United Mitochondrial Disease Foundation

MITOCHONDRIAL NEWS

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Nutritional, Pharmacological and Exercise Treatment Strategies for Mitochondrial Disorders

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Introduction

Dysfunction of the mitochondria leads to a reduced ability to generate adenosine triphosphate (ATP) from fats, proteins and carbohydrates. ATP is the energy "currency" of cells and must be constantly regenerated through two main biochemical systems:

1. The anaerobic (without oxygen) system is relatively inefficient with energy coming from three sources; adenylate kinase/myoadenylate deaminase, phosphocreatine/creatine, and anaerobic glycolysis /glycogenolysis (in order of ATP-generating capacity).
2. The aerobic (with oxygen) system is ~15 to 20 times more effective at generating ATP from fat, protein and carbohydrates and is dependent on the availability of oxygen and the mitochondria.

The cells are very similar to a car in that they require a properly functioning engine (mitochondria), oxygen, and a fuel source (gasoline for cars and fat, protein, and carbohydrates for mitochondria). When an engine is not functioning properly it does not provide optimal power and generates smoke due to incomplete combustion of fuel. Likewise, when the mitochondria do not work properly, less energy is derived and lactic acid and free radicals are produced in excess (smoke equivalent). In summary, a dysfunctional mitochondrion results in low energy output, increased oxidative stress (free radical production), increased use of alternative energy sources (phosphocreatine and anaerobic glycolysis) and the production of products of incomplete combustion (lactate) (Table 1, see page 8). The cell attempts to compensate for the defects by increasing the total number of mitochondria, anti-

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Mark your calendars NOW!!
Mitochondrial Medicine 2004
Streams of Energy

Scientific Sessions: August 4-7, 2004
Family Sessions: August 6-8, 2004
Clinician Sessions: August 7, 2004
Standards Workshop:
August 7, 2004
Westin Hotel-Convention Center,
Pittsburgh, PA

Sneak Preview of Program on Page 14

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.

Responder for this issue: David Thorburn, Ph.D., Royal Children's Hospital, Melbourne, Australia

The Question Is:

I am curious as to what your explanation would be for a patient that has had two fresh muscle biopsies in known mitochondrial labs, and one showed defects in all complexes (although no known mutation was found), and the other showing completely normal. This is a patient with severe developmental delay, seizures, GI issues, etc. One lab claimed there might have been mishandling of the lab and the other claimed their lab was correct. Can a patient of mito have no defects shown if they have mitochondrial disease? In the positive lab, the complex one level was 0. In the negative lab the complex 1 level was high. This seems confusing to me and leaves me wondering where to go.

Response From: David Thorburn, Ph.D.

It is clearly very frustrating to get results from two different labs that appear to be in total disagreement. Unfortunately, this is not the first time I have been asked about such an occurrence and without seeing the lab reports and having a detailed knowledge of the labs and methods used it is impossible to determine which lab is correct, or (at least in theory) if both may be correct. Your best option is probably to ask an independent lab expert whether they will look at the clinical story and both lab reports and see if they can give an opinion.

In general there are several possible reasons for discrepant results of respiratory chain enzyme assays. Some possibilities are:

1) Real biological variation. If the patient does have a mitochondrial DNA mutation, it is theoretically possible that two biopsies obtained from different muscle sites or at different times could have a large difference in heteroplasmic load. For example, in one the proportion of mutant DNA might be above the threshold needed to cause an enzyme defect and in the other there could be enough healthy DNA to maintain normal activity.

2) Methodological variation. Different labs often use very different methods to do their assays. For example, we measure complex I directly using the "NADH-CoQ1 reductase" assay. This assay uses an electron acceptor (CoQ1) that is more water soluble than the natural electron acceptor (CoQ10). Some labs use a different assay, "NADH-cytochrome c reductase", which measures both complex I and complex III together using the natural electron acceptor (CoQ10) present in the muscle biopsy itself. There are advantages and disadvantages to both assays. We feel our assay is more robust and less prone to artifactual low activity, particularly in frozen biopsies, if the sample handling has not been optimal. However, since it uses an artificial electron acceptor, it is theoretically possible it could give normal activity for an abnormality that affects binding of just the natural electron acceptor.

3) Artifacts caused by improper sample processing or inexperience in testing pathological biopsies. One has to be alert to problems with sample processing leading to aberrant decreases in enzyme activity. An experienced lab tends to know the patterns of enzyme activity that suggest this may have occurred. For example, we are always somewhat wary of samples that show low activity of complex II or of all complexes. Although such results can be real, they may be more likely to be an artifact, and should prompt reconsideration of whether there could have been a problem.

4) Human error. Although diagnostic labs have stringent procedures to minimize the risk of mistakes being made it is unlikely that any system can be 100% fool-proof. Even with really good staff this has to happen occasionally, eg. when someone is interrupted at a crucial stage and perhaps leaves out a reagent (giving a false positive enzyme defect) or mixes up samples (potentially giving a false positive or negative enzyme defect). Most labs try to be alert to this, for example by doing replicates in different runs, always having a normal control, keeping leftover sample (in case an assay needs to be repeated &/or confirm it is from the expected patient using a forensic kit). But often there is not enough sample to repeat assays. So one might expect human error to contribute to an incorrect result, but probably in less than 1% of samples tested in a lab with proper pathology accreditation.

So unfortunately I haven't been able to give you a very satisfactory answer. Mitochondrial enzyme diagnosis is a highly specialized area. The enzyme assays require considerable expertise to perform reliably and false positive and false negative results are both a concern. My impression is that false positives are a worse problem in labs without a major diagnostic and research emphasis on mitochondrial disorders, since such labs tend not to gain the experience of obtaining enzyme results on large numbers of patients also found to have nuclear or mitochondrial DNA mutations. It could be argued that false negative results occur in all labs, since the available methods don't allow us to recognize every type of mitochondrial problem. Our attitude is that it is very difficult to absolutely exclude a mitochondrial disorder and we like to use diagnostic criteria that emphasize the need to obtain strong evidence from at least two independent sources (eg. clinical, enzyme, pathology, DNA, metabolic) for a definite diagnosis.

