Mitochondrial News

United Mitochondrial Disease Foundation

Adult Presentations of Mitochondrial Disease

by Robert K. Naviaux, M.D., Ph.D.
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Mitochondrial medicine has become one of the fastest growing new disciplines in medicine (Luft 1994; 1995, Graff 1999). New mitochondrial diseases are being described every year. Nearly one hundred different mutations in mitochondrial DNA have been described, and nearly 500 nuclear gene defects are associated with mitochondrial dysfunction. Not all of these genetic defects cause measurable declines in oxidative phosphorylation - the process by which food and oxygen are combined to make energy (ATP). Nevertheless, even the mitochondrial diseases that do not cause measurable energy failures can be catastrophic and difficult to diagnose. Our expanding knowledge of the molecular, biochemical, and clinical features of mitochondrial disorders has forced a change in how scientists understand these complex diseases. This article will review some of the hallmarks of these disorders in adults, and outline some of the tests that are required for diagnosis.

"Any disease. Any organ. Any age." This is perhaps the best general summary of the spectrum of mitochondrial disease available (Christodoulou 1999). Mitochondrial diseases are notorious masqueraders (Kerr 1998). They can cause symptoms that are indistinguishable from those caused by common disorders. Only the behavior of the mitochondrial disease over time sets it apart from its more common cousins. Mitochondrial dysfunction has now been linked to common maladies as diverse as infertility (Jansen 1998), cancer (Susin 1998), migraine headaches (Welch 1995), diabetes (Damore 1999), heart disease (Hatch 1998, DiMauro 1998), blindness (Latkany 1999), deafness (Fischel 1999), kidney disease (Niaudet 1996), liver disease (Treem 1998), stroke (Heales 1999), the toxicity of AIDS drugs (Barile 1998), Parkinson disease (Kosel 1999), Alzheimer dementia (Fiskum 1999), and the aging process itself (Wallace 1997). Epidemiologic studies have established beyond doubt that when these chronic disorders are studied as groups, they are complex and have multiple causes - both genetic and environmental. Mitochondrial disease does not cause a majority of any one of the disorders listed. However, it is important to remember that mitochondrial disease can be a cause of

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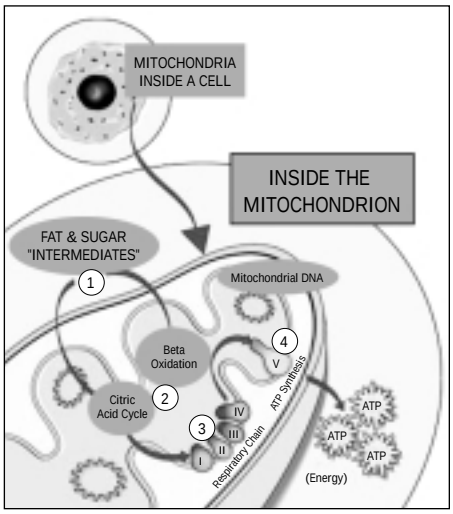

This is the first of a two-part Quest series [Excerpts] about mitochondrial myopathy. This article covers the basic biology of mitochondria and explains inheritance patterns and determinants of severity in mitochondrial diseases. Part 2 will discuss diagnosis and treatment, including a look at new information about mitochondrial diseases in the research pipeline.

Mitochondrial Myopathy: An Energy Crisis In The Cells

by Sharon Hesterlee, Quest, Volume 6, Number 4, August 1999 (Excerpts)
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WHAT MITOCHONDRIA DO, AND WHAT CAN GO WRONG

When the breakdown products of the food that we eat enter the mitochondria for processing, they're passed along a well-orchestrated assembly line made up of hundreds of proteins, each with a specific role to play in the energy production process. Raw materials enter the beginning of the assembly line, and ATP energy molecules come out the other side.

The major steps in the energy extraction process are (see illustration):

1. Import and export of materials, such as fat and sugar derivatives, to and from the mitochondria
2. The breakdown of fatty acids through beta-oxidation and the removal of electrons in the citric acid cycle
3. The passage of electrons through the major complexes of the respiratory chain, or electron transport chain, and
4. The manufacture of ATP by ATP synthase.

When any one of these steps is blocked, usually because a genetic defect has prevented the manufacture of a protein required for that step, mitochondrial

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Chairman's Report

WHAT CAN YOU DO?

I believe every day poses new challenges as well as new opportunities but being a results oriented person I sometimes have a problem waiting for my opportunities to catch up to my challenges. Don't we all want it yesterday? And doesn't our society force us to expect it yesterday? Drive-through banks and drive-through restaurants, 1-hour photo developing, pagers, cell phones and fax machines, the Internet and e-commerce! And you expect me to understand and accept the fact that I have been waiting six months for the results of a muscle biopsy! And when the results finally arrive I am expected to understand and accept the fact that effective treatment, as well as a cure, is far off in someone else's immediate future!

Let's take a deep breath and address this frustration together. That's exactly what your board of directors did at the first board meeting of the United Mitochondrial Disease Foundation. No one said, "let's invent a cure!" We, however, took a very important and necessary step towards a cure by defining and developing the UMDF mission: To promote research for cures and treatments of mitochondrial disorders and to provide support to affected families.

A few years ago, I had the opportunity to speak to a group of parents and doctors about the goals of the UMDF. Afterwards, one of the doctors approached me and wanted to know who I thought I was and what medical background I had qualifying me to discuss the approaches necessary to reach a cure. He really got my attention when he said, "You volunteers are all alike." I told him I consider myself a donkey not a volunteer. A donkey harnessed to a large wagon. I told him he shouldn't spend any time thinking about the donkey, he should be telling this donkey what he needs to find a cure for mitochondrial diseases. I told him I couldn't develop the complex formulas for treatments and cures and I certainly couldn't design the equipment that would test for the diagnosis BUT, I could get him the test tubes, the computers, the nuts and bolts that would be essential for his research. I told him to load the wagon and not worry about the donkey. When the wagon gets too heavy for me to pull alone I would find others that would push and together we could help him find the cure.

UMDF has been pulling that wagon for the past 5 years and it sure has gotten bigger and loaded with more requests than we ever expected but it hasn't gotten any heavier because every time we look around we can see more and more people pushing. I guess that's volunteerism.

