with perfection. Yet, my son, Shay, cannot learn or understand things as other children do. Where is God's plan of perfection reflected in my son?"

The audience was stilled by the query. The father continued, "I believe that when God brings a child like Shay into the world, an opportunity to realize the Divine Plan presents itself. And it comes in the way people treat that child."

Then, he told the following story:

Shay and his father walked past a park where some boys were playing baseball. Shay asked, "Do you think they will let me play?" Shay's father knew that most boys would not want him on their team. But the father understood that, if his son were allowed to play, it would give him a much-needed sense of belonging.

Shay's father asked one of the boys on the field if Shay could play. The boy looked around for guidance. Getting none, he took matters into his own hands. "We're losing by six runs in the eighth inning. I guess he can be on our team and we'll try to put him up to bat in the ninth inning."

In the bottom of the eighth inning, Shay's team scored but was still

Upcoming Fundraising Events . . .

- May 10, 2003 - Matthew Dudgeon Memorial Walk. Benefits UMDF and other local charities. Visit www.themattyfund.org.
- May 10, 2003 - 4th Annual Shelly's Heroes 5K Run/1 Mile Walk. Contact Delaware Valley Chapter - see page 3.
- May 31, 2003 - One Step Closer to a Cure UMDF 5K Run/Walk events held simultaneously in Ohio and Pittsburgh. See page 4 for details on the Ohio event and contact Sandy at 412-793-8077 for the Pittsburgh event.
- June 19, 2003 - 6th Annual UMDF Pittsburgh Golf Outing, Churchill Country Club.
- June 21, 2003 - Kuk Sool Kick-A-Thon at Lucchesi Park in Petaluma, CA.
- July 28, 2003 - 4th Annual UMDF Ohio Golf Outing, Shaker Heights Country Club.

Check www.umdf.org for more upcoming events!

Chairman's Report

continued from page 10

behind by three. In the bottom of the ninth inning, Shay's team scored again. Now, with two outs and the bases loaded, the potential winning run was on base. Shay was scheduled to be the next at-bat. Would the team actually let Shay bat and give away their chance to win the game?

Surprisingly, a teammate gave Shay the bat. Everyone knew that a hit was all but impossible. However, the pitcher moved in a few steps to lob the ball so Shay could at least make contact. The first pitch came, and Shay swung clumsily and missed. The pitcher took a few more steps forward to toss the ball softly. Shay swung and hit a slow ground ball to the pitcher.

The pitcher picked up the soft grounder and could easily have thrown the ball to the first baseman. Shay would have been out, and that would have ended the game. Instead, the pitcher threw it on a high arc to right field, far beyond the reach of the first baseman.

Everyone started yelling, "Shay, Shay, run to first. Run to first." Never in his life had Shay ever made it to first base. He scampered down the baseline, wide-eyed and startled. Everyone yelled, "Run to second, run to second!"

By the time Shay was rounding first base, the right fielder had the ball. He could have thrown the ball to the second baseman for a tag. But he threw the ball high and far over the third baseman's head. Shay ran towards second as the runners ahead of him deliriously circled toward home.

As Shay reached second base, the opposing shortstop ran to him, turned him in the direction of third base, and shouted, "Run to third!" As Shay rounded third, the boys from both teams were screaming, "Shay! Run home!" Shay ran home, stepped on home plate, and was cheered as a hero, for hitting a "grand slam" and winning the game.

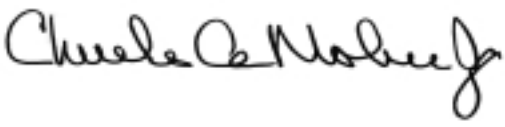
"That day," said the father softly with tears now rolling down his face, "the boys from both teams helped bring a piece of the Divine Plan into this world."

We all have thousands of opportunities a day to help realize a Divine Plan, we can re-define hope. Many seemingly trivial interactions present us with choices: Do we choose to re-define hope for someone? Or do we pass up that opportunity, and leave the world a bit colder in the process? Would you drop the ball in order to let someone get on first base?

The hope comes in realizing we do have options, we can be proactive; we can get involved on various levels and our involvement, on any level, will make a difference.

What can you do when you are told there is nothing you can do? Do you do nothing because there is no immediate cure or do you choose to help and participate? There is no man living who is not capable of doing more than he thinks he can do.

Yours Toward a Cure,



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UMDF MISSION
To promote research for cures and treatments of mitochondrial disorders and to provide support to affected individuals and families.

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