Chairman's Report

Lance Armstrong, 4 time winner of the Tour De France, in his book, *It's Not About the Bike* writes;

"A man is caught in a flood, and as the water rises he climbs to the roof of his house and waits to be rescued. A guy in a motorboat comes by, and he says, 'Hop in, I'll save you.' 'No, thanks,' the man on the rooftop says. 'My Lord will save me.' But the floodwaters keep rising. A few minutes later, a rescue plane flies overhead and the pilot drops a line. 'No, thanks,' the man on the rooftop says. 'My Lord will save me.' But the floodwaters rise even higher, and finally, they overflow the roof and the man drowns.

When he gets to heaven he confronts God. 'My Lord, why didn't you save me?' he implores.

'You idiot,' God says. 'I sent you a boat; I sent you a plane.'

I think in a way we are like the guy on the rooftop. Things take place; there is a confluence of events and circumstances, and we can't always know their purpose, or even if there is one. But we can take responsibility for ourselves and be brave.

Pain is temporary. It may last a minute, or an hour, or a day, or a year, but eventually it will subside and something else will take its place. If I quit, however, it lasts forever.

In my most painful moments on the bike, I am at my most curious, and I wonder each and every time how I will respond. Will I discover my innermost weakness, or will I seek out my innermost strength?"

What an insight into life's problems! Do we face our demons and fight or do we bury our heads, cross our fingers and hope? Do we say, "There's nothing I can do," or do we search for the things we can do?

UMDF helps our members re-define hope with one motto in mind; empower the parent and patient! We try to convince our members to search and discover their innermost strength.

We can't all go to medical school to become doctors or PhDs dedicating ourselves to mitochondrial medicine and research but we can promote and support those who have. We can solicit and guide existing research into the fields of mitochondrial disorders.

Every member and donor of the UMDF wants to see a cure for mitochondrial disease. That requires research, which requires funding. That funding comes from UMDF supporters, many of whom are on a tight budget.

However, there is another source for funding mitochondrial research--our taxes. No, we can't tell the government how to spend our money. But we can move from passive philanthropy-in which we hope the government will spend our money on the cause we care about-to active philanthropy-in which we direct the funds ourselves.

What's more, active philanthropy can yield tax savings and advantages that can actually help your finances at the same time.

Helping yourself at the same time you're helping us… this proposition is the core of a new fund-raising initiative being undertaken by UMDF, called *Taking Control*. With the help of

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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.

Chapter Activities

KANSAS CITY CHAPTER

Kansas City, MO
President: Heidi Harmon
Phone: 816-554-8530
Email: KCChapter@umdf.org

SAVE the DATE!

1st Annual 5K Mito-What? Race

Saturday, June 26, 2004
Contact Heidi for more information.

NEW ENGLAND CHAPTER

Boston, MA
Phone: 412-793-8077
Email: NEngChapter@umdf.org

Changes in Store for Chapter

Justine Fargo, the New England Chapter president, recently resigned to devote more time to her daughter. Several members have offered their services to keep the chapter alive and well. These wonderful individuals will work with Bridget Willis, chapter secretary, and the national office to build a new leadership team!

If you are interested in joining this team, please contact UMDF.

ARIZONA CHAPTER

Phoenix, AZ
Interim Leaders: Sharon Shaw, Thom Montgomery and Jane Shumaker
Phone: 480-563-8562
Email: AZChapter@umdf.org

The Arizona Chapter is in the process of reorganizing. Sharon Shaw, Thom Montgomery and Jane Shumaker have graciously accepted interim leadership positions as the chapter rebuilds -- please join your interim leaders and help strengthen this wonderful chapter!

Thank You

- $100 was raised during the Glass Family Reunion.
- Potluck Dinner for Ashton Anderson raises $1,010 - Special Thanks to the Holy Trinity Greek Orthodox Church for supporting the Anderson Family and the Arizona Chapter of UMDF.
- $123.32 was raised during the Tryon Family Yard Sale in honor of Paisley Flitsch.

Mark your calendars for April 24th - Dr. Bruce Cohen to speak at chapter meeting. Details will be posted on www.umdf.org (AZ Chapter Page) and a notice will be mailed to all chapter members!

NEW YORK METRO CHAPTER

Manhattan, NY
President: Tom Shubeck
Phone: 973-635-6354
Email:NYMetroChapter@umdf.org

Upcoming Events:

- Annual Matthew Dudgeon Walk and Dinner Dance -- May 8, 2004
- Mito-What? Walk in North Haven, CT -- May 15, 2004
- The Annual Nunno Dinner -- Friday, October 22, 2004

The chapter raised $260 during a recent Denim Day!

Dear Nicholas Nunno,

Please accept our apologies for putting Brendan's name in the last issue of Mitochondrial News instead of your name. Since you are both such GREAT kids, we asked your mom for a family picture so we could see you all together.

What an awesome family!

SOUTHERN CALIFORNIA CHAPTER

Lakewood, CA
President: Christine Trojahn
Phone: 562-438-5883
Email: SCalChapter@umdf.org

Upcoming Events

- Wine Tasting and Silent Auction on May 1, 2004
- Bowl-a-thon in Fall of 2004

More information will be available on these and other events in future issues of *Mitochondrial News* and via the chapter web site at www.umdf.org (UMDF Services/Chapters & Groups).

Chapter Activities

OHIO CHAPTER

Cleveland, OH
President: Jennifer Lyman
Phone: 330-929-4430
Email: OHChapter@umdf.org

Mark Your Calendars!

3rd Annual KFC/UMDF 5K Run/Walk
Saturday, June 12, 2004
Forest Hills Park
Cleveland Heights, Ohio
Visit www.umdfohio.org

Correction and Continued Thanks!!