A very good friend of mine once told me, "If you want to solve a problem, never state it to yourself in the same terms that it is presented to you in." Yes, I do want a cure and I know it will come as long as I concentrate on that which I know I can do. I can provide the test tubes!

What can you do, or more importantly, what have you done and what will you continue to do? Fundraising, establishing support groups or developing UMDF Chapters or just helping your friends pronounce the word mitochondria. Don't be afraid to feel fear, but be sure it mobilizes you and doesn't immobilize you.

Remember; the best time to plant an oak tree was twenty ago, the next best time is today!

Towards a Cure,

Chuck Mohan

Chairman, UMDF
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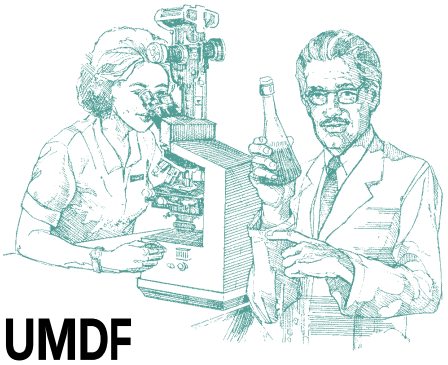


UMDF Research Grant Update

By Mark Fleming, UMDF Research Grant Coordinator

Exciting things are happening with the UMDF Research Grant Program. The program is only three years old and we've awarded more than $100,000 for mitochondrial disease research. And, our growing research endowment has already surpassed a goal originally set for 2005. The endowment will enable us to sustain research funding for years to come through the investment income it generates.

We've had a good response to this year's grant cycle. After a review of proposals by our Scientific Advisory Board we have invited eight researchers to submit formal proposals. Research is occurring from the most basic level to the clinical. We would like to fund all of these projects, but will select one or two with the most promise.

We appreciate the support this program receives from members and donors. Thank you for making it a success.

Grant packets become available in July and can be found on the Internet at http://www.umdf.org/RESEARCH.HTM to all mitochondrial disease researchers at that time. If you would like to be included on the mailing list in July, please contact the UMDF main office now with your current postal address, at 412-793-8077.

Mitochondrial Myopathy

Continued from page 1

disease can occur. The body can't function properly because the cell's ability to make energy is reduced or stopped, and metabolic intermediates and toxic by-products begin to build up.

The energy shortage in the tissues is the major cause of muscle weakness, fatigue and problems in the heart, kidneys, eyes and endocrine system. The buildup of toxic intermediates can be responsible for liver problems, muscle cramps, brain dysfunction or even greater mitochondrial damage. Many times these two types of problems reinforce one another, each making the other worse. (The specific problems and symptoms that occur in mitochondrial disorders, and their management, will be discussed in greater detail in Part 2 of this series.)

Salvatore DiMauro, a neurologist at Columbia University in New York, says that, although there are many different types of defects that cause mitochondrial disorders, the term mitochondrial encephalomyopathy has come to refer only to disorders of the respiratory chain (numbers 3 and 4 in the illustration on page 1). (The respiratory chain is part of the cell and has nothing to do with a person's breathing.)

The respiratory chain consists of four large protein complexes: I, II, III and IV (cytochrome c oxidase, or COX), ATP synthase, and two small molecules that ferry around electrons, coenzyme Q10 and cytochrome c. The respiratory chain is the final step in the energy-making process in the mitochondrion where most of the ATP is generated; as DiMauro puts it, it's "the business end of mitochondrial metabolism." Mitochondrial encephalomyopathies that can be caused by deficiencies in one or more of the specific respiratory chain complexes include MELAS, MERRF, Leigh's syndrome, KSS, Pearson, PEO, NARP, MILS and MNGIE.

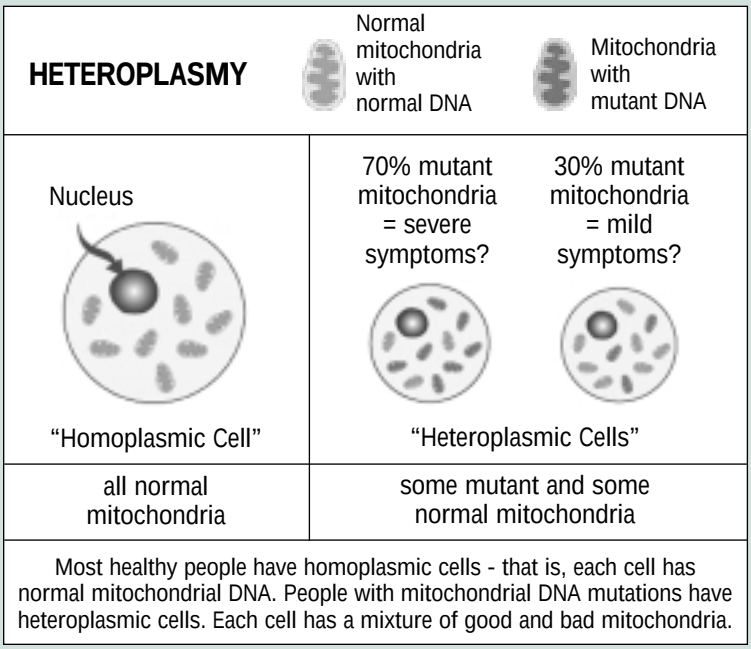
THE MITOCHONDRIAL GENETICS MAZE

The inheritance patterns of the mitochondrial encephalomyopathies can be quite complicated. The mutations that cause these diseases can be in the chromosomes; this is what's usually meant when people talk about a genetic or inherited disease.

But mitochondrial encephalomyopathies have a unique situation. People can also inherit one of these diseases through mutations in the mitochondrial DNA (mtDNA), which comes from the mother only. Mitochondria are the only parts of the cells that have their own DNA, separate from that of the chromosomes in the cell's nucleus, called nuclear DNA.

This situation occurs because the mitochondrial respiratory chain, which is the final step in the energy-making process, is made up of proteins that come from both nuclear and mtDNA (see illustration on Page 1). Although only 13 of roughly 100 respiratory chain proteins come from the mtDNA, these 13 proteins contribute to every part of the respiratory chain except complex II, and 24 other mitochondrial genes are required just to manufacture those 13 proteins. Thus, a defect in either a nuclear gene or one of the 37 mitochondrial genes can cause the respiratory chain to break down. (This respiratory chain has nothing to do with breathing.)

