Mitochondrial News

United Mitochondrial Disease Foundation

Management Strategy for Acute Illness in Patients with Mitochondrial Cytopathy

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Introduction

The precarious health of a patient with a mitochondrial cytopathy represents the fine line between little energy reserve and potential energy deficiency. When demands of added energy requirements occur, as they do in an acute illness, the decreased reservoir of stored energy in a patient with a mitochondrial cytopathy often cannot compensate for the new energy demand. When combined with the decreased inherit capacity to manufacture energy, the patient's bioenergetic health is altered and a bioenergetic crisis can occur. This is especially true in young children, who have little energy reserves to begin with, and in those with a severe mitochondrial cytopathy. Although the number of things that can cause excessive bioenergetic stress is large, we mostly see compromised bioenergetic health in the context of another illness. Viral illnesses and fevers for example, can have mitochondrial consequences.

Dr. Saneto speaks with another attendee at the June 2000 conference in Cleveland.

A quick and simple review of mitochondrial function is important to understand this article. We consume food to make the energy our body needs to function. The energy in food is contained in the cleavable bonds between the atoms in molecules of sugars (carbohydrate), fats, and proteins. Healthy mitochondria will generate 36 molecules of ATP (adenine triphosphate, each ATP represents a unit of energy) for each molecule of glucose that the mitochondria can burn or oxidize. If the mitochondria do not function (which is not compatible with even a brief life of any person), glucose is not fully burned and only 2 ATP molecules will be produced. In this situation, there is also the production of two molecules of lactic acid. Studies of mitochondrial function in some of our sicker patients show that under ideal laboratory conditions, only about 40 - 60% of the maximal energy can be produced (14 - 21 ATP molecules for each glucose burned). This is an estimate of theoretical ATP production, which would decrease if laboratory conditions mimicked what occurs in the body during severe viral illnesses, dehydration, and high fever.

A useful analogy is to think of an eight-cylinder car that is running on only 6 or 7 cylinders. As long as the car is on horizontal ground the car's performance can appear acceptable. However, when the demands are increased, such as when the car is loaded with passengers, attempts to climb a hill, or accelerates to enter the freeway, there is not sufficient energy performance to accomplish the task. The car knocks, sputters, and lags in acceleration. Under

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Mitochondrial Disease in Perspective Symptoms, Diagnosis and Hope for the Future

by Sharon Hesterlee, QUEST,
Volume 6, Number 5,
October 1999 (Excerpts)

Each of our cells contains, on average, 500 to 2,000 little "factories" called mitochondria that are responsible for supplying our energy needs. When the mitochondria aren't working properly, the effects are particularly apparent in parts of the body with high energy requirements, such as the nervous system, skeletal muscles and heart.

This is the second article in a two-part series on mitochondrial diseases affecting these organs. Part 1 (vol. 6, no. 4) covered mitochondrial anatomy, the basics of mitochondrial disease inheritance and common types of mitochondrial disorders affecting muscle.

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Mitochondrial Medicine 2001
March 2-4, 2001
Hyatt Islandia Hotel
San Diego

"Breaking Through Our Genes: Taking Mitochondrial Medicine to the Next Level"

If you have not received your registration form, please contact the office at 412-793-8077

Don't delay in getting your registration in - last year's banquet sold out early

Chairman's Report

A Wish for This Holiday Season

Oh, if only wishes could come true I would...

My wish list has changed tremendously over the years. Almost as much as my hopes my dreams and my goals. How simple my wishes used to be; snow for skiing, good weather for vacation, a new car or motorcycle and time to enjoy them. My dreams; getting through high school and into college, finding that special person and getting married, buying a home and starting a family, a new motorcycle and time to enjoy it. My goals; developing a profitable business, growing my family and my business, getting involved in, and giving back to, my community, finding time to ride a motorcycle.

Don't our wishes seem to originate from the need existing at the time of making the wish?

The holiday season means many different things to many different people, but to UMDF, this season centers around two very important things; hope and support.

Let us pause in sober contemplation of the millions of people around the world who do not have happiness this holiday season, who have lost hope and are in need of support. We must be humbly grateful for the privilege of living in a country where spiritual values have not been completely subordinated to material things. Where our freedoms still allow us to support initiatives that promote research, aid support and redefine hope.

When we "wish" this holiday season, we will not ask for worldly possessions. Instead, we want only your good will... to serve you that you will continue to think well of us, as surely we do of you.

May your good will continue so our mission of promoting research for cures and treatments of mitochondrial disorders and to provide support to affected families may also continue.

Oh, if only wishes could come true I would wish...

- that you be successful in redefining hope
- that you receive the support you and your family are in need of
- that we gain a true sense of what is really important in our lives
- that we realize regret and fear are twin thieves that rob us of today
- that we laugh more and cry less
- that we stop counting our days and start making our days count
- that we understand that we are always the same age inside.
- that as soon as we feel too old to do something, we do it!
- that we understand that satisfaction comes not from getting what we want, but from helping others get what they want.
- that we realize that life isn't a matter of milestones, but of moments
- that we could convince our spouse that it's never too late to ride a motorcycle
- that the UMDF could close it's doors because of lack of business

Oh, if only wishes could come true I would...

Blessed holidays and a better new year to all,

Chuck Mohan
Chairman, UMDF

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08-09-00 to 12-11-00

The United Mitochondrial Disease Foundation wants to thank the many people who have made contributions that will support our initiatives.

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DCA-MELAS Clinical Trial

Reprinted from NORD's Orphan Disease Update, Volume 19, Edition 1, Winter-2001

The purpose of this study is to determine whether the investigational drug dichloroacetate (DCA) is safe and beneficial for patients who have MELAS (mitochondrial encephalomyopathies with lactic acidosis and stroke-like episodes). It is being conducted through the Mitochondrial Research Center of Columbia University.

MELAS, a metabolic disorder, is associated with a point mutation in the mitochondrial DNA. It is inherited through the maternal lineage, which means it is transmitted from a mother to all her children but passed on to the next generation only by daughters.

The mutation is thought to cause impaired energy metabolism in all cells of the body, leading to the abnormal buildup of lactic acid. The resulting acidosis interferes with the functioning of the brain and other organs, and can be life-threatening.

DCA is an investigational drug that may reduce the amount of lactic acid in the blood and brain. Although this research will compare DCA with a placebo, all participants will receive DCA over the course of the three-year study. Patient recruitment is expected to continue until August 2001. Mercy Medical Airlift, a non-profit organization providing travel assistance, will help eligible patients obtain transportation to the study site.

For information, visit the Mitochondrial Research Center's web site at www.hnrc.cpmc.columbia.edu/melas.html or contact the research coordinator, Franklin Ortiz, at the following address: The Neurological Institute, 710 W. 168th Street, New York, NY 10032; Tel: (212) 305-6834; Fax: (212) 305-0431; E-mail melas@columbia.edu.

Management Strategy for Acute Illness

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these circumstances, the car can stop working completely. In everyday life, the patient with a mitochondrial cytopathy may function well enough to get by. But when the demands of an illness or other stressful situation require a higher performance state, the ability of the body to manufacture the needed energy to meet that demand is not optimal. It takes longer for a mitochondrial patient to recover from an illness, and sometimes the illness is far more severe than if the same illness happened to someone with normal mitochondrial function. So when illness occurs, the mitochondrial cytopathy patient is faced with a situation of having both less energy reserves to fight off the illness and the inability to maximize energy production, to help overcome and recover from the illness' effects on the body.

Little is known how to prevent an energy imbalance and possible subsequent physiological damage. There is not much in the medical literature that is instructive in medically managing the crises of illness or other stressful event in a mitochondrial patient. What follows is based on our experience and understanding of some of the practical and theoretical implications of how the body's biochemistry affects the bioenergetic health of a mitochondrial patient.