Jeff Gallop (not Galloway as noted incorrectly in the last newsletter) raised a total of $10,200 to benefit UMDF -- in honor of his little buddy Cooper Adelstein.

Pictured above is Ned, Jeff and Jack Gallop celebrating Dad's victory.

First Annual Family Spaghetti Dinner is a Delicious Success!

The Arnold & Keeney Families hosted a family spaghetti dinner in Honor of Maiya Keeney and the many individuals affected by mitochondrial disease on January 10, 2004. The dinner raised $11,058. Excellent!

INDIANA CHAPTER

Indianapolis, IN
President: Sue Ann Bube
Phone: 317-894-9099
Email: INChapter@umdf.org

Pack the House Night

The Indiana Chapter families participated in the annual "Pack the House Night" for the Indianapolis ice hockey team.

The chapter received $5 from each ticket bought and totals will be printed in the next issue.

☆UMDF'S NEWEST STARS!☆

Indiana Officially Becomes a Chapter!

Please join us in welcoming our newest chapter and their officers: *Sue Ann Bube - President; Bob Thomas - Vice President; Chris Gaughan - Treasurer; Amy Glass - Secretary; and Celanie Christensen - Medical Advisor*.

DELAWARE VALLEY CHAPTER

Philadelphia, PA
President: Maripat Shelly
Phone: 215-256-0273
Email: DelValChapter@umdf.org

NEWEST ***RAVE*** *Award Winner:*
Kevin Shelly
Kevin is a magician and donates his talents to numerous chapter activities. He also donates his services as raffle prizes for many of the chapter fundraisers.

Mark your Calendar - Lots of FUN for ALL

- 5th Annual Shelly's Heroes 5K Run/1 Mile Walk -- Saturday, May 1, 2004 at St. Maria Goretti Church. Visit www.shellysheroes.org for more information.
- 1st Annual Brew at the Zoo -- Saturday, June 19, 2004 from 5:30pm-9:30pm at the Elmwood Park Zoo, Norristown, PA. Attendees will pay $35 per person and enjoy door prizes, food, beer samples and a souvenir cup. Tickets may be purchased by credit card by calling the UMDF National Office at 412-793-8077 or by sending checks made payable to DelVal UMDF to: DelVal UMDF-Brew, 211 Alderfer Rd., Harleysville, PA.

Challenging Financial Myths and Clichés

By Nick Nicholson

Death and Taxes:

"The only two things certain in life are death and taxes" -- the two things you just can't avoid. That's the cliché, and like most such sayings there is an element of truth in it. Certainly these two "eventualities" constantly confront, challenge and battle members of UMDF daily.

Death is perhaps the ultimate price exacted by mitochondrial disease, and taxes. Taxes are the two edged sword decreasing net income desperately needed to care for a stricken family member, and at the same time, a potential source of funding for the research needed to fight and defeat the disease. If only the "powers that be" would allocate enough of our hard-earned tax dollars toward our problems.

The larger truth is, however, that death and taxes are two things we can work to limit and control, to avoid, if we just commit to doing so. And committing to that effort is at the heart of a new initiative being undertaken at UMDF, *Taking Control*.

In a nutshell, this is an effort, a drive, by which you can control that portion of your hard-earned income otherwise sent to Washington as tax dollars, and direct them to a specific use - mitochondria research, education and support - while at the same time, potentially improving your own bottom line.

The tools to accomplish this dual initiative exist today, fully sanctioned and endorsed by Congress and the IRS for the public good, and available to each of us. Available to each of us, but like various tax deductions and credits, granted only if we elect to use them. The program we are launching today is designed to provide you with the tools, the vehicles and the assistance you need to *Take Control*.

Charity Begins At Home:

We should begin with the observation that there are two forms of philanthropy -- active and passive philanthropy.

Passive, or involuntary philanthropy takes the form of taxation. Simply put, we passively allow a portion of our gross income, the tax portion, to be collected and sent to Washington, where we allow others to determine exactly where these dollars will be spent for the public good -- so much for new roads, for medical research, for foreign aid, the arts, for a mission to Mars, and seemingly the inevitable, for Congressional porkbarrels.

Active or voluntary philanthropy is a conscious effort to choose how some of those dollars otherwise sent to Washington are spent, by directing them to a specific, approved use through a recognized charitable destination, such as mitochondrial education, research and support,

Now, your first reaction to this might be "That's all well and good, but I don't have a choice - I have to pay my taxes, and I can't afford to give more than I do now. I'm not wealthy enough for 'Philanthropy'."

That is a myth, and finally, that is the bottom line we're here to discuss. You do have a choice, and it's not just via donations and cash-out-of-pocket. Charity begins at home… your home and ours!

In many cases, you can, in large measure, choose who gets a share of those dollars, and you can improve your own bottom line at the same time! Imagine, not only benefiting mitochondrial research without taking money out of your pocket and away from your family, but instead materially benefiting your family!

You may have thought "I can't afford to," but you should be asking "How can I not?"

Enlightened Self-Interest

It should be obvious by now that we're talking about more than getting a deduction for a charitable donation on our tax return, much more. What might not be so obvious is that we don't really have to go out of our way to do more, to accomplish more. Most of us are already doing many of the very things that allow us to *Take Control*, but we are not choosing the benefit we need. We should, we must. And again, it's in your own best interest to do so, for your own financial bottom line.

Your involvement in our initiative can take many forms, and potentially benefit your family in many divergent ways. You may take part as a means of improving your finances… by increasing the payout generated by your retirement assets, or with an asset protection plan providing safeguards for you or your children against creditors, malpractice liability and more.

You may take part by implementing a tax planning and management strategy for highly appreciated assets, by creating an estate plan for your heirs, or by drafting a benevolent trust to pay for the care of a mitochondrial patient when you aren't here.