When mitochondrial disease is caused by defects in the nuclear DNA, the inheritance follows a "Mendelian" pattern, just as other inherited disorders do (named for Gregor Mendel, the 19th-century scientist who first explained inheritance). These inheritance patterns include autosomal dominant, autosomal recessive and X-linked. Leigh syndrome (caused by defects in complexes I and IV) is one of the most common forms of mitochondrial encephalomyopathy inherited in this fashion. It's usually autosomal recessive, meaning that two copies of the defective gene, one from each parent, are required to produce the disease.



Although nuclear DNA defects are relatively straightforward, when a disease is caused by defects in the mtDNA, it gets more complex. Mitochondrial genetics are made thornier by the fact that, instead of inheriting two copies of each mitochondrial gene (one from the father and one from the mother) in the way that nuclear genes are inherited, you inherit from your mother literally hundreds of thousands of copies of the 37 mitochondrial genes, while you inherit no mtDNA from your father. (Each of the roughly 100,000 mitochondria in the mother's egg cell may contain between two and 10 copies of the mtDNA genes.)

Also, when a mutation occurs in the mtDNA, only some of the many copies of mtDNA distributed within the mitochondria of each cell will carry the mutation — a situation known as heteroplasmy (see illustration above). The

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Mitochondrial Myopathy

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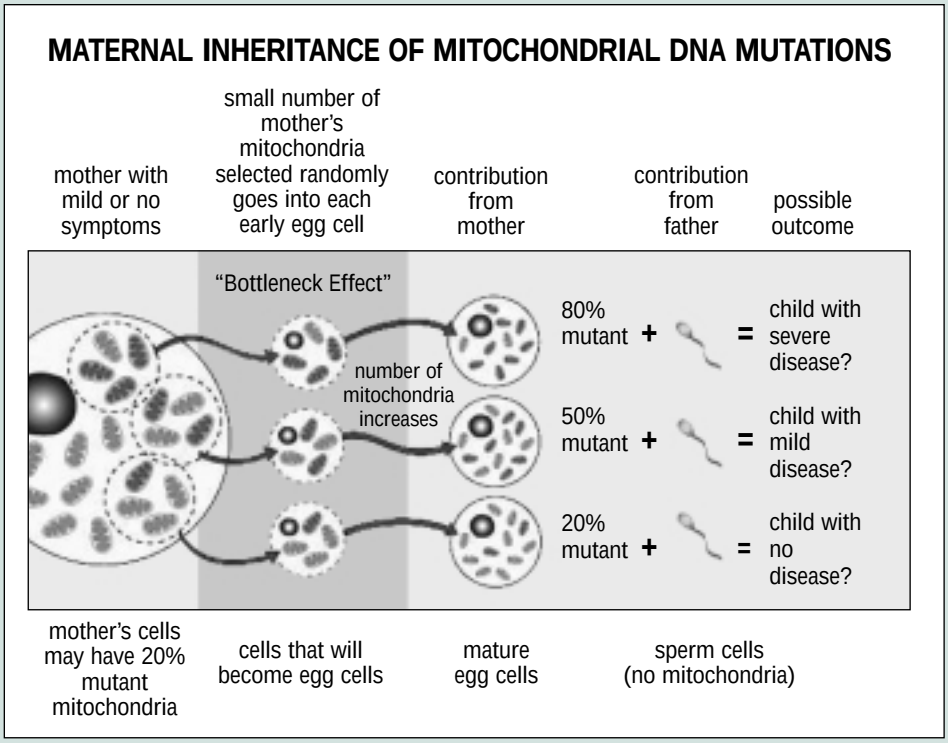
ratio of mutant to normal mtDNA in each tissue, along with other factors, may determine the severity of the disease in an individual.

Most healthy people have homoplasmic cells — that is, each cell has normal mitochondrial DNA. People with mitochondrial DNA mutations have heteroplasmic cells. Each cell has a mixture of good and bad mitochondria.

"And therefore the nice rules that Mendel introduced over a century ago to explain autosomal recessive, dominant and X-linked inheritance do not apply," says Salvatore DiMauro, an MDA researcher at Columbia University in New York, who has studied mitochondrial disorders for over 30 years.

The only "rules" for inheritance of mtDNA mutations that can be counted on are that a father can't pass on mtDNA mutations and a mother will pass on mtDNA mutations to 100 percent of her offspring. This pattern is known as maternal inheritance.

But, even though all of a woman's children will inherit her mtDNA mutations, that doesn't make it easy to predict how severe the disease will be in each child. This is because the ratio of mutant to normal mtDNA passed from mother to child can vary dramatically and unpredictably with each pregnancy. Thus a mother with very mild symptoms of mitochondrial disease, perhaps not even diagnosed as such, may give birth to one child with a very severe disease and a second child with no disease symptoms at all. Some researchers believe this is caused by a "bottleneck" effect during the maturation of the mother's egg cells (see chart).



MATERNAL INHERITANCE OF MITOCHONDRIAL DNA MUTATIONS

Some mitochondrial encephalomyopathies that may be caused by mtDNA mutations and are subject to the rules of maternal inheritance are MERRF, MELAS, NARP, PEO and MILS.

In some syndromes, mtDNA mutations tend to occur spontaneously — that is, the mutation isn't present in the mother or the father but has, instead, occurred very early in the development of the embryo. This is often the case for KSS, PEO and Pearson, three diseases that result from a type of mtDNA mutation called a deletion (specific portions of the DNA are missing) or mtDNA depletion (a general shortage of mtDNA). These types of spontaneously acquired mutations aren't usually passed to the next generation.

A third kind of mitochondrial disease inheritance is a combination of nuclear and mtDNA defects. This type of disease is inherited in a Mendelian fashion, indicating the involvement of a nuclear gene, but is also characterized by mtDNA deletions. In this case, the mtDNA deletions occur because there's a "breakdown in communication" between the nuclear and mitochondrial DNA.