Preparation is the Key to Energetic Health

There is a wide spectrum of mitochondrial cytopathies. Each one is expressed in a unique way that is particular to a specific person. Therefore, there is no "one" best treatment for those with a mitochondrial cytopathy. Each patient has to be cared for on an individual basis. Furthermore, our current understanding of mitochondrial diseases is limited and hence, a best treatment protocol does not exist. At present, there are many more unknowns than proven treatments in the medical care of a patient with a mitochondrial cytopathy.

The fragility of someone with a mitochondrial cytopathy requires a working knowledge of what signs to look for during an acute illness. For the purposes of this discussion, we will be discussing the management of fevers, inability to consume enough liquid and food, and dehydration. Some patients vomit excessively, others have increased tremulousness, while still others stop drinking and eating, and some have cognitive changes. It is important for the parent or caregiver to know these signs (Table 1) for their loved one and call their doctor if these signs develop. In addition, there should be a good working relationship with the primary care physician, so when the parent or caregiver begins to see the signs of rapid bioenergetic decline, the physician can make arrangements for hospitalization. A plan for such events should be well developed by the physician prior to a crisis. Past experiences will dictate the need for hospitalization and the immediate treatment once the patient has arrived at the hospital. Unnecessary hospitalization may occur on occasion, when the patient is not as sick as originally believed to be, but both physician and caregivers quickly learn when and when not hospitalization is needed.

Table 1. Some Worrisome Signs

Unexplained or excessive fever
Alteration of usual level cognitive function
Confusion, excessive sleepiness, excessive crying
Vomiting
Loss of appetite
Rapid breathing
Abdominal pain

At the first signs of an illness, the parent or caregiver should be quick to implement treatment. This generally includes fluid and sugar, and we find that some common sports drinks such as Gatorade help. High carbohydrate meals, given by frequent feedings, also may help replenish and sustain the needed levels of glucose for metabolism. For example, we have used added uncooked corn starch in a meal to increase the level of glucose in the meal.

The use of medication to reduce fever, such as ibuprofen or acetaminophen should be used. The doctor should calculate the proper dose of these medications (10 - 15 mg / kg / dose given every 4 - 6 hours), so that there are no fevers.

Treatment for Worsening Clinical Status

It is difficult to pinpoint the time when the patient needs hospitalization. Experience and communication with the physician / heath care team are needed. Decisions can be made when the parent / caregiver notices that, despite the added measures of increased fluids and extra carbohydrate-containing meals / drinks, the patient has not responded appropriately. This would be more urgent if the patient continues to worsen. For each patient, the dictating symptoms are different, however, through consultation with the health care team the appropriate decision can be made.

Once the decision is made, the patient and parent / caregiver should go to the nearest hospital. We tend to have our patients admitted directly to the hospital, but this will vary according to the patient's doctor. Our decisions on what to do next are based on our knowledge of what deficit our patient may have. Once the patient has been checked into the hospital, we have a general plan for proceeding ahead. Most patients will need blood and urine tests, placement of an IV, and fluids initiated.

Laboratory Tests: The underlying reason for the change in bioenergetic status needs to be addressed. For example, if there is an infection, this may need to be treated. If it is asth-

ma, then the proper respiratory medications need to be given. Laboratory tests may need to be obtained, including lactate, pyruvate, ammonia, electrolytes and urine analysis. These values may assist in understanding the depth of bioenergetic compromise. For instance, if the lactate level is high, then the amount of dextrose added to the balanced salt solution used for hydration can be determined. The level of BUN will help determine the level of dehydration and the rate of fluid administration. If the urine analysis indicates that ketone bodies are being excreted in the urine, this is an indication that fats are being mobilized and maybe carnitine needs to be added to the fluids.

Dehydration: The degree of dehydration is very important. This is because dehydration may adversely affect the brain, muscle, heart, and kidney. Even mild degrees of dehydration, caused by vomiting, diarrhea, or fever may greatly limit the kidney's ability to get rid of a toxic metabolite, set the conditions for rising metabolite levels and induce further injury. This is the likely mechanism for the evolution of basal ganglia injury in cases of methylmalonic aciduria and type I glutaric aciduria.

We usually begin dextrose containing a balanced salt solution, usually D5 or D10 with 1/4 or 1/2 normal saline (a salt mixture containing 5% or 10% dextrose) and added carnitine. Given a particular situation, the amount of salt or sugar could be higher or lower in the IV solution. The percentage of dextrose containing fluid depends on the abnormality of the patient. The rate at which fluid is given is individualized depending on the degree of dehydration, and is the same regardless of whether or not someone has a mitochondrial disease. The normal criteria used to decide whether to administer IV fluids should be abandoned in those with acute illness and dehydration, as oral rehydration therapy does not offer the same degree of control and there is not as much room for error in someone with a mitochondrial disease.

Glucose: Why use added dextrose (glucose) in a mitochondrial cytopathy patient that is dehydrated and/or has lactic acidosis? Let's use the automobile engine analogy again. In a mitochondrial cytopathy patient, the need for fuel is more pronounced than in a normal patient. Since the engine does not function optimally, we need to either increase the octane of the fuel so the engine gets more output from the fuel or give the engine more fuel to burn. By giving the patient more glucose in intravenous fluids we are accomplishing both, more glucose or fuel to burn and a higher octane by enhancing the purity of the fuel to burn, and therefore produce more immediate energy (instead of the fatty acids from the breakdown of fats). By treating dehydration, we are also producing an environment for the engine, which is better for energy efficiency.

In more scientific terms, what we are trying to do is decrease the lactic acidosis while expanding the volume of fluid in the body. Lactate, but also other toxins, can be poisons to the brain and as previously mentioned dehydration can concentrate toxic metabolites and decrease the kidney's ability to get rid of these metabolites. Lactate is the by-product of inefficient glucose metabolism due to mitochondrial dysfunction. When lactate builds up, it causes the blood to become acidotic. The liver, in a non-mitochondrial patient, can utilize much of the lactate produced to remake glucose for storage and also burn it for fuel. However, when the pH falls below a certain point, below 7.1, the liver ceases using lactate and instead produces lactate. By giving fluid, we are expanding the volume of the blood and allowing the kidneys to help remove some of the toxins. In addition, the added fluid is helping the kidneys reverse the acidosis. Under conditions of severe illness, it is easier for the body to burn glucose, rather than fat, for energy. The hopeful result of IV fluids with added glucose and carnitine is the resolution of lactic acidosis, correction of electrolyte balance, and the resolution of symptoms. It is critical to note that excess of glucose can be highly toxic to a person with pyruvate dehydrogenase (PDH) deficiency. In some situations of severe mitochondrial failure, excess glucose can result in worsening lactic acidosis as well.

In certain emergent cases, we have had to add an insulin drip (0.03 units/kg/hr - 0.1 units/kg/hr) to help improve mitochondrial function by making glucose more available to the mitochondria and lowering free fatty acid levels, which can improve the function of sick mitochondria. These are very select cases, and consultation with a mitochondria expert is needed to assess and implement insulin in these special cases.

Levo-Carnitine: In some patients, we will give a bolus of levo-carnitine (usually 50 mg/kg, followed by 100 mg/kg/day in 3 divided doses) as these patients usually present with a lactate acidosis and have begun to break down fats into fatty acids. In the analogy of the car engine, when the fuel is improper for the engine there are by-products produced that can decrease the performance of the engine. One can think of carnitine as a fuel additive to help prevent the build up of toxic by-products created by inefficient fuel utilization.

Carnitine binds toxic-free fatty acids and organic acids. In addition, it acts as a mitochondrial membrane stabilizer (seals the "leaky" gasket). Often patients with mitochondrial cytopathies have a secondary carnitine deficiency as a result of overproduction of free fatty acids. The carnitine deficiency would be worsened by an acute insult to the mitochondria and the metabolic machinery. Added carnitine during the acute stage of an illness would help in removing toxins and improving the carnitine deficiency. However, there are situations when added carnitine may not be needed or may potentially worsen the situation

Other Supplements: There are

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Ways to Raise Money In Order to go to the San Diego Symposium

The cost of one family member attending
the symposium will be the cost of registration
($150 which covers nearly all meals),
two nights in a hotel ($154 each night)
and ground or air transportation.
It can seem like a huge financial hurdle for some -
but, there are ways to raise funds!