You can take part with active asset management of your investments, or simply by starting an individual retirement plan, even when paying alimony. You may

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Fundraisers

Candy Machines

· Candy Machines in Mohan's Restaurant, LaCava Italian Market and Dunkin Donuts have generated $311.25 in the past few months.

Energy for Life

· Capps Tavern & Eatery in Painesville, Ohio raised $728 in honor of Emily Plesko by selling lightbulb cutouts for $1.

Murder Mystery Ransom

· During a recent Murder Mystery event, an inflated Pink Flamingo was held for ransom. Hard to explain but anyway, $305 was donated to UMDF.

Pampered Chef Party

· The Cincinnati Support Group held a Pampered Chef fundraiser and raised $725.50 to benefit UMDF.

Holiday Gift Recycling Party

· Elizabeth and Tom Hefferon of Mclean, VA, raised $4,635.50 during their annual Holiday Gift Recycling Party. The party is centered around a silent auction of "recycled gifts" from Christmas. Keep up the great work!

National Association of Tax Professionals Conference

· Silent auction during the Eastern and Western Conferences raised a total of $982.50 in honor of Franklin Blum. Thank you Shirley Brock of St. Marys, PA.

Pictured from left to right: Stan Carter, Sandy Turi, Chuck Mohan and Tova

Wine Tasting Event Huge Success in Dallas, TX - $12,875 Raised to Benefit UMDF!

Christopher and Tova Sido held a wine tasting event on December 5th to honor the memory of their son, Charlie. Charlie lost his battle to mitochondrial disease this past summer and the Sido Family will always hold Charlie close to their hearts as they join UMDF in the quest for a cure. The Sidos have also started a support group in Dallas! Outstanding!!!

Fillmore Elementary/Haunted Gym Scares up $1,000 to Benefit UMDF

In October of 2003, proceeds from the haunted gym and a donation from the PTO were sent to UMDF in honor of Nicholas McFarland (Pictured right with Jacob McFarland). Nicholas is the grandson of Carol Whitt, a teacher at the school.

Thank you Fillmore!!!!

Tomato Face Foods™

Tomato Face Foods -- Needs YOU

In the Summer 2003 issue of the Mitochondrial News, we provided an update regarding Barbara Bruck's no fat spaghetti sauce and its availability in more than 114 stores in Indiana, Illinois, Ohio, Virginia, and Wisconsin.

The Cleveland Magazine recently ran a huge story on Barbara Bruck, her husband Allen Segal, and daughter, Dana. With every jar of sauce purchased, UMDF receives dollars for research and the term "mitochondrial disease" has reached one more person. The media coverage has been priceless in supporting the UMDF mission.

YOU can help Tomato Face Foods continue reaching thousands across the U.S. Do you know someone in your local supermarket or grocery chain? If so, please contact kara@umdf.org or 412-793-8077, ext. 106. Kara will pull all interested parties together for Barbara - Yes, team work!

2003 Cooper Mitochondrial Golf Open

In Honor of Rebecca, Julia and Monica Cooper, $6,825 was raised to benefit UMDF in Portsmouth, NH. Thank you Amy Caldicott, Deb, Ken, Rebecca, Julia and Monica Cooper for a job well done!

Nutritional, Pharmacological and Exercise Treatment Strategies for Mitochondrial Disorders

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Table 1. Consequences of Mitochondrial Dysfunction

Consequence	Marker/Measurement
↑Free radical production /oxidative stress	Urine 8-OH-2d-guanosine, malondialdehyde.
↓Aerobic energy production	Low oxygen consumption (VO_{2max}).
↑Anaerobic energy use	↑lactate, ↓ phosphocreatine content.
↑Mitochondrial proliferation	Ragged red muscle fibers.

8-OH-2d-guanosine = 8-hydroxy-2 deoxy-guanosine (a marker of oxidative DNA damage);
VO_{2max} = maximal oxygen consumption.

oxidant enzymes, and lactate transporters.

Treatment strategies attempt to ameliorate these negative consequences of mitochondrial dysfunction. The ultimate treatment for mitochondrial disorders would be to replace all the mitochondria or the specific component of the mitochondria that are not functioning properly. Currently, however, this is not possible in humans, and treatment strategies rely on optimizing the function of the mitochondria, preventing negative consequences from toxic by-products, and providing alternative sources of energy. Strategies to improve the function of the mitochondria involve: exercise training, providing compounds to bypass defective enzymes, reducing lactate, preventing free radicals damage, and the provision of alternative sources of energy (Table 2).

Considerations in Treatments for Mitochondrial Disorders

Perhaps due to the fact that mitochondrial disorders are often unrecognized and their incidence has been underestimated, there have been very few clinical trials evaluating efficacy of any intervention. Furthermore, there is often a sense that research money should be invested in "cures" and not in treatments that do not correct the underlying defect.

Consequently, funding for large scale clinical trials has been lacking. To date, many of the publications regarding the treatment of mitochondrial disorders have focused on the results of single case reports or small case series. Unlike cancer and cardiovascular disease trials where many thousands of patients are studied for long periods of time under ideal settings (i.e., randomized double blind trial where patients are assigned to a drug or placebo yet neither the patient nor the investigators are aware of the treatment allocation until the study is completed), many of the mitochondrial studies were performed with both the patient and the investigator aware of the allocation. Due to the placebo effect and unintentional biases, these smaller studies tend to provide positive results that ultimately must be confirmed with larger studies.