An example of this type of disease is MNGIE. Editor's Note: We would like to thank the Muscular Dystrophy Association (MDA) for sharing portions of their August 1999 article. Although some UMDF members may have already read this article, we found it very informative and a reprint would give those who have not read it a chance to see it.

To read the complete articles (Part 1 and Part 2) by Sharon Hesterlee, please visit the MDA website at http://mdausa.org/publications/Quest/q64mito.html or you may call the UMDF office for other contact information.

COMMON MITOCHONDRIAL DISEASES AFFECTING MUSCLE

(also part of MDA Quest Excerpt)

The terminology used in describing mitochondrial disorders can be confusing. A single syndrome (combination of symptoms) may have many different causes, while more than one syndrome may have the same cause.

In most cases, the underlying causes of these syndromes are deficiencies in the respiratory chain of the mitochondria (see "What Mitochondria Do" page 1). You may be given a diagnosis named for the cause, such as COX deficiency or complex I and IV deficiency. The following have names based on the symptoms of the disease, but are caused by respiratory chain deficiencies.

■ Mendelian Inheritance

● Maternal Inheritance

▼ Sporadic

KSS: Kearns-Sayre syndrome ▼

Onset: Before age 20

Disease characteristics: May cause blindness, eye muscle paralysis, severe heart problems, coordination problems, mental retardation and coma.

Leigh's syndrome: Subacute necrotizing encephalomyopathy ■

Onset: Infancy; progression can be fast or slow.

Disease characteristics: May cause brain abnormalities, vomiting, seizures, feeding difficulties, heart problems, epilepsy, speech difficulties and muscle weakness.

MELAS: Mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes. ●

This is the most common type of mitochondrial encephalomyopathy.

Onset: Before age 20

Disease characteristics: May cause exercise intolerance, seizures, dementia, muscle weakness, heart problems.

MERRF: Myoclonus epilepsy with ragged-red fibers ● ▼

Onset: Usually before adolescence; variable progression.

Disease characteristics: May cause epilepsy, coordination loss, dementia and muscle weakness.

MILS: Maternally inherited Leigh's syndrome ●

Disease characteristics: Same as Leigh's syndrome

MNGIE: Myogastrointestinal encephalomyopathy ■

Onset: Before age 20

Disease characteristics: May cause eye muscle paralysis, muscle weakness, digestive tract disorders, loss of coordination and brain abnormalities.

NARP: Neuropathy, ataxia and retinitis pigmentosa ●

Onset: Infancy or childhood

Disease characteristics: May cause vision problems, lack of coordination and mental retardation. This syndrome may represent a less severe form of MILS.

PEO: Progressive external ophthalmoplegia ▼ ● ■

Onset: Usually in adolescence or early adulthood; slow progression.

Disease characteristics: May cause paralysis of eye muscles, drooping eyelids, muscle weakness and fatigue.

Pearson syndrome: ▼

Onset: Childhood

Disease characteristics: Severe anemia and pancreas malfunction; children who survive the disease may develop KSS as adolescents.

Mohan Receives Prestigious Jefferson Award

Chuck Mohan, Chairman of the UMDF Board, was honored as a recipient of the Jefferson Award on January 20, 2000. He received the award for founding UMDF, for the countless hours he spent talking with families devastated by a mito diagnosis, and for his unselfish commitment to raising research money for a disease that had already claimed the life of his daughter.

Two hundred people in the southwestern Pennsylvania area were nominated for the award. Of this group, forty-six were given the "Community Champion" designation. From forty-six Community Champions, 11 judges chose six winners of the 1999 Jefferson Award. Chuck was one of the six.

Chuck and his story appeared in the January 13, 2000, edition of the Pittsburgh Post Gazette. The two-page story detailed Chuck's personal story as well as information on mitochondrial disease. As a result of the article, UMDF received many calls, and one person hand-delivered a sizable donation, "because [he] was inspired by the work of one man."

Chuck was also honored at a reception and ceremony on January 20 at the Pittsburgh Carnegie Science Center. As he accepted the award, he gave a heartfelt speech that moved most of the audience to tears.

This is the second member of UMDF's Board of Trustees to receive a Jefferson Award. In 1997, Marsha Barnett received the award for her efforts in establishing the Michael and Charles Barnett Center for the study of Mitochondrial Disorders.

UMDF Mission Statement

To promote research for cures and treatments of Mitochondrial Disorders and to provide support to affected families

The 2000 International Conference on Mitochondrial Diseases

UMDF is pleased to invite you to attend the third international symposium on mitochondrial diseases. This intensive two-day conference will provide you an opportunity to learn more about the latest developments in the study of the disorder as well as treatments, psycho-social issues, and other concerns related to this illness.

We want to you to come away from the conference armed with a better understanding of how to help yourself and other affected family members. We have invited experts in the field to speak - from researchers and clinicians to dieticians and social workers. Whether you are "new" to mitochondrial disorder, or have been dealing with it for a while, you will find information of value at the symposium.

THE SCHEDULE:

FRIDAY, JUNE 2, 2000

9:00-12:00	Hospitality Suite hosted by the Ohio Support Group
12:00-1:30	Registration and Box Lunch
1:30-2:00	Welcoming Remarks Chuck Mohan, Chairman, UMDF Leslie Boyer, Executive Director, UMDF Sheryl Cohen, LISW, Support Coordinator
2:00-3:00	Introduction and Overview of Energy Metabolism Bruce H. Cohen, M.D., Chief, Section of Child Neurology, Cleveland Clinic Foundation
3:00-3:30	Beverage Break
3:30-4:30	Issues in Adults with Mitochondrial Diseases Robert K. Naviaux, M.D., Ph.D., Assistant Professor, Biochemical Genetics and Metabolism, Mitochondrial and Metabolic Disease Center, UCSD School of Medicine
5:00-5:45	Keynote Address Bernadine P. Healy, M.D., President and Chief Executive Officer, American Red Cross
5:45	Break
6:30-7:00	Reception (Cash Bar)
7:00-10:00	Banquet