Here is a formula for raising $350 in just a week:

Develop a *"San Diego or Bust"* pledge sheet. Then...

Day 1: Sponsor yourself.
Pay the fundraising kitty $25.
Day 2: Ask five friends to contribute $20
Day 3: Ask two relatives to sponsor you for $25
Day 4: Ask five co-workers to sponsor you for $10
Day 5: Ask five neighbors to give $10
Day 6: Ask your company for a contribution of $25
Day 7: Ask two businesses you frequent (such as your doctor, dentist, dry cleaner) for $25

Most people are happy to give when they are asked. In fact, many people who have raised funds have commented that it is gratifying to see how much others want to help. Other people want to do something positive for you!

Be Creative

Don't forget that funds can also be found by contacting your church or synagogue, the local United Way, the March of Dimes, Muscular Dystrophy Association, Easter Seals, Kiwanis, Rotary and Lions Club. Perhaps you can put the symposium on your holiday list and have people contribute toward your trip. Sometimes people are even willing to donate frequent flyer miles. And, since there are two months until the symposium, try saving money each month. The cost may not seem so formidable!

The IRS May Even Help

On May 8th, 2000, through the efforts of Congressman George Miller, the IRS issued a ruling that will allow parents to deduct some of the costs associated with attending medical meetings related to their child's health condition. Parents will be able to deduct "amounts paid by an individual for expenses of admission and transportation to a medical conference relating to the chronic disease of the individual's dependent." See IRS Bulletin 2000-19 at http://ftp.fedworld.gov/pub/irs-irbs.

Management Strategy for Acute Illness

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occasions when other supplements, in addition to those above, may be needed. We have patients who have severe muscle and peripheral nerve impairment when illness also induces changes in bioenergetic homeostasis, very similar to chronic inflammatory demyelinating polyneuropathy. Other patients have severe movement disorders, such as dystonia. We have found that intravenous gamma globulin (1 - 2 gm/kg in 1 or 2 doses) temporarily improves these conditions. Although not FDA approved for these diseases, we have seen this treatment help reverse neuropathic weakness and dystonic movements. There is some experience with the use of creatine in patients having mitochondrial myopathies. We have used creatine as only a short-term treatment when trying to prevent a patient from being placed on a breathing machine. The body adapts to long term use of creatine and presumably its effectiveness lessens. We would only recommend these types of treatment in consultation with a mitochondria expert.

Conclusion

There are a few important points to remember when dealing with an intervening illness in a person with a mitochondrial cytopathy.

1. The patient or caregiver, along with the primary care physician, should develop a plan of how these illnesses will be approached ahead of time.

2. In many patients, there is little ability to compensate during an acute illness, so early intervention and the use of IV fluids are often warranted.

3. Once IV hydration has started, it may be necessary to stop all attempts at feeding, allowing the bowel to rest, until the patient begins to request fluids or food.

4. Improvement can be slower than would be expected in otherwise healthy persons, but most patients restart oral hydration and feeding within 12 - 24 hours of the IV fluids having begun.

5. The source of infection should be sought, and if there is a bacterial infection, it should be treated with appropriate antibiotics. Viral infections should not be treated with antibiotics, as these do not work against viruses and many antibiotics can further limit mitochondrial function.

Glossary of Terms

Sugars: a general term used to define a simple carbohydrate.

Glucose: a common sugar contained in sucrose (table sugar) or lactose (milk sugar).

Dextrose is the pharmaceutical term for glucose.

Bioenergetic Health: a descriptive term used to define the ability to produce an adequate supply of energy that will meet the body's energy demands.

Our thanks to the University of California at San Diego, Drs. Haas and Naviaux, for inviting us to join them!

Registration Filling Fast for San Diego

Don't Miss Out - March 2-4, 2001

Please join us for the "Mitochondrial Medicine 2001 Symposium" to be held at the Hyatt Islandia Hotel in San Diego. The Family Portion of the symposium offers a dynamic line-up of physicians and professionals and one of the best programs ever. The registration forms have been mailed out. If you have not received one, please contact us at 412-793-8077.

The physician's portion of the meeting, which will be held February 28 through March 4 also promises to be the best of its kind. For physician registration, please contact the University of California, San Diego, Office of Continuing Medical Education at 888-229-6263 or 858-534-3940.

The last conference in Cleveland was a sell-out and this one promises to be just as successful. Based on what you told us on our conference evaluation forms, we have built in more time for physicians to answer your specific questions. We are also providing you more time to see friends and meet new people. On Friday night, we are hosting a welcoming reception and on Saturday a fundraising banquet. If you know any individual or business that might be willing to support our banquet with a donation, please contact us at 412-793-8077.

Travel News by Ellie Miller
ESM Travel Services of Durham, CA
www.esmtravel.com
Phone: 530-894-2039
Fax: 530-894-0222

UMDF member, Ellie Miller, has offered her services as a travel specialist for the San Diego Conference. For airline, hotel and tourist information, please call her. Ellie has generously agreed to donate her commissions to UMDF!

Announcing the 2002 UMDF Symposium

Dallas, Texas, June 6 - 9, 2002

UMDF is working with the Parents and Grandparents of Mary Quincy Parsons to host the 2002 Dallas Symposium. Plans are well underway for this, the fifth mitochondrial joint symposium for Scientists and Physicians and Families. We are excited to announce the prestigious physicians and researchers **Dr. John Shoffner of Children's Healthcare of Atlanta (Georgia), Dr. Michael Bennett of The University of Texas Southwestern Medical Center at Dallas and Dr. Fernando Scaglia of Baylor College of Medicine at Houston as the Steering Committee for the Scientific Conference.** Kathryn Parsons - a UMDF founder, former Trustee, and Quincy's mom and Jane McManus - Quincy's Grandmother and a UMDF Trustee - will be working with the UMDF staff and the Scientific Steering Committee to host hundreds of researchers and physicians and families from around the world. As predicated by the conference in Cleveland, there will be a mitochondrial specialty conference as well as a mito primer for primary care and referring clinicians. Mrs. Parsons and Mrs. McManus are dedicated to using the symposium as a springboard for extensive medical education and PR campaigns to increase awareness with the public of mito disease and to inform primary care physicians and specialists in the southwest about mito disease and management.

An informative weekend for the family attendees is outlined that will include networking time, medical lectures and practical small group sessions. Topics for the information sessions will range in complexity to suit newly diagnosed patients as well as previous symposium attendees, and there will be a special session for Adult Patients.

MARK YOUR CALENDARS NOW!

Families will have the opportunity to choose among a selection of seminars.

Tentative topics include:

- Fundraising 101 and 102
- Practical Tools for Spouses
- Alternative / Complementary Medicine
- GI Management for the Mito Patient
- Cranial Sacral Therapy Applications
- Pragmatic Speech Therapy - home applications
- Training the Young Brain - home applications
- Estate Planning
- Panel on Educating the Special Needs Child and IDEA
  and of course, mitochondrial genetics, a mito primer, and a panel session with experts

There will be a special track specifically for adult patients, and there will be ample networking time for families to meet one another. On Friday afternoon, networking space will be set up for people to meet others with similar symptoms and diagnoses. At the Saturday dinner, Dinner by Direction, people will be seated next to others in similar geographical areas. There will be a banquet dinner Friday evening for both scientific and family conference attendees.

Working with Mrs. McManus and Mrs. Parsons heading the fundraising committee is B. Bender, the grandmother of mitochondrial patient seven-year-old Duncan Bender. They are moving forward with a fundraising project that is budgeted to raise at least $100,000.

Also, they will be hosting a meeting for developing a Gulf States or Texas Chapter; those in the south and southwest without a chapter in your state, look for information to arrive in the mail before the year's end.

Mitochondrial Disease in Perspective

Continued from page 1

Part 2 takes a closer look at diagnosis, symptoms and their management. In addition, MDA researcher and mitochondria expert Eric Schon of Columbia University gives an inside view of projects in the research pipeline that hold promise for mitochondrial disease treatments.