Although a "cure" for mitochondrial disorders may theoretically include a mitochondrial "transplant" or genetic therapy to correct the underlying defect, these therapies are a long way off. In the meantime, it is important to minimize further mitochondrial damage and to improve function at the tissue and whole body level. Although none of the non-genetic therapeutic strategies mentioned above are "curative," it is important that progressive mitochondrial and tissue structure and function are maintained until genetic therapies become a reality. For example, a complete cure of MELAS 3243 is not as valuable to a patient who has sustained a large stroke, loss of speech, and motor skills, as opposed to a person who has avoided a stroke (assuming that treatments will do so). Another factor to consider in therapies for mitochondrial treatments is that single therapies targeting only one of the final common pathways of mitochondrial dysfunction are not likely to be particularly beneficial. It is probable that the best therapy for mitochondrial disorders would be to target a number of negative consequences of mitochondrial dysfunction simultaneously *(see Tarnopolsky MA, and MF Beal. Potential for creatine and other therapies targeting cellular energy dysfunction neurological disorders. Annals of Neurology: Vol. 49, No. 5, pp. 561-574, 2001)*.

In general, this approach has been taken by many clinicians in that most patients are treated with a mitochondrial "cocktail" of supplements. The rationale behind cocktails is not too dissimilar as to how cancer is treated. For example, single agents are rarely used in the treatment of cancer and the greatest successes come when combination chemotherapies are

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Nutritional, Pharmacological and Exercise Treatment Strategies for Mitochondrial Disorders

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employed to target multiple pathways involved in carcinogenesis. Although the cocktail strategy makes sense conceptually, it is difficult in a clinical trial to know for sure which of the therapies is actually working and if all of the components of the cocktail are truly required. Furthermore, it is important to consider synergistic toxicities between two or more compounds in a cocktail and it is often difficult to sort out which component caused the problem. Fortunately, most of the components of mitochondrial cocktails are relatively benign agents. The decision to initiate therapy for mitochondrial disorders and the choice of the agents must be made on a case by case basis and with consultation from a physician with experience in the theory and practical issues related to mitochondrial therapies. The purpose of this article is to outline theoretical issues, clinical studies, and practical issues such as doses and side effects of therapies for mitochondrial disorders.

Specific Therapies for Mitochondrial Disorders

1. Alternative energy sources:

Creatine monohydrate is a substance synthesized in the human body and is found in all meats. Creatine functions as an energy buffer/alternative energy source in the cell, a weak but abundant antioxidant, and can protect against ischemic injury in the brain.

Studies: Several small clinical trials in one case report have shown that creatine supplementation can improve high intensity and aerobic exercise performance, timed exhaustion on a cycle ergometer, and some indicators of daily activity performance. We have recently shown that creatine reversed paracrystalline inclusions in the muscle of a patient with a cytochrome b mutation and that creatine improved cell survival in cultured cells made from this patient *(Tarnopolsky, M.A., Muscle and Nerve, IN PRESS, 2004)*.

Usual dose: 5 grams per day; 0.1-0.15 grams/kg/day.

2. Bypass strategies:

a) CoEnzyme Q10 is a lipid soluble molecule that facilitates the transfer of energy between complex 1 and 3 of the mitochondrial electron transport chain. CoEnzyme Q10 may also function as an antioxidant, depending on the energy status of the cell.

Studies: There have probably been more studies with CoEnzyme Q10 than any other compound with sporadic indications of decreased seizures, reduced fatigue, improvement in clinical status and various biochemical markers such as phosphocreatine recovery time and a reduction in lactate. CoEnzyme Q10 appears to be well tolerated and there is probably more experience with this compound with reasonable theoretical evidence for efficacy; however, a large scale dose escalation study is needed. One issue with CoEnzyme Q10 is that the original formulations were not very soluble and did not enter the brain and muscle; however, several formulations have "hydrosoluble" forms of CoEnzyme Q10 that appear to be better absorbed. Perhaps the most convincing evidence for the use of CoEnzyme Q10 is in patients with recently described CoEnzyme Q10 deficiency and cerebellar atrophy where high doses of CoEnzyme Q10 showed evidence of some clinical improvement.

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Table 2. Non-genetic Strategies to Improve Mitochondrial Dysfunction.

Strategy	Theoretical Basis	Examples
1. Enzyme bypass	Provide energy beyond the site of enzyme defect	Succinate, CoEnzyme Q10.
2. Anti-oxidants	Reduce free radical damage to cell structures	Vitamin E + C, a-lipoic acid.
3. Alternative energy	Use an anaerobic system not requiring mitochondria	Creatine monohydrate.
4. Reduce lactate	Reduce acidosis, more energy into the mitochondria	Dichloroacetate, thiamine.
5. Strength exercise	Improve strength, reduce number of mutant mtDNA	Weights, isometrics.
6. Endurance exercise	Improve endurance, reduce cardiovascular risks	Jogging, cycling, walking.
7. Nucleotide precursors	Prevent depletion of nucleotide pool (for DNA synthesis)	Triacetyluridine.
8. Vasodilatation	Prevent vascular spasm in MELAS stroke	L-arginine

mtDNA = mitochondrial DNA; MELAS = Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes.

Idebenone (a synthetic analogue of CoEnzyme Q10) has been studied predominately in Freidriech's ataxia where some improvement in heart function was noted with no change in neurological status. Recently, idebenone at doses as high as 360 mg three times a day, did not show any evidence of improvement in patients with Alzheimer's disease (a disease with secondary mitochondrial dysfunction).

Usual dose: Mitochondrial disease = 60 to 120 mg twice daily (3 -5 mg/kg/day in divided doses); CoEnzyme Q10 deficiency = 100 to 300 mg three times a day; Idebenone = 120 - 360 mg three times a day (5 - 15 mg/kg/d in divided doses).

b) Succinate is an energy carrier to complex 2 of the electron transport chain. Theoretically, this would be of most benefit to patients with isolated complex 1 deficiency to try to bypass this defect.

Studies/Usual Doses: There have been isolated case reports of improvement with a slow dose increase to a maximum of 6 grams daily in divided doses.

3. Precursor supplementation/ enzyme co-factor:

a) Riboflavin (Vitamin B2) can function as a flavin precursor for complex 1 and 2 and theoretically may enhance their function.