SATURDAY, JUNE 3, 2000

8:00-9:00	Continental Breakfast
9:00-9:45	Breakout Session A "End of Life Care" - Sarah Friebert, M.D., Pediatric Medical Director, Hospice of the Western Reserve; Mary Kay Tyler, RN. PNP, Pediatric Team Leader, Hospice of the Western Reserve
10:00-10:45	Breakout Session B "Families Dealing With Chronic Illness" - Sheryl Cohen, LISW, Clinical Social Worker
11:00-11:45	Breakout Session C "Nutritional Support" - Phyllis Acosta, Ph.D., Director of Metabolic Disease, Ross Product Division, Abbott Laboratories; Najeebah Shine, Registered Licensed Dietician, Cuyahoga County Board of Health
12:00-1:30	Luncheon with Physicians A panel of six clinicians will field questions from the audience
1:30-2:30	Genetics of Mitochondrial Diseases John Shoffner, M.D., Director Molecular Medicine, Children's Healthcare of Atlanta
2:30-3:00	Beverage Break
3:00-4:00	Treatment for Mitochondrial Diseases Richard Haas, M.D., Professor of Neuroscience and Pediatrics, Mitochondrial and Metabolic Disease Center, UCSD School of Medicine
4:00-5:00	Review of the Medical Meeting - Bruce H. Cohen, M.D. will review the proceedings of the June 1-2 Scientific Meeting and will summarize important information
5:00-5:30	Business Meeting A general membership business meeting will be held. UMDF Bylaws Amendments and other business will be covered at this time.

HOTEL RESERVATION INFORMATION

A block of rooms has been reserved at the Marriott Airport Hotel at the special rate of $85.00/night. Please call 800-228-9290 or 440-542-2312 to make reservations. Be sure to say that you are part of the "UMDF" meeting in order to get the special rate.
Reservations must be booked by May 4, 2000. After that date, the special rate may not apply. However, space is limited, so please make your reservations early! Any advance deposit is refundable if the reservation is cancelled at least 48 hours in advance.

IMPORTANT INFORMATION

CANCELLATION POLICY

If cancellations are received in writing by May 15, 2000, the reservation fee will be refunded. There will be no refunds after May 15, 2000. If you wish to send an alternate attendee, please notify us. Refunds will be mailed after the conference.

CHILD ATTENDANCE POLICY

Children will not be permitted at conference sessions. The conference is intended as a professional and educational weekend for adult participants. Please make other child-care arrangements. Additionally, though the doctors have generously agreed to participate in the family meeting, there will be no doctor appointments taken during the conference.

STOP BY THE HOSPITALITY SUITE!

Symposium registrants are encouraged to visit a hospitality suite that will be hosted by the Ohio Support Group on Friday, June 2, from 9:00 a.m. to noon, at the Marriott Airport Hotel. Signs will direct registrants to the hospitality area.

Participants that arrive the night before or get in earlier in the morning will be able to meet other families over a cup of coffee. It will also be a time to share itineraries or get together with old friends.

UMDF thanks the Ohio group for its generosity and time in hosting this event!

Is Your Child in Pain? Basic Assessment Tips for Parents

By Tracy Pasek, RN, MSN, CCRN
Advanced Practice RN, PICU, Children's Hospital of Pittsburgh

Before discussing pain assessment techniques, we must briefly address the fact that pain myths still exist in society—-even today. Many misconceptions surround the notion that children do not experience pain. Perhaps the most blatant manifestation of these beliefs is the continued practice of performing circumcisions without analgesia (pain medication). Here is some simply stated data to store for when you encounter individuals who think this way.

Early in the gestational period, fetal peripheral nerve endings are present and functional. An intrinsic opioid analgesic system (similar to circulating endorphins) is also in place. It is not totally clear what this system does for the fetus. It is thought that the analgesic system protects the fetus from asphyxia (lack of oxygen) and acidosis (low pH) during the labor and delivery process.

Two types of nerve fibers exist that are capable of pain impulse transmission - A delta fibers and C polymodal fibers. The former are myelinated (coated with a protein sheath) and tend to predominate in more superficial structures. These fibers are most likely responsible for quick withdrawal of a body part away from a hot iron, for example. C polymodal fibers tend to predominate in deeper structures and are unmyelinated. Contrary to what some believe, myelin is not necessary for pain impulse transmission. Though children's nerves are not completely myelinated until approximately school age, this does not mean they cannot feel pain. Myelin enhances the smoothness and rapidity of pain impulse transmission-it does not need to be there for impulse transmission to occur. If you watch a baby closely who is experiencing a heel stick, for example, you will observe that the baby has a delayed response to the pain stimulus. He cannot react immediately because the impulses are taking a bit longer to reach his cerebral cortex or brain. This delayed transmission time is balanced by the shorter distance impulses have to travel in a small infant or young child.

Another goal to achieve before becoming an expert in assessing your child's pain is understanding your "pain prejudices." We all have them and they are not always as overt as believing people of certain cultures "are stoic when they are hurting" or believing that "adolescent boys are babies if they cry when they are hurt." Pain prejudices may be as seemingly insignificant as priding yourself in not being a "pill taker" or boasting that you did not require an epidural during labor. Get in touch with what you really think about pain-it will influence how you proceed with pain assessment. Also, consider moving suspicion of pain more to the forefront of your thoughts. Instead of assuming that a sick baby is crying because he is hungry, ask yourself "Is there any reason why he might be in pain?" Is something about the disease process causing pain?

How does one know when a child is in pain? Pain responses are not always as obvious as writhing and crying intensely. Children with limited vocabulary may only be able to describe pain as an "owie" or "boo boo" making it challenging to manage the pain without a clear, detailed description. Pre-verbal or nonverbal children present an entirely different set of challenges.

BEHAVIOR

Babies can anticipate negative stimuli as early as 6 months of age. Behavioral pain responses in very sick or compromised infants (birth to 1 year) may be subtle. Research has demonstrated some of the following behaviors as being indicative of pain in infants: lip smacking, facial grimacing, yawning & eyebrow furrowing. Neonates and premature neonates may simply lie still with their eyes closed when they are in pain. Though they appear to be sleeping, they may be totally overwhelmed with stimulation and cannot tolerate any more environmental input. They don't have the reserve to cry, kick or withdraw like a healthy infant can.