Mitochondrial disorders differ from other genetic disorders affecting the muscles in a number of ways. Most significantly, although mitochondrial disease can present as a "pure myopathy," meaning that only the skeletal or heart muscles are affected, it more often causes problems in many different organ systems, including the nervous, visual, renal (kidneys), digestive and circulatory systems.

The mitochondria are essential for turning the food we eat into energy in the form of the molecule ATP. Although there are many working parts in each mitochondrion, the mitochondrial encephalomyopathies (those disorders affecting brain and muscle and the type covered in MDA's program) are most often caused by defects in the proteins that make up the respiratory chain. The respiratory chain inside the mitochondrion is an assembly line of protein complexes that combines electrons with oxygen to generate potential energy in the form of ATP. (This respiratory chain has nothing to do with breathing.)

BEYOND MUSCLE WEAKNESS

Despite the fact that mitochondrial diseases can be so variable and affect so many organ systems, a few symptoms are common to many of these disorders. These include muscle weakness, muscle cramps, extreme fatigue, gastrointestinal problems (constipation, acid reflux), droopy eyelids (ptosis), eye muscle paralysis (external ophthalmoplegia), retinal degeneration (retinitis pigmentosa) with visual loss, seizures, ataxia (loss of balance and coordination) and learning delays. See the illustration below.

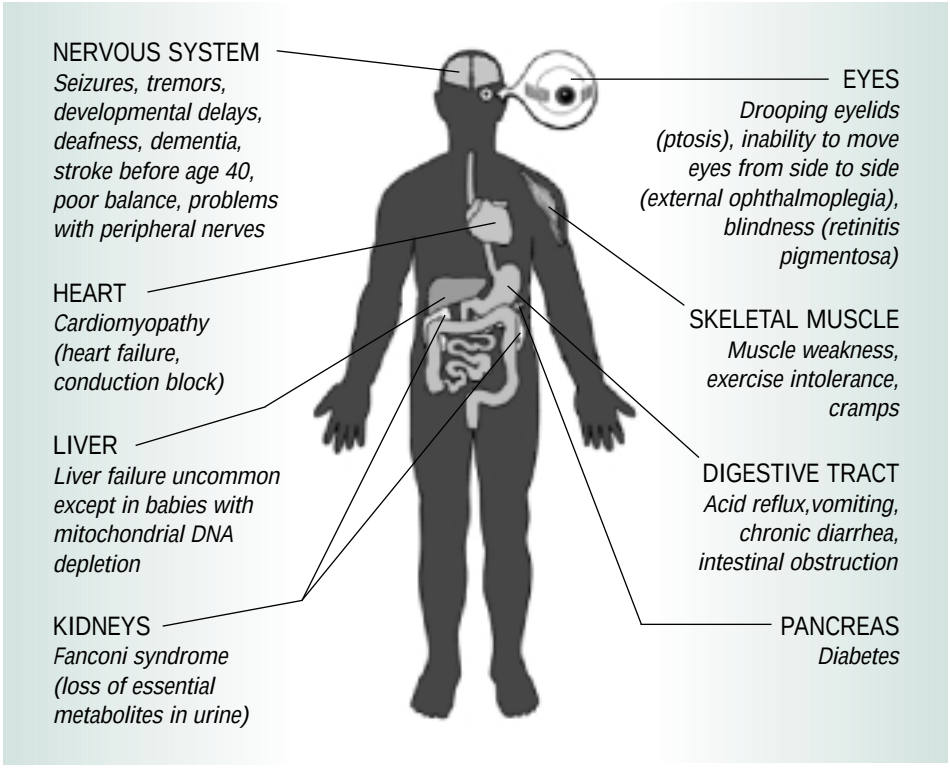
COMMONLY AFFECTED SYSTEMS IN MITOCHONDRIAL DISORDERS

The main problems associated with mitochondrial disease — low energy, free radical production and lactic acidosis — can result in a variety of symptoms in many different organs of the body. This diagram depicts common symptoms of mitochondrial disease, of which most people have a specific subset. Many of these symptoms are very treatable.

Another category of symptoms called "soft signs" may be noticeable in people who have none of the more overt symptoms of mitochondrial disease. Soft signs include deafness, mild exercise intolerance, diabetes, short stature and migrainous headaches.

Sometimes when a person is found to have a mitochondrial disease on the basis of more severe symptoms, the soft signs of the disease may be recognized in hindsight in other family members.

All of these problems start when something goes wrong in the mitochondria. Some are a direct result of interruptions in the energy supply, while others may be due to the secondary buildup of toxic byproducts, and still others to combinations of these two problems.



When key components of the respiratory chain in the mitochondria are missing or defective, the result is kind of like the aftermath of a train derailment. First, because a component of the assembly line isn't working, electrons aren't delivered. ATP isn't made efficiently and the cells lack the energy to perform their normal functions.

Second, all of the steps behind the point where the problem starts become backed up — often leading to abnormal chemistry that produces toxic charged molecules. These byproducts include free radicals and excess metabolites, such as lactic acid, that can be harmful in large quantities.

These observations lead to three prime suspects as causes of the symptoms of mitochondrial disease: energy deficit, free radical generation and the buildup of toxic metabolites. Researchers are looking for ways to

address these underlying causes. In the meantime, it's good to keep in mind that, although mitochondrial diseases are rare, many of their specific symptoms, such as heart failure and seizures, are relatively common in the general population. Thus, good medical treatments exist to help manage these symptoms.

ENERGY LOSS AND DIET

Tissues that need large amounts of energy, such as the brain, heart, skeletal muscles, eye muscles and the renal tubules of the kidney, probably malfunction, in part, because they run out of fuel. The result is muscle weakness, cardiomyopathy, renal problems, droopy eyelids, cognitive problems and general fatigue.

Although there's no way to combat this type of energy loss directly, eating a healthy, well-balanced diet is important. Sometimes special diets are necessary or beneficial in the management of specific mitochondrial and metabolic diseases. Always consult your doctor on this point, as dietary changes can be dangerous in some of these disorders.

Also, a preliminary report indicates that the dietary supplement creatine may produce modest increases in muscle strength in people with a variety of neuromuscular disorders, including mitochondrial diseases.

Creatine is a small molecule similar to an amino acid that's converted to a compound called phosphocreatine in the body and used as a source of energy. Phosphocreatine actually contains even more energy than ATP and is normally used by our muscle cells for supplying the first burst of energy at the start of strenuous physical activity.

But keep in mind that the experimental results with creatine are very preliminary, and the long-term effects of creatine supplementation in people with any kind of neuromuscular disorder aren't yet known.

Also, although dietary supplements are available over the counter without a prescription, that doesn't mean they're always harmless. You should consult your physician before taking any dietary supplement.

FREE RADICALS AND ANTIOXIDANTS

Free radicals are highly reactive charged molecules that can damage DNA and cell membranes by oxidizing them (the same chemical process that causes iron to rust). Normally, the mitochondrial respiratory chain generates a low level of free radicals during the process of making ATP. When there's a malfunction in the respiratory chain, the scale may be tipped toward higher free radical production.

These free radicals, in turn, may cause further damage to the mtDNA (the unique DNA that's found only inside the mitochondria), creating a vicious cycle of damage and free radical production. It's unclear exactly how large a role the generation of free radicals plays in causing or worsening the symptoms of mitochondrial disease, but to play it safe, many doctors recommend antioxidants to their patients.