Clinical trials: A few small groups of patients have shown some clinical and biochemical improvements; however, one larger study with 16 patients did not show any benefits.

Usual Doses: 25 to 50 mg twice daily.

b) Triacylglycerol/high fat diet. The rationale behind this strategy is that much of the energy from fat can be transferred through electron transport flavo-protein to complex 2 and bypass a complex 1 deficit.

Clinical trials: Biochemical studies have shown that triglyceride infusion improved endurance and decreased lactate in patients with a complex I deficit. Uncertainties about the long term effectiveness of a high fat diet and the potential negative effects on cardiovascular disease will likely limit the effectiveness of such treatments. In young children with complex 1 deficiency and seizures that are difficult to control, a ketogenetic diet (very high in fat) may be particularly effective for the rationale presented above.

c) Thiamine (Vitamin B1) is a co-factor and activator of pyruvate dehydrogenase which is the enzyme responsible for directing pyruvate into the aerobic pathway and away from lactate production.

Clinical Trials: There have been isolated reports of some improvement in patients but a larger study in 1993 found no benefits.

Usual Doses: 100 to 300 mg three times daily.

d) Dichloroacetate is a drug that increases pyruvate dehydrogenase activity by inhibiting pyruvate dehydrogenase kinase. Consequently, more pyruvate is directed into the mitochondria and away from lactate generation. A theoretical issue with dichloroacetate (and thiamine) is that activating the pyruvate dehydrogenase complex without improving the "downstream" function of the mitochondria may make the lactate concentrations appear lower in blood but probably does little to improve the actual energy production of the mitochondria. This is analogous to placing more wet wood on a smouldering fire.

Clinical trials: There have been short term improvements in muscle and brain function; however, longer term use can cause a peripheral neuropathy. Dichloroacetate may be considered in severe cases of Leigh's disease with very high lactic acid levels or in PDH deficiency, which is associated Leigh's disease.

Usual Doses: 20 - 30 mg/kg/day (divided doses).

4. Antioxidant supplements:

Free radicals are natural by-products of aerobic energy respiration in the mitochondria and can function as signalling molecules. Defects in the electron transport chain, particularly at complex 1 and 3, lead to an excessive production of free radicals which can damage protein, DNA, and lipids, and are likely responsible for the massive mitochondrial proliferation seen in certain mitochondrial disorders. The beneficial effects from antioxidants are not likely to be realized in the short-term as these agents should prevent the gradual progressive accumulation of damage to various cellular components and only very large long term trials will likely demonstrate the clinical benefits of these medications. Given the safety of these compounds and the well-documented excessive free radical production seen in most mitochondrial disorders, there is reasonable evidence to include these in therapy.

a) Vitamin C is a water soluble vitamin with numerous functions in addition to being an antioxidant. Vitamin C alone in high doses may actually function as a pro-oxidant rather than an antioxidant and it is important to give Vitamin C and Vitamin E together in any cocktail.

Clinical Trials: There have been a few studies demonstrating some improvement with Vitamin C and a form of Vitamin K (K3); however, the use of Vitamin C on its own has not been reported, to my knowledge.

Usual Dose: 250 to 500 mg twice daily; 10-15 mg/kg/day - divided doses.

b) Vitamin E is a lipid soluble antioxidant. Vitamin E and Vitamin C work together to regenerate each other and either of these given alone is potentially counter-productive as they may function as a pro-oxidant on their own.

Clinical Trials: There are no clinical trials using Vitamin E in isolation and one case report suggested improvement in vision with high dose Vitamin E in a patient with Leber's Hereditary Optic Neuropathy.

Usual Dose: 200 to 400 IU(mg) twice daily; 10 mg/kg/day (divided doses).

C) Alpha lipoic acid is a disulfide compound present in the mitochondria which functions as a co-enzyme for pyruvate dehydrogenase and alpha keto-gluatarate dehydrogenase, and is an antioxidant.

Clinical trials: Some studies have shown reductions in markers of oxidative damage in patients with diabetes, CPEO and hypercholesterolemia. Several studies have reported improvements in diabetic neuropathy.

Usual Doses: 150 to 300 mg twice daily; 20 mg/kg/day (divided doses).

5. Miscellaneous therapies:

L-arginine is an amino acid which can cause vasodilatation. There have been a few small case reports showing improvement for stroke-like episodes in MELAS syndrome.

Nucleotide precursor production is coupled to the electron transport chain of the mitochondria. Mitochondrial dysfunction can lead to a depletion of these components. In humans, most experience has been with a compound called triacetyluridine (a lipid soluble uridine compound) which improved renal dysfunction in patients with Leigh disease.

Copper supplementation may theoretically help in a recently described defect in the gene called synthesis of cytochrome oxidase (SCO2) which results in severe complex 4 deficiency. In vitro, there was some improvement in SCO2 derived cell function with copper supplementation. Because this condition is uniformly fatal and there is not much else to offer, copper salt supplementation is probably warranted in such rare cases.

6. Exercise treatment strategies:

Essentially there are two main forms of exercise: endurance and resistance/strength. Endurance exercise in healthy individuals increases mitochondrial content, oxygen consumption, and reduces lactate production at any given exercise intensity. Resistance/strength exercise uses predominately anaerobic pathways and results in an increase in muscle size and strength.

a) Endurance exercise. The rationale behind using endurance exercise in mitochondrial disease is to increase mitochondrial capacity, oxygen consumption and to decrease secondary de-conditioning. Theoretically, increasing the number of abnormal mitochondria may not be advantageous; however, a well conducted small scale clinical trial did show improvement in work capacity, oxygen consumption, oxygen extraction by the muscle, activity of mitochondrial enzymes, reduced blood lactate levels and improved MR spectroscopy indicators of mitochondrial function. If exercise is started at a low level and very gradually increases, this appears to be well tolerated.