Toddlers exhibit unique behaviors when they are in pain. Unfortunately, they are often described as being aggressive in a painful threatening situation. Toddlers are particularly vulnerable because they have very limited vocabulary and little to no concept of time. They may be forced to express themselves motorically. Kicking, punching and attempts at biting are not uncommon. It is particularly important with this age group

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Pain Syndromes In Mitochondrial Disease

Provided by Bruce H. Cohen, M.D., The Cleveland Clinic Foundation

ORGAN	SYMPTOMS
Brain	Migraine
Gastrointestinal	Gastroesphageal reflux, bowel pseudo-obstruction
Muscle	Cramping and aching
Nerve	Burning or knife-like

Fundraisers

Mom Runs Race of Her Life

As is so often the case with families dealing with mitochondrial disease, Becky Resch was a mom who felt that she wanted to do more for her child, Morgan. "Morgie" as she was affectionately known, was three years old before her symptoms began to occur. She developed tremors, her balance and walk deteriorated, and her energy level became low. After months of doctor visits, she was diagnosed with Leigh's Disease and Cytochrome C-Oxidase Deficiency.

Becky and her husband were desperate to find help, but they were told that the most they could hope for was at most - two more years with their child. Morgie was only four years old.

But Morgie was full of strength and determination. She battled and overcame the odds. She attended school and played regularly with her friends. She was an inspiration to others, and while her body sometimes gave way, her spirit endured. She was a delight to be around and she brightened everyone's day.

While Becky was giving Morgie supplements and doing everything possible to slow the progression of her disease, she wanted to do more. She got the word out to her local community and began to raise awareness about mitochondrial disorders.

This summer, Becky and her friend, Stephanie Freeman, decided to train for and run in the Quad City Marathon. A 26.2 mile race is grueling by any standard, but Becky turned this race into an opportunity to raise money and raise awareness of mitochondrial disease. She decided to get people to pledge money to UMDF for each mile she completed in the race.

"I was amazed at the outpouring of love and generosity from family, friends and other acquaintances, but also from total strangers," remarked Becky. "It seemed like people were grateful to be asked to help."

On September 24, 1999, Becky and Stephanie ran the race. It was a metaphor for life - the race was difficult, but like any challenge, it was rewarding. They completed all 26.2 miles. Becky was able to get media coverage for her cause, and raised an astounding $15,000! UMDF is grateful for the Resch's unselfish support and work on behalf of all those who suffer from mitochondrial disorders.

Morgan Elizabeth Resch passed away on October 15, 1999. Becky wanted to tell us that, "knowing what I know now, that I would not have Morgie more than 8 years, would I go through it all again?" " Yes," she said, "in a heartbeat."

You Just Never Know *by Kara Strittmatter*

The UMDF National Office receives numerous calls from persons interested in organizing a fundraiser (which is GREAT). The staff will provide them with materials, which will hopefully help them get started. Fundraising can be fun, but it can also be challenging. "First timers" are often surprised by their success.

Mr. William Webbe, of England, decided to give fundraising a try. In May of 1999, Mr. Webbe emailed me that he planned to cycle in the Etape du Tour De France. He asked for a layman description of mitochondrial disease and a pledge form. I immediately emailed him back with an easy to understand description of mitochondrial disease, a pledge form (tailored for cyclists), and then mailed hard copies along with 15 UMDF brochures.

Mr. Webbe obtained sponsorships for his cycle ride in the Etape du Tour, which was held in July. The Etape is an opportunity for amateur cyclists to participate in one of the stages of the Tour De France, the most prestigious race of the cycling world. Mr. Webbe was one of 5,500 riders who tackled a 125-mile course through the Massif Central region of France. On November 11th, the office received a check (made out in U.S. currency) for $7,056.56. Mr. Webbe single handedly raised this money by obtaining pledges for his ride.

When that fundraising call comes in, "you just never know" how it will turn out!! Thanks again Mr. Webbe!

Fundraisers

First Annual Nicholas Nunno Dinner to Benefit Mitochondrial Disease Research

Chairman of Rutherford Elks Club, Joseph Europa, presents $1,000 to Angela & David Nunno

Angela and David Nunno are not new to the outstanding fundraising efforts accomplished by UMDF members. In the past few years, they have brought in over $30,000 including their most recent endeavor on September 25, 1999! The Nunnos held their First Annual Benefit Dinner in honor of their five-year-old son, Nicholas. The Dinner raised $15,010 and now the Nunno's hope to continue this event on an annual basis. Angela and David noted the following in their dinner program:

> On January 12, 1998, after months of testing, Nicholas was diagnosed with Mitochondrial Encephalomyopathy, an incurable neuromuscular disease. From that moment, our lives changed forever. The future of our son's life became very uncertain. But through everything, the people that love Nicholas have worked very hard to keep him as healthy and happy as possible.
>
> We, Nicholas' parents, would like to thank everyone who has helped with this dinner. We would also like to thank everyone who has purchased a ticket, donated a gift or sent in money directly to the UMDF. We must work to find a cure now, and this dinner is a step towards a cure.
>
> *Angela & David Nunno*

UMDF gratefully acknowledges Angela and David's efforts. Their hard work and generosity will help pave the way to that "path to a cure!"

Airline Information

The National Patient Travel Center
(formerly National Patient Air Transport Helpline)
4620 Haygood Road, Suite 1
Virginia Beach, VA 23455
Email: mercymedical@erols.com
www.patientticket.org or 1-800-325-8908
www.patienttravel.org or 1-800-296-1217

Miles for Kids in Need
American Airlines offers one flight per patient, must be referred by a non-profit organization, based on financial need.
Phone: 817-963-8118

Continental Care Force
Continental Airlines offers free flight certificates for patients.
Run by a volunteer - Bob Jack.
Phone: 281-261-6626

AirLife Line
A national network of volunteer pilots who donate free air transport for ambulatory patients and time critical cargo. Goes strictly on basis of need. Limited to 800-900 miles one way.
Phone: 916-641-7800 (PST)
Phone: 800-446-1231

Halligan's Pub Hosts Another Successful You Go Girl Golf Outing

On October 6, 1999, Halligan's raised over $6,500 to benefit UMDF and local newspaper coverage was great! Chairperson for the event, Jane Jacquinto, organizes the annual event in honor of the Shelly Family - Maripat, Pat, Kevin, Brendan and Maili. This unique women's golf outing offers nine holes of golf, refreshments, course contests, great prizes and a buffet lunch at Halligan's Pub. What more can a golfer ask for!!!! Thank you for your continued support!