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DIAGNOSTIC TESTS IN MITOCHONDRIAL DISEASES

Type	Test	What It Shows
Blood Enzyme Test	1. Lactate and pyruvate levels	1. If elevated, may indicate deficiency respiratory chain; abnormal ratios of the two may help identify the part of the respiratory chain that is blocked.
	2. Serum creatine kinase	2. May be slightly elevated in mitochondrial disease but usually only high in cases of mitochondrial DNA depletion.
Muscle Biopsy	1. Histochemistry	1. Detects abnormal proliferation of mitochondria and deficiencies in cytochrome C oxidase (COX) activity.
	2. Immuno-histochemistry	2. Detects presence or absence of specific proteins — can rule out other diseases or confirm loss of respiratory chain proteins.
	3. Electron microscopy	3. May confirm abnormal appearance of mitochondria. Not used much today.
	4. Biochemistry	4. Measures activities of specific respiratory chain enzymes. A special test called polarography measures oxygen consumption in mitochondria.
Molecular Test	1. Known mutations	1. Uses blood sample or muscle sample to screen for known mutations, looking for common mutations first.
	2. Rare or unknown mutations	2. Can also look for rare or unknown mutations but may require samples from family members; this is more expensive and time-consuming.
Family History	Clinical exam or oral history of family members	Can sometimes indicate inheritance pattern by noting "soft signs" in unaffected relatives. These include deafness, short stature, migraine headaches and PEO.

Mitochondrial Disease in Perspective

Continued from page 9

Antioxidants, usually in the form of vitamins or cofactors, help neutralize free radicals. These same antioxidants and vitamins may also help the struggling enzymes of the respiratory chain run more smoothly. Unfortunately, studies of their effects in people with mitochondrial diseases have produced mixed results, usually because some of the trial participants respond to the supplements and others don't.

"It probably won't hurt, but it probably won't do much good," says one researcher of taking antioxidants. "It's a bit like emptying the ocean with a teaspoon."

Some examples of antioxidants are vitamin E, coenzyme Q10, idebenone (related to coQ10, but penetrates the nervous system more easily), lipoic acid, vitamin C, vitamin K and riboflavin (B2). Many doctors prescribe a "cocktail" of these supplements tailored to the individual patient.

TOXIC METABOLITE BUILDUP AND CARNITINE

When the mitochondrial respiratory chain is blocked, metabolites that are normally processed by its enzymes may build up in the cells and cause problems.

For example, pyruvate is a chemical derived from glucose that's normally shipped into the mitochondria and then processed further so that its potential energy can be harvested by the respiratory chain.

However, when the respiratory chain is blocked, pyruvate accumulates outside the mitochondria, and when too much pyruvate has accumulated, the cells start to convert it to lactic acid.

"Many patients with mitochondrial disease have lactic acidosis — lactate in the blood," neuroscientist Eric Schon of Columbia University in New York says. "And there's decent evidence that the lactate isn't just a sign of faulty mitochondria, but that the lactate itself is bad — especially in the brain, but probably also in the muscle. If this is true, then holding that lactate down would help the patient."

With this in mind, two groups, one at the University of Florida led by Peter Stacpoole and one at the University of California-San Diego led by Richard Haas, are conducting clinical trials with a drug called dichloroacetate (DCA) to try to lower lactate levels in children with Leigh syndrome, Pearson syndrome, MELAS or MERFF (all mitochondrial myopathies).

A third group of researchers led by Darryl DeVivo of Columbia University is also planning to start a DCA trial next spring, but it will limit the enrollment to people with MELAS who have the A3243G mutation. DeVivo says lactate levels in the brain are higher in MELAS than in other mitochondrial diseases, and he hopes that, by narrowing the participation criteria, the study will produce more meaningful results on the effects of DCA.

In addition to lactic acid, other metabolites that normally feed into the respiratory chain can build up in the cells of people with mitochondrial diseases.

In an attempt to rid the body of certain of these extra metabolites, carnitine supplementation is sometimes tried. Carnitine is a natural compound made in the body that functions as a "molecular escort" for other molecules.

One of the duties of carnitine is to move long-chain fatty acids into the mitochondria. Another of its important roles is to bind to extra metabolites and escort them out of the cells and into the kidneys for excretion in the urine.

In this way, carnitine helps the body rid itself of certain extra metabolites.

Carnitine supplementation is often prescribed in mitochondrial disorders, but, as with antioxidants, the evidence that it's helpful is controversial. Carnitine can be bought over the counter at health food stores or can be taken in the prescription form Carnitor (the maker of Carnitor, Sigma Tau, guarantees the purity of its product). Again, consult your doctor before taking any kind of drug or supplement.

Although it may not be possible to treat all of the primary causes of mitochondrial diseases, a recent study in the journal Neurology suggests that people with diseases such as MELAS, MERFF and progressive external ophthalmoplegia (PEO) are actually in greater danger from the treatable complications such as heart failure or stroke than from the mitochondrial disease itself. The authors advise that people living with a mitochondrial disease could benefit by more actively monitoring these conditions and seeking prompt medical attention when necessary.

Fortunately, good treatments do exist for many of the associated complications of mitochondrial disease. For instance, seizures can be managed with antiepileptic medications such as carbamazepine. However, the common antiepileptic valproic acid should be avoided because it depletes the body of carnitine.

Heart failure or arrhythmias can be managed with medications or pacemakers.

Also, people at risk for stroke can reduce that risk with medication, and diabetes can often be managed through careful diet and medication. Specialists treating these symptoms should always be informed about your mitochondrial disorder.

GENE THERAPY FOR MITOCHONDRIAL DISEASE?

Most genetic diseases are caused when mutations in a gene render the protein it encodes nonfunctional. With this in mind, researchers in neuromuscular diseases and other areas of medicine are exploring "gene therapy" — attempts to treat these diseases at their source by providing cells with healthy copies of the damaged genes.

MDA grantee Eric Schon believes that the same gene therapy techniques being developed for the muscular

dystrophies and other diseases should be applicable to mitochondrial diseases caused by mutations in the chromosomal DNA. This type of DNA resides in a cell's nucleus and it's what's almost always referred to when scientists talk about genetic diseases.

But the body has another type of DNA, one that resides inside the cells' mitochondria (mtDNA), and defects in this DNA can also lead to mitochondrial disorders.

"When you start talking about mtDNA, there's a whole other order of complexity to it [gene therapy] for a number of reasons," says Schon, who has been working on gene therapy to fix a mitochondrial gene called ATP synthase subunit 6. Defects in this gene lead to maternally inherited Leigh's syndrome or MILS.

Schon explains that when the defective gene is in the mitochondria, delivering a functional gene to the cell is only half the battle. Although the new DNA can get into the cell, it can't get into the mitochondria, because mtDNA doesn't use the same genetic code as chromosomal DNA.

"So you couldn't just stick a new gene in the nucleus and expect it to work," Schon says. "It wouldn't make the proper protein."

(If you've ever tried to coax a PC computer to read a Macintosh file you'll understand the problem. Although the PC may eventually be persuaded to open the file, it interprets the Macintosh computer code incorrectly and displays gibberish on the screen.)

To get around this problem, Schon and the members of his laboratory have painstakingly "translated" the mtDNA code of the ATP synthase 6 gene into a code that the rest of the cell can understand. Presumably it doesn't matter if the mitochondrial gene can't get into the mitochondria because the cell nucleus should be able to make the proper protein.

Schon also added a bit of DNA sequence to the gene to give the resulting protein a special routing tag instructing it to go into the mitochondria.

Now the modified mtDNA gene can be read outside of the mitochondria and the resulting protein is automatically taken up by the mitochondria.

"The good news," Schon says, "is that we don't think that you have to import a lot of the protein into the mitochondria to correct function. So, that's not such a tall order then.

"Now we're trying to see if the protein goes into the right part of the ATP synthase complex," Schon says. If that works, he'll test the procedure in human cells from a person with MILS.

Schon's laboratory is also trying to find ways to fix problems with the mitochondrial transfer RNAs (tRNAs). The tRNAs aren't proteins, but are molecules needed to manufacture proteins from the genes. Many mtDNA diseases, including MELAS and MERFF, can result from defects in one of the 22 mitochondrial tRNAs.

Schon has met with some initial success in his search for a way to get healthy tRNAs into the mitochondria.

TILTING THE SCALE TOWARD 'GOOD' mtDNA

Gene therapy is one way to go, but researchers are also studying a different strategy for dealing with defective mtDNA. This strategy takes advantage of the fact that the cells of almost all people with mtDNA mutations are heteroplasmic — that is, each cell has a mixture of normal and mutant mtDNA.