b) Resistance exercise: Depending on the type of mitochondrial disorders, some patients have actual weakness instead of just decreased endurance. Consequently, strength exercise may be very important. Furthermore, if strength is increased then any activity with a given absolute mass will represent a lesser percentage of the maximal strength and will be less taxing on the person. Given that strength/resistance exercise does not require aerobic metabolism, many patients can perform several of these contractions. Resistance exercise is dependent on aerobic mitochondrial function, therefore it is important for patients with mitochondrial disease to have a prolonged rest period between each exercise set to allow for ATP recovery. Theoretically, resistance exercise may cause damage to the muscle and proliferate a satellite cell (a form of stem cell in muscle) which could reduce the percentage of abnormal mitochondrial DNA (DNA shifting). This has been shown with direct damage to the muscle with various toxins and more recently with resistance exercise. In patients with mitochondrial disorders, resistance exercise can improve strength; however, the concept of DNA shifting remains to be fully explored. Again, it is very important to start at a low level and tailor the program to the base line strength of the individual and most importantly to allow for a very long

Continued on page 12

Nutritional, Pharmacological and Exercise Treatment Strategies for Mitochondrial Disorders

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recovery. (Normally the two minutes between each set should be extended to five to ten minutes between sets. A circuit set type program works best -10 arm curls, followed by 10 sit ups, followed by 10 calf raises, followed by 10 knee extensions, and then back to the arm curls with at least a minute or two between each bout of activity.)

Future/Conclusions

There are a number of synthetic compounds that are being tested that will target the mitochondria more specifically (i.e., Jauslin, et al., FASEB J, 17:1972-74, 2003). These compounds may ultimately be more effective than the relatively "non-specific" compounds that are currently in use. Ultimately, we need safe and effective treatments and the only way to attain that goal is through a tight integration between basic and clinical mitochondrial medicine.

It is difficult to suggest a uniform mitochondrial cocktail based on the evidence gathered to date. Given the safety and relative low expense, an antioxidant selection, plus creatine monohydrate and one of the bypass or precursor compounds, may be considered. Again, this needs to be tailored to the specific defect and planned out with the treating physician. In addition, exercise is very important and in our experience almost every patient will tolerate some form of physical activity. This should be completed under supervision and with the considerations given above. Before any type of exercise program is started, it is reasonable to complete baseline strength measurements. A 12 lead ECG with progressive exercise testing should be completed to screen for any potential cardiac complications and to be used as a monitor of the effectiveness of the intervention. It is our policy to use objective (blood lactate levels, oxidative stress markers in urine, VO2 max) and subjective (overall perception of efficacy, real or perceived side effects) criteria to evaluate whether a given therapy will be of benefit. In the future, it is hoped that larger scale studies will be instituted, using carefully planned mitochondrial cocktails and exercise therapies. Large numbers of patients with fairly homogeneous types of mitochondrial disorders will be required in order to provide more accurate guidelines.

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DISCLOSURE:

Dr. Tarnopolsky has received samples of creatine monohydrate and CoEnzyme Q10 and lipoic acid for clinical trials in mitochondrial cytopathies. He has received no funding from any company for any mitochondrial trials.

Dr. Tarnopolsky will be speaking at the Mitochondrial Medicine 2004 Conference in August. We look forward to meeting Dr. Tarnopolsky and all of our speakers noted on Pages 14-15. We appreciate their dedication to Mitochondrial Medicine and the UMDF Mission!

Chairman's Report

Continued from page 3

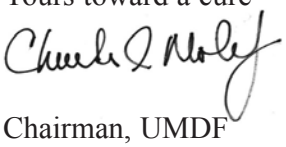
The Monteverde Group and, through them, the resources of Partners Financial, one of the nation's most highly respected financial services firms, we hope to do just that…. help you while you help us…. and substantially increase research funding in the process.

We have the tools and the vehicles. You owe it to yourself to learn just how they can benefit you, your family, and our entire UMDF family. All that is required is your willingness to be involved and to help, just as you've always done. You may already be doing something that could provide a benefit if you just knew how to structure it.

There will be future articles on specific programs, but you don't have to wait. If you'd like details specific to your individual circumstances, we're ready. Call or email us today; we'll both be glad you did.

"I am only one, but still I am one; I cannot do everything, but still I can do something;
And because I cannot do everything I will not refuse to do the something I can do."
-Edward E. Hale

Yours toward a cure



Chairman, UMDF

Challenging Financial Myths & Clichés

Continued from page 6

wish to maximize ESOP exit planning from a business, fund a grandchild's education, or just enable a gifting program to your own children and grandchildren.

We have the tools and the vehicles. You owe it to yourself to ascertain just how they can benefit you, your family, and our entire UMDF family. All that is required is your willingness to be involved and to help, just as you've always done. You may already be doing something that could provide a benefit if you just knew how to structure it.

You'll be receiving specific information and details on *Taking Control* as a regular part of this newsletter, in the mail, and in special programs and presentations. But you don't have to wait. If you have an immediate need or question, or if you'd like details specific to your individual circumstances, we're "at the ready."

Nick Nicholson is a Senior Financial Advisor with The Monteverde Group, a member of Partners Financial, and is a Registered Representative of NFP Securities, Inc. of Austin Texas. Nick is our contact person, and is spearheading the development of all components of the "Taking Control" initiative sponsored by UMDF. He has been appointed to develop, coordinate and implement the necessary planning, strategies, and financial instruments for our members. He can be reached by phone at 800.722.0098, or via e-mail at stnick@monteverdegroup.com.

UMDF Wants Your Email - Please READ This Notice

The national office recently started using a Microsoft Exchange Server and many email providers (such as AOL, Earthlink, Yahoo, etc) are viewing the umdf.org emails as spam or bulk mail. To ensure that you receive emails from our office, please add these addresses to your address book or contacts:

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rparr@umdf.org
sandy@umdf.org
scalchapter@umdf.org
toni@umdf.org

Don't Forget to Nominate the Hero in your area for the LEAP Award and/or Heartstrings Award!