Support UMDF -

Win a Weekend in New York City

Joe Rice, of St. James, New York, is holding a raffle to benefit UMDF as a memorial to his wife, Linda Rice. "A Weekend in New York", May 19th and 20th, will include a luxury hotel suite, dinner for two and a Broadway show for two. Cost for one chance is $5 or six chances for $25. Drawing date is April 30, 2000, 9:00am, at the Café Testarossa, Syosset, New York. Winners do not have to be present to win. Anyone interested in purchasing tickets should contact Joe at 516-236-3998.

We thank Joe for his unique and generous idea! Joe has already brought in over $1,000 and we hope to print the final tally in the next newsletter as well as the WINNERS! Thank you in advance to all who participate in the raffle and we wish the winner a great time in NYC!!

Is Your Child in Pain?

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to NOT use the words "good" and "bad" during painful situations. Rather, they should be rewarded for surviving a painful procedure by being told they are brave. Lying still is not "good" nor is crying "bad."

At this time, it is necessary to discuss pain assessment scales or tools. Many pain scales exist. None are ideal. Pain scale development has been the result of many a doctoral dissertation. They are often useful for children between the ages of 3 and 7 (preschool and early school age.) Children in this age span have difficulty quantifying. They may have a hard time using a numeric scale (1-10) because they may not understand that "5" means worse pain than "2." Obviously, this age group cannot use scales with words on them—these should be reserved for use with children who can read. Pain scales for this age group are often comprised of faces. A child can choose which face "looks" like the degree of pain he is having.

School-age children are rule-oriented. They may cope with pain by "behaving" and being "good patients" similar to being "good students." They may not want to complain or cause trouble. These kids may even deny pain to avoid getting a "shot." In fact, many children-regardless of age-will go to great lengths to avoid needles. This age on through adolescence is where a new set of challenges with pain assessment begins. Typically, people think that unless there are overt signs of pain-crying, screaming, etc.-a child is not experiencing pain. Adolescents may also cope with pain through activity and may even play computer games in the presence of pain. Both school-agers and teens may begin to be able to use more sophisticated pain scales due to their advancing cognitive level. However, this is not a given.

OTHER SIGNS OF PAIN

The autonomic nervous system (ANS) responds to pain. Increased heart rate (tachycardia), sweating, decreased oxygen levels, increased blood pressure are a few nonspecific pain responses. They are called nonspecific because these things can happen as a result of stressors other than pain like anxiety or fear, for example.

HOW CAN YOU ADVOCATE FOR YOUR CHILD?

Take an active role in assessing your child's pain. Keep a diary. Track pain responses at home, at the doctor's office and in the hospital. Observe for trends and similarities during different situations. Record what works and what doesn't work for your child. Review your findings with your child's nurses and doctors. Work with your healthcare providers to secure a pain assessment scale that suits your child's needs. Numerous ones are available and the literature on this topic is vast. Laminating will allow you to wipe your pain scales clean. Scales should match your child's cognitive level. Partner with your healthcare providers to learn how to use the tool so that there is consistency. Using pain scales takes practice for both the parents and the child. Though this may be awkward at first, perseverance will pay off. Never introduce a pain scale to your child the first time during an acute episode of pain. Learning will not occur. Practice using it when your child is comfortable.

You can play a significant role in your child's ability to cope during painful times. Your presence is vital. If you can manage to stay with your child during painful situations (some parents may get sick or faint), then do so! Being in the room with your child can greatly reduce his anxiety which will, in turn, decrease his perception of pain and make it seem better or more tolerable. Remember, you know your child better than anyone. Ask questions and provide input. Healthcare providers will value your expertise and your child will benefit.

The following are some valuable resources with accompanying reference lists that will assist you with learning more about pediatric pain.

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You can also subscribe to the following quarterly newsletter for the latest research pertaining to pediatric pain:

Pediatric Pain Letter
Psychology Department
Jill Hatchette, Managing Editor
Dalhousie University
Halifax, Nova Scotia, BeH4J1
email: jhatchet@is.dal.ca

If you are looking to start or add to your art collection UMDF may have something of interest

UMDF would like to thank Mr. & Mrs. Richard Perry for their generous donation of Red Skelton Lithographs (the Perrys donated the lithographs in honor of Heidi Marie Daniels). Mr. & Mrs. Perry graciously donated a total of 12 Red Skelton Canvas Transfer Lithographs; each print is framed and has a certificate of authenticity signed & thumbprinted by Mr. Skelton. He personally autographed them only after they were sold and all issues are sold out. Many of the images did not reach their full edition quantities before his death and this fact makes some scarce, which affects value.

UMDF may already have a buyer for the entire collection. Interested parties may still contact the UMDF office at 412-793-8077 to check status of the lithographs.

Adult Presentations

Continued from page 1

any of these disorders, because mitochondrial disease tends to extend to other organ systems, progress with age, and respond poorly to current therapy. A comprehensive listing of signs and symptoms of mitochondrial disease is beyond the scope of this article. This is true in part because the general statement quoted at the beginning of this paragraph is a clinical fact. The more patients we evaluate with proven mitochondrial disease, the broader the spectrum of signs and symptoms becomes that we normally associate with any particular disease. A few examples will be reviewed below to clarify this point.

Even a single point mutation in mitochondrial DNA can produce many different diseases. Perhaps the best studied example of this is the A3243G mutation first linked to the disease called MELAS (mitochondrial encephalomyopathy, lactic acidemia, stroke-like episodes). In our experience at the Mitochondrial and Metabolic Disease Center (MMDC), adults bearing this mutation in mitochondrial DNA frequently presented with diabetes years before onset of brain disease. Some patients first suffered psychiatric disease and hearing loss for decades before the onset of recurrent stroke-like episodes and diabetes led to the correct diagnosis. Other patients had early onset dementia in their 30s that was undiagnosed until the occurrence of a seizure and stroke-like episode. In still other patients, the single manifestation of this mutation was an unexplained cardiomyopathy and mildly elevated lactate. Nearly a third of the patients who carry the A3243G mutation had near normal blood lactic acid levels. In these patients, only the cerebrospinal fluid lactic acid was elevated. In 10-15%, lactic acid was elevated neither in the blood nor spinal fluid. The message is that not all patients with the A3243G mutation have MELAS. Similarly, most adult patients who carry the T8993G mutation, often referred to as the NARP mutation, do not have the "neuropathy or neurogenic muscular weakness, ataxia, or retinitis pigmentosa", for which the acronym was coined. These facts illustrate that the name of a mitochondrial disease can be misleading. Physicians and patients who rely on an acronym like MELAS or NARP to guide them in making a diagnosis will be wrong more often than not.