This quality of having the good mixed with the bad may be useful because the mitochondria in individual cells are constantly dividing. If something could be done to selectively block the replication of the mutated mtDNA, then the cells might gradually be able to replace the defective mtDNA with normal mtDNA.

"The trick is, how are you going to get the bad ones specifically?" asks Schon.

A group of researchers, led by R.N. Lightowlers of the University of Newcastle upon Tyne in the United Kingdom, is attempting to do just this.

The researchers are using little molecules called peptide nucleic acids that are like homing missiles: They're designed to seek out and bind to specific sequences of mutated mtDNA. The scientists hope these molecules will prevent the mutated mtDNA from being copied so that the only mtDNA being produced is normal.

This type of therapy would require very specific tailor-made molecules for each person's mutation.

Schon's laboratory is also trying to find a way to increase the amount of good vs. bad mtDNA in the muscles of people with mitochondrial diseases. They're currently experimenting with a toxin called oligomycin.

"Oligomycin is poisonous — it will kill you," Schon says.

"But we have found that if we add tiny amounts of oligomycin to cells that are heteroplasmic for the mtDNA mutation that causes MILS, over a period of one week we could shift the heteroplasmy in the cells in a good direction toward more normal mtDNA and less mutant. Now we're working on analogues of oligomycin that are less toxic. We've made a little list that includes, among other things, the AIDS drug AZT."

Another approach being evaluated by Schon's laboratory is the way good and bad mtDNA are mixed within muscle cells. Some muscle fibers have sharp dividing lines between areas that contain normal mtDNA and areas that contain mutant mtDNA, Schon explains. His idea is to try to spread out the normal mtDNA more evenly in the muscle fibers so that most fibers have some functional mitochondria.

This strategy may work because often only a small percentage of normal mitochondria is needed to get a significant improvement in cell function.

Schon also speculates that mixing the two types of mtDNA may shut down production of the mutant kind. His laboratory is currently testing a compound that may promote mixing at the cellular boundaries between normal and mutant mtDNA.

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Mitochondrial Disease in Perspective

Continued from page 11

Another strategy along the same lines that doesn't involve any fancy designer molecules and has already shown some initial benefit to one patient is being tried by Eric Shoubridge of Montreal Neurological Institute in Quebec. Shoubridge and his colleagues have managed to shift the ratio of mutant to normal mtDNA for the better in the arm muscles of one man with PEO through a specific type of exercise.

During exercise, some damage is normally done to the muscle. It's repaired when immature muscle cells called satellite cells divide and fuse with the damaged muscle to help it regenerate.

In the Montreal experiment, the subject had normal mtDNA everywhere in his body, except in his mature skeletal muscle cells (giving him a "pure myopathy"). Because the satellite cells were full of normal mtDNA, the researchers wondered whether exercise-induced muscle damage that stimulated satellite cell fusion might be a way to add more normal mtDNA to the mature muscle cells.

When they tried this strategy, the researchers found that "concentric" exercises, which involve shortening muscle contractions, increased the proportion of normal mtDNA in the arm muscles of the patient from 12 percent to 33.4 percent.

Despite this improvement in the muscle's genetic makeup, the man didn't experience any measurable increase in strength in the exercised arm. Shoubridge and colleagues suspect the exercise program didn't last long enough to yield any noticeable increases in strength.

This type of therapy would only apply to those people who have normal satellite cell DNA and mutated muscle cell mtDNA. The technique wouldn't correct problems that occur in organs other than muscle.

RESOURCES

- For more information about the DCA trial in Florida, contact Leigh Ann Perkins at (352) 392-2321; Web site: cla-dca.gcrc.ufl.edu/cla-dca/physinfo.html; e-mail: perkila@medicine.ufl.edu.
- For more about the DCA trial in California, contact Jean Stewart at (800) 353-4447; e-mail: alongenecker@ucsd.edu.
- For more on the DCA trial in New York, patient inquiries may be directed to Clara Leon at (212) 305-6834 and professional or institutional inquiries to Alice Kwan at (212) 305-5388. The Columbia group is also interested in hearing from people with MELAS due to the A3243G mutation or people with MERFF due to the A8344G mutation for a natural history study designed to yield information on disease progression and severity.
- For more on mitochondrial encephalomyopathies, see "Mitochondrial Myopathy: An Energy Crisis in the Cells" in Quest, vol. 6, no. 4.
- For more about creatine, see "Research Updates" in Quest, vol. 6, no. 2, and "Creatine: Frequently Asked Questions."
- For more about carnitine and coenzyme Q10, see "Carnitine and CoQ10: Miracle Cures or Money Down the Drain?" in Quest, vol. 6, no. 1.
- For more about heart problems, see "The Heart Is a Muscle, Too, Part 1" in Quest, vol. 6, no. 2 and "The Heart Is a Muscle, Too, Part 2" in Quest, vol. 6, no. 3.

To read Parts 1 and 2 in their entirety by Sharon Hesterlee, please visit the MDA web site at http://mdausa.org/publications/Quest/q64mito.html or you may call the UMDF office for other contact information.

UMDF's newsletter volunteers - gracious friends of the Mohan Family offer their services every issue to fold the Mitochondrial News for our members.

Thank You Ladies!

Looking for a Physician who Manages other Mito Patients?

In the past issues of the Mitochondrial News, the UMDF asked its membership to provide names of doctors who manage Mito patients. For all those members who submitted doctor names, thank you! Once a member provided a physician name, we requested (from the physician's office) permission to release the doctor's name and contact information for print in the UMDF newsletter. However, for many of the submitted names, the physician's office did not respond. As a foundation, we cannot make referrals or recommendations, but we know it is difficult to find doctors who treat other mitochondrial patients.

The doctor referrals listed in the Summer 2000 issue were submitted by our membership and the physicians gave UMDF permission to release this information. Please help us broaden our list of physician names for the benefit of all those affected by mitochondrial disease.

If you are pleased with your physician(s), please take a few moments to fill out this form, and send it in ASAP so that we may publish results in the next issue. To expedite the process, please ask your physician to complete Part B of this form and then fax or mail the form back to our office at your earliest convenience. The UMDF fax number is 412-793-6477.
Thank you.

Part A (to be completed by the UMDF member)

Name of Physician _____

Your Name _____

Your Phone Number (____) _____

Mito Patient's diagnosis and age _____

(If you wish to remain anonymous, please complete the information below and we will contact the physician's office).

Part B (to be completed by the Physician's office)

Institution (if any) _____

Address _____

City _____ State _____ Zip _____

Phone (____) _____ Fax (____) _____ Email _____

Specialty _____

Pediatric ☐ Adult ☐ Both ☐

Please indicate the following:

☐ Yes, I give my permission to print my name, address and phone numbers as listed above in an upcoming issue of the Mitochondrial News.

☐ No, I do not give my permission to print my information in the newsletter.

☐ No, I do not give my permission to publish my information in the newsletter but the UMDF office staff may provide the information on an as needed basis to members.

Please sign and date:

_____ _____

Physician Signature Date

UMDF Redefining Hope
UNITED MITOCHONDRIAL DISEASE FOUNDATION

UMDF Chapter Activities on the Rise

Arizona Chapter

The Arizona Chapter held its first annual Mitoween Party and Karen Lipps, chapter president, said everyone had a Boo-rific time.

The Desert Angels, a support group affiliated with the Arizona Chapter and led by Cathleen Kane, started a fundraiser through Albertson's Supermarkets. The local grocery chain has a Community Partner's Program and ID cards were provided to anyone interested in participating. The clerk scans the card and Albertson's contributes a portion of the bill to UMDF. The more you spend, the higher the percentage that goes to UMDF. Let the shopping begin!

UMDF also received $475 from friends and family of Linda McGeorge of Tucson in honor of her birthday, the Desert Angels and the Arizona Chapter. Happy Birthday Linda and thank you for your continued support.

New Mexico - New Chapter!