Nomination forms are available via the UMDF Web Site at www.umdf.org (Activities/Current Events). Or request forms by calling Kym at 412-793-8077 or emailing kym@umdf.org.

Mito Adults Corner

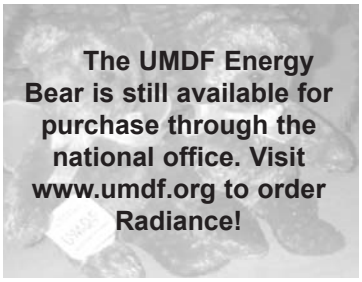
Calling all Mito Adults: The Mitochondrial News Needs YOU!

UMDF could use more helpers. Please consider joining the committee, submitting an article for review or sending us your experiences with a specific topic of interest. If you are willing to help, please email Kara Strittmatter at kara@umdf.org or call 412-793-8077, ext. 106. We look forward to hearing from you!

Fundraisers

Save these DATES:

- March 6, 2004 - Grand Night for Singing in honor of Kyle Kobunski.
- March 20, 2004 - Baylee Thompson's 1st Annual Casino Night in Roseville, OH
- April 17, 2004 - St. Louis Walk/Run in Bellville, IL. For more info, email Marsha Hohe (marshamarshamarshah@charter.net).
- April 22, 2004 - Power Up Pittsburgh with Senator Sean Logan at a special benefit reception. All proceeds will benefit Mitochondrial Medicine 2004.
- May 16, 2004 - Spring Corvette Cruise at Day Chevrolet in Monroeville, PA.
- June 6, 2004 - Skeet Shoot in Colorado Springs, CO. Contact UMDF for more information.
- June 5, 2004 - 2nd Annual Pittsburgh UMDF 5K Run and 1 Mile Walk at North Park.
- June 24, 2004 - 7th Annual Pittsburgh UMDF Golf Outing at Churchill Valley Country Club.
- July 19, 2004 - 5th Annual Ohio UMDF Golf Outing at Chagrin Valley Country Club.



United Mitochondrial Disease Foundation

Mitochondrial Medicine 2004

Streams of Energy

Mercy
MERCY HEALTH SYSTEM

Mitochondria Research Society
Mitochondrial Medicine Society

Topics & Speakers

Scientific Sessions

Wednesday, August 4

Nuclear Regulatory Pathways in Mitochondrial Biogenesis	Richard Scarpulla, Ph.D.
Molecular Mechanisms for the Repair of DNA Damage in Mammalian Mitochondria	Nadja C. de Souza Pinto, Ph.D.
hMiDas and hMitChip: New Opportunities in Human Mitochondrial Genomics and Bioinformatics	Salvatore Alesci, M.D., Ph.D.
Optical Nanosensors: Physiological Measurements in Small Spaces	Martin Philbert, Ph.D.

Thursday, August 5

Key Roles of the Mitochondrial Lon Protease in Oxidative Stress	Kelvin Davies, Ph.D.
Mitochondrial Thioredoxin: A Redox Sensor for Oxidative Stress	Dean Jones, Ph.D.
Complex III: The Proton-Pumping Cytochrome bc1 Complex	Diana Beattie, Ph.D.
Clinical Aspects of Electron Transport Chain Complex III Deficiency	Michio Hirano, M.D.
Cytochrome c Oxidase: Current Insights into Mechanism and Regulation	Shelagh Ferguson-Miller, Ph.D.
Complex I Deficiency: 14 Causative Genes and Counting	David Thorburn, Ph.D.

Friday, August 6

Analyzing Mitochondrial Function in Cell Culture Models of Neuronal Dysfunction	David Nicholls, Ph.D.
The Pathophysiology of Mitochondrial Disease	Douglas C. Wallace, Ph.D.
DCA Trials - Florida	Peter Stacpoole, Ph.D.
DCA Trials - UCSD	Richard H. Haas, MB, B.Chir
Exercise expansion of wild-type mtDNA: a therapeutic approach for mitochondrial disorders	Ronald Haller, M.D.
Nutrition and Nutraceutical Treatments in Mitochondrial Disorders	Mark Tarnopolsky, M.D., Ph.D.
Mitochondrial Disease: A Way Forward - Banquet Keynote	Anthony Linnane, Ph.D.

Clinical and Family Sessions

Saturday, August 7

Overview of Mitochondrial Medicine	Michio Hirano, M.D.
Neurology	Ron Haller, M.D.
Dysmotility and Pseudo Obstruction	Mahmoud Sabri, M.D.
Symptom Management	Bruce Cohen, M.D.
Nutrition and Exercise	Mark Tarnopolsky, M.D., Ph.D.
Pain Management	TBA

Registration Forms for the Scientific and Clinical Sessions will be Mailed in March 2004
Registration Forms for Family and Clinical will be Mailed in April 2004
Call for Abstracts will be posted soon on the UMDF Web Site at www.umdf.org

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Mitochondrial Medicine 2004: Topics & Speakers

Continued from page 14

Family Sessions

Friday, August 6

1:00	Mito Basics	John Shoffner, M.D.
2:00	Behavioral Issues and Mitochondrial Disorders	Antonio Hardan, M.D.
3:30	Research Update	UMDF Grant Recipients

Saturday, August 7 - Family

Navigating in the Mito World & Financial Issues	Bruce Molyneaux, MSW, LCSW and Denise Bergey, RN
Palliative Care: Adult & Children Issues	Denise Stahl, RN, MSN, BC-PCM
Art Therapy for Siblings and Patients	TBA
Genetics of Mitochondrial Disease	David Thorburn, Ph.D.
Muscle Biopsy - What to Expect Before, During and After	John Shoffner, M.D., Kate McFadden, M.D., and Jeff Upperman, M.D.
Managing your Child's IEP	ACHIEVA

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In This Issue:

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

Deadline for next issue is 04/01/04