This is a UMDF's newest chapter, with Laura Owen leading the way. They held their first fundraiser, Trot for Tots Walkathon, in conjunction with the Tyler for Life Foundation and raised over $800. Laura's group will have a booth at an upcoming Health Fair on January 26-28 at the New Mexico State Fairgrounds.

For any members interested in starting a chapter but discouraged in the number of UMDF members in your area, please don't give up. Laura is proof that if there is a will, there is a way. Laura moved to New Mexico in June of 2000 and UMDF only had four members registered with the national office. After many hours of contacting local hospitals and doctor offices (as well as other organizations), Laura has now increased the numbers in New Mexico to 25. Well done Laura - keep up the good work!!!

Ohio Chapter

UMDF's first official chapter is busy selling sweatshirts to raise money and awareness. If you did not receive information about the sweatshirts (sent with the dues mailing), please contact Jennifer at 330-929-4430 or via email at ohiomitoinfo@yahoo.com.

Southern California Chapter

Sharon Shaw, chapter president, has been keeping her group busy. The chapter held their first official fundraiser for UMDF and, to date, raised over $3,500. Chapter members sent out letters to raise money and awareness and distributed plastic "piggies" for people to put loose change in. On November 18, at a Pizza Party, the chapter members brought in their collections and celebrated the outcome of the fundraiser.

Seventy people attended the "Pennies for Piggies" Pizza Party.

Mark Fleming, chapter member and UMDF Trustee, and Sharon Shaw have been working diligently preparing for the San Diego Conference. And yet, they took the time to work on the "Piggies" fundraiser. UMDF is fortunate to have such dedication from its members and Mark and Sharon are definitely no exception. Thanks!

Wisconsin Chapter

Sue Hendrickson, a friend of chapter officer Pam Dobke, decided to particpate in the LaSalle Bank Chicago Marathon in honor of Pam and Dave's 18 month old daughter, Brianna. Sue raised over $3,600 on behalf of UMDF. Thanks Sue!

Delaware Chapter

Chapter members gathered at the Forest Jam 2000

Delaware Valley has been busy as usual. In July, the Forest Jam 2000 raised $5,308.03 and in October, the You Go Girl Golf Outing brought in over $8,000.

From Left to Right, Tim Shelly, Maripat Shelly (Chapter president), Kathy Delvacchio, Connie Lowney (chapter member) and Lisa Polsky (chapter member) enjoy the You Go Girl Golf Outing.

On November 11 the New Jersey members of the Delaware chapter including (L to R) Maria Chuisano, Ken Hirsch, M.D., and Laurel Smith held a benefit dinner and raised over $9,500.

New England Chapter

People are running all over New England and bringing in the money for UMDF.

First Event

In keeping with their tradition of helping people in the community, the Foxboro Jaycees joined forces with friends and family of 3 1/2 year old Kacey Gaffey to support UMDF's mission, fund research and raise awareness so that children like Kacey may some day have a fighting chance. The September 30th run raised over $10,000 and the chapter actively participated during the event.

Second Event

Renee and Steven Wojciechowski held their first Mito-What? 5K Road Race in honor of their daughter Hayley and raised over $7,600. The race took place on October 14 in South Kingstown, Rhode Island and the Wojciechowskis plan to make this an annual event.

Hayley modeling the race t-shirt.

Third Event

With the help of A. W. Hastings Co. & Inc., Jackie and John Tyler, parents of Emily Tyler, organized their first Mito-What? on October 22 and raised $12,000.00 for the New England Chapter. The race was held in Enfield, CT and we hope to see this as an annual event - how about Jackie and John?

The New England members of UMDF are focused on reaching out to their communities and raising the dollars necessary to pave the path to a cure. Keep up the excellent work.

New Deadline for the Delaware Valley Recipe Cookbook is January 15, 2001.

The chapter is still collecting recipes and would like to have 500 before going to print. Please send in your recipes ASAP.

If you need a form or would like more information, call Maripat Shelly at 215-256-0273 or email Maripat at delvalumdf@aol.com.

UMDF Chapters

Chapters also serve as Support Groups for Members

Arizona Chapter

Contact: Karen Lipps
Email: azchapter@earthlink.net
Phoenix, AZ

Delaware Valley Chapter

Contacts: Maripat Shelly
Email: delvalumdf@aol.com
Philadelphia, PA

New England Chapter

Contact: Bill Shea
Email: bshea@oceanspray.com
Boston, MA

New Mexico Chapter

Contact: Laura Owen
Email: Abqowen@qwest.net
Albuquerque, NM

NY Metro Chapter

(Newly Forming)
Contact: Joe Rice
Email: umdfnymetro@aol.com
Long Island, NY

Ohio Chapter

Contact: Jennifer Lyman
Email: ohiomitoinfo@yahoo.com
Cuyahoga Falls, Ohio
(Cleveland area)

Southern California Chapter

Contact: Sharon Shaw
Emails: shshaw@aol.com
Orange, CA (Los Angeles area)

Wisconsin Chapter

Contact: Anne Juhlmann
Email: juhlmann@execpc.com
Milwaukee, WI

Support Groups

Desert Angels

(affiliated with the Arizona Chapter)
Cathleen Kane or John Sheedy
Phone: 480-807-8271 (Kane)
jsheedy@aol.com
Phoenix, AZ

Atlanta Area Support Group

Contact: Fair Franklin
Email: lancefair@mindspring.com
Atlanta, GA

Australia Support Group

Contact: Tara Collyer
Email: tarac@powerup.com.au
Kingston, Queensland, Australia

Tri State Mitochondrial Support Group

Contact: Andrea Gropman, M.D.
Email: agropman@nhgri.nih.gov
Bethesda, MD

New York, Northern area

(newly forming)
Contact: Angela Geising
Email: annjelyca@hotmail.com
Buffalo, NY

New York, Southern area

Contact: Beth DeArce
Email: drc@infomine.net
New Paltz, NY

The group held their first meeting on November 4 and will meet again on April 21, 2001, 1pm to 3pm, at the State University of New York at New Paltz (van den Berg Learning Center, Room 106). Due to the San Diego symposium and the holidays, they postponed holding more meetings until April 21.

Central Ohio Support Group

Contact: Shawna Steele
Email: ssteele817@juno.com
Columbus, OH

New Groups are trying to form in Illinois, Minnesota, Virginia, Northern Florida, Texas and the Kansas City area.

Anyone interested in these areas or wish to start a group in another area, please call us at 412-793-8077.

Left to Right - UMDF Members Tom Shubeck and Caroline Shubeck, Angela and David Nunno, Gina and Jim Dudgeon and Pat and Joe Rice.

The Nunno and Rice families have successfully held fundraisers for UMDF and we thank them for their continued support. The Dudgeons are also planning a fundraiser for May of 2001. *Outstanding!*

New Fundraisers are Popping Up Everywhere

The UMDF Board of Trustees, and the national office, continue to be amazed by the drive and enthusiasm of its members. The UMDF office receives calls such as "I want to do a fundraiser"; "What can I do to raise money?"; "I've already set a date for a dinner, what next?" and then the office staff does its very best to provide materials, guidance or whatever else the caller may need. There are no words that can express how much we appreciate all of the fundraising efforts of our members. We cannot provide support to our families or award grants to the growing numbers of mitochondrial researcher projects without such efforts. Although these words do not seem to be enough - we truly thank you!

Pictured at the First Annual Ohio Golf Outing are Chuck Mohan, Norma Markowitz and Stan Davis with a check for $50,000.00.

First Annual UMDF Golf Outing in Ohio Raises $50,000.00

Stan Davis, grandfather of Carly Platt and newly appointed UMDF Trustee, started planning his golf outing in November of 1999 and after the event on August 21, 2000, he pleasantly surprised Mr. Mohan with a check totalling $50,000 - the largest fundraising effort yet!!!! Norma Markowitz, grandmother of Jordan and Arielle Cohen and Hannah and Emma Bruder, was happy to volunteer her gift of raising funds for the outing. A big thanks to Stan, his committee and all who supported the event through contributions or participation.

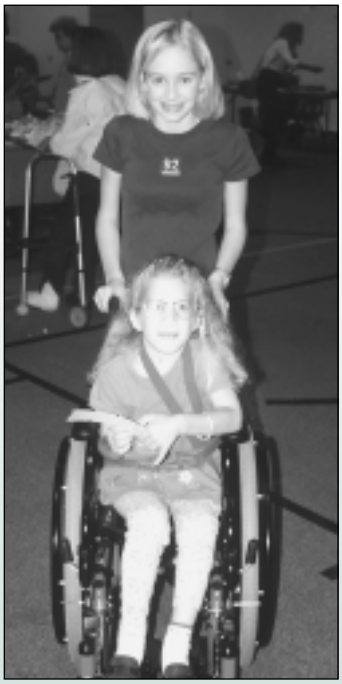
Stan has generously offered to help others interested in organizing a golf outing. If you would like to speak with Stan, please contact the national office at 412-793-8077.

Holiday Card 2000

Just a note to thank everyone who is participating in the Holiday Card Project this year. And a big thank you to Kaylee Owen who provided the beautiful artwork for this year's card. We really appreciate your help! If you are interested in receiving more cards or have questions regarding the Holiday Card Project, please call the UMDF office at 412-793-8077.

Some Simple Ways to Raise Money and Awareness

- Chuck Mohan, UMDF Chairman, raised close to $4,000 at a 50th birthday celebration for this wife, Adrienne.
- In Seekonk, Massachusetts, the George R. Martin Elementary School raised $145 during its monthly "Dress Down Days" fundraiser. Particpants paid $5 to dress down on Fridays (a different charity is selected each month).
- Anne Dixon sent a donation of $25 with the following note: "This donation was collected by a group of children operating a lemonade stand on a neighborhood street corner. The children, ages 4 to 11, sold lemonade on three afternoons on behalf of UMDF in honor of Christopher Timothy Dixon. The children donated their entire earning."
- Concert held in memory of Tyler Grey Robinson raised $600 for UMDF.



It's a Carnival!

On November 11th, Chris, Karis, Alyssa and Andrew Mott, organized a carnival and raised over $5,500 at the Lake Murray Presbyterian Church in Chapin, SC.

Alyssa enjoying the carnival with friend and babysitter, Lacy Lee.

The Billy Hacket Open

The Billy Hacket Open was held August 5th in Ballston Spa, NY - This is an Annual Golf Tournament and the organizers chose UMDF as its charity and raised $900 in memory of Kayla Elizabeth Naughton. Pictured are family & friends of Kayla and sponsors for the event.

The Nunnos Tackle Two Benefit Dinners

David and Angela Nunno were successful once again this year but instead of hosting one benefit dinner, they held two dinners and raised over $28,000 in honor of their sons, Nicholas and Brendan. The Nunnos worked extremely hard to make the dinners special and all who attended walked away with a new appreciation for the needs of all those affected by mitochondrial disease. We look forward to working with Angela and David in 2001 - thank you both for your continued support!

Incredible Journey to Redefine Hope

On October 7, 2001, the Scrivener Family, of the United Kingdom, is bringing a 1936 Vintage Talbot Car across the Atlantic Ocean to take an incredible journey across the United States - from New York to California. To honor the memory of their son, Angus, the Scriveners will seek sponsorships and/or donations for the Journey. The Talbot will stop in various cities and towns (where UMDF families are large in numbers) to raise awareness and funds for research.

If anyone is interested in helping the Scriveners promote the Journey or if you have questions about their route, please contact the UMDF office at 412-793-8077.

Friends of Matthew Benefit Dinner

The Abatos hosted their first benefit dinner in honor of their son, five year old Matthew, on September 30th and found it very rewarding - And raised $4,668! A local company may match that amount which would take their total over the $9,000 mark! “Jeff and I couldn’t have been happier with the support we received from our family and friends. Word spread fast and we were getting letters and donations from people we had never met. . . . Friends have been approaching us about our next fundraiser . . . Matthew had everyone in tears when he thanked them all for coming. He won everyone’s hearts.” - Diana Abato, Matthew’s Mother

Safari Dinner

Marjorie and John McLellan held a Safari Dinner Party in memory of their grandson, Angus McLellan Scrivener and raised $1,056. Fifty neighbors joined together for the dinner party, each paying a set price. Five houses each hosted ten people per course with each person moving on to a different house for the next course. By the end of the evening, all fifty people had eaten together and had a thoroughly good time. We recommend this as a very enjoyable way to raise money for this worthwhile cause.

Golf Tournament in South Carolina for McKinsi Thompson

On July 29, 2000, friends, family and complete strangers gathered at the Clarendon County Golf and Country Club in Manning, South Carolina and raised $3,000 in honor of five year old McKinsi Faye Thompson. Kinsi’s mother, Jami and her grandparents, Mr. & Mrs. Goehring, organized the event and hope to make it an annual event to benefit UMDF. The Thompson family wishes “to thank everyone who made the tournament possible and would also like to extend a sincere and loving thanks to all who are affected by these types of disorders for their never-ending encouragement, hope and faith. May God bless each and everyone of you.” - Jami & McKinsi Thompson.

UMDF MEMBERSHIP AND DONATION FORM

UNITED MITOCHONDRIAL DISEASE FOUNDATION

☐ Enclosed are my $35 Annual Membership Dues (Outside U. S. $50 in U. S. Currency)
☐ Enclosed is my gift of $ _____ to UMDF to help sustain research and family support.
☐ Donors of $40 or more wishing to receive a complimentary issue of Mitochondrial News.
☐ Change of address

MEMBER / DONOR

Name _____

Address _____

City _____ State _____ Zip _____

Phone: Home _____ Work _____ FAX _____

Email Address _____

PLEASE CHECK

☐ Patient ☐ Spouse
☐ Parent
☐ Relative
☐ Friend / Teacher / Other
☐ Medical Professional
Specialty _____
☐ Professional Organization
Name _____

Affected adult(s) / child / children's name and date of birth:

_____
_____
_____
_____
_____

MAKE CHECKS PAYABLE TO: U.M.D.F.

UMDF is a 501(c)(3) Organization.
Gifts are tax-deductible according to IRS regulations.

UMDF can now accept MAC and VISA credit card charges for donations and dues. Fax or mail the following information to UMDF: credit card number, expiration date, names as listed on the card and signature.

Mail membership, donations and address changes to:
UMDF
P.O. Box 1151
Monroeville, PA 15146-1151

UMDF MEMBERSHIP RELEASE FORM

UNITED MITOCHONDRIAL DISEASE FOUNDATION

Name _____

Address _____

City _____ State _____ Zip _____

Phone _____ FAX _____

Email Address _____

GENERAL RELEASE

Please ☐ DO ☐ DO NOT provide my name and address to other members in my area.

☐ DO ☐ DO NOT include my phone number.

☐ DO ☐ DO NOT include my email address.

Signature _____ Date _____

☐ Yes, I want to Network!

I will complete this form and send to UMDF.

Please give me the apppropriate from to receive network information from the UMDF Patient Registry.

By signing the undersigned Release, the signator authorizes the release of name, addresses and/or phone numbers to be provided to other UMDF members.

If a physician or scientist requests names and addresses, the member will be contacted and given the doctor's name. Under no circumstances will any member's name be released to anyone but another member, and only if you have approved such release by indicating above. UMDF assumes no responsibility for the protection of the data except as described specifically in this release. At anytime, you may revoke your approval by delivering a written request to UMDF. Confidentiality is of utmost importance to UMDF and is essential to encourage networking among members.

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In This Issue:

Mitochondrial Medicine 2001 Conference

March 2-4, 2001

San Diego, California

The UMDF is pursuing new avenues to support mitochondrial research.
An effort has been underway for the past five months to expand mitochondrial research.
At the 2001 conference in San Diego, we will talk about the initiatives
during the interactive discussion on Saturday, March 3. We hope you can join us.
For more information about the interactive discussion, please contact
Mark Fleming at 412-795-8077 or email at mflemi@earthlink.net