TABLE 1. RULES OF THUMB

Think mitochondria when:

1. A "common disease" has atypical features that set it apart from the pack.
2. Three or more organ systems are involved.
3. Recurrent setbacks or flares in a chronic disease occur with infections.

TABLE 2. DIAGNOSTIC TESTING FOR MITOCHONDRIAL DISEASE

1. Blood for mtDNA (PCR and Southern)
2. Blood and CSF for Lactate and Pyruvate, or Brain MR Spectroscopy
3. Urine Organic Acids (by GC/MS)
4. Plasma and Urine Amino Acids
5. Blood and Urine Carnitine
6. Brain MRI
7. Muscle Biopsy
   Neuropathology and Electron Microscopy
   Mitochondrial Electron Transport Studies
   Fresh (coupled) mitochondrial Polarography
   Muscle mtDNA (PCR and Southern)

Even classical mitochondrial diseases like Kearns-Sayre syndrome can be difficult to diagnose when the first symptoms appear. Neither the onset nor the rate of progression to other organ systems is stereotyped. When ptosis, ophthalmoplegia, retinopathy, ataxia, weakness, exertional fatigue, cardiac conduction block, elevated cerebrospinal fluid protein, and ragged red fibers are all present together, the diagnosis is simple. However, it may take decades of slow progression before all these symptoms are present together. Most often in adults, the symptoms will appear one by one over several years. When progression is relatively slow, adult patients will typically be referred to a new medical specialist every few years, to take care of each new symptom as it appears. Often it is a medical student trying to make sense of the multisystem disease who prompts a referral to a mitochondrial and metabolic disease center where the final diagnosis is made.

If mitochondrial disorders are so complex and protean, how can general physicians make the diagnosis? A systematic approach is essential. It would be wrong to say that everyone with diabetes or heart disease should be checked for mitochondrial disease. Table 1 lists three rules of thumb that can help guide anyone who suspects mitochondrial disease. If the answer to any two of the three rules of thumb is yes, and the reasons for these affirmative answers are not explained by the patient's present diagnosis, then a mitochondrial work-up is justified. Table 2 lists the standard tests that are required in the evaluation of suspected mitochondrial disease. I call this the "5 + 2" evaluation. Frequently, the results of these tests will suggest other studies that may need to be performed, but these 7 tests will provide a solid database upon which the rational selection of additional studies can be based. The first five tests listed (omitting brain spectroscopy for the moment) are relatively non-invasive and can usually be performed for about $1500. The last two tests are more costly, but are considered by many specialists to be the most informative. The brain MRI and muscle biopsy, along with the associated respiratory chain assays, and mtDNA testing may cost about $5000. When the results of these seven studies are combined with careful medical history, family history, and serial physical examinations,

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Adult Presentations

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and assembled by a metabolic specialist with expertise in neurometabolic disease and mitochondrial medicine, an accurate diagnosis can be reached in about 50% of the adult patients referred for suspicion of mitochondrial disease. Among children, the yield is higher. These studies permit an accurate diagnosis in about 75% of the children referred for evaluation of suspected mitochondrial disease.

The figures quoted in the paragraph above are influenced by the current state of the art, and by the nature of the patients referred to a specialty center for diagnosis. Research is being conducted today that will change these figures significantly. New diseases are being discovered. New methods of diagnosis are being developed. New experimental systems and animal models of mitochondrial disease are being constructed, and new treatments are being tested. Both clinical and basic research are absolutely essential for this progress. The history of scientific progress has taught us that the most monumental discoveries are not predictable. We cannot foresee what the next five years will be like for mitochondrial medicine, but based on the current rate of growth, it is safe to say that there are still a number of surprises in store, that many cherished beliefs will fall, and new ideas about the role and function of mitochondria in human disease will be expanded dramatically.

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SUPPORT GROUPS

Arizona Support Group, the Desert Angels
Leader: Cathleen Kane
Phone: 480-807-8271 or 480-807-3201

Delaware Valley Mitochondrial Support Group, Pennsylvania
(meetings in Philadelphia area)
Leaders: Maria and Dave Chuisano
Email: DelValumdf@aol.com

Melbourne Mitochondrial Support Group, Florida
Leaders: Kathy McElhinny and Christine Golden
Email: mcelhinn@digital.net or Goldenfam4@aol.com

Massachusetts Support Group
Leaders: Eileen Mitchell, Bill Shea & Deb Shea
Email: eimitch@nii.net

Ohio Mitochondrial Support Group
(provisional status of becoming a UMDF Chapter)
Leaders: Jennifer & Marty Lyman
Email: jennmarty@yahoo.com

Southern California Mitochondrial Support Group
Leader: Lissa Mirand
Email: rlmirand@earthlink.net

Western Pennsylvania
Leader: Chuck Mohan
Email: umdf@nb.net

For more information on Support Groups, call the UMDF office at 412-793-8077 or email at UMDF@nb.net

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

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Address _____

City _____ State _____ Zip _____

Phone: Home _____ Work _____ FAX _____

Email Address _____

PLEASE CHECK

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

Please list the affected adult(s) / child / children's name(s) and date of birth:

_____

_____

_____

_____

_____

MAKE CHECKS PAYABLE TO UMDF

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

UMDF accepts MC/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

IF YOU WANT TO NETWORK, please fill out this form and send to UMDF even if you are already a member

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 _____

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.

UNITED MITOCHONDRIAL DISEASE FOUNDATION

P.O. Box 1151
Monroeville, PA 15146-1151
Phone 412-793-8077
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email: umdf@nb.net
http://www.umdf.org

Volume 5 • Issue 1 • Spring 2000

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SYMPOSIUM 2000 REGISTRATION FORM (Tear off and return this portion) (Please duplicate this form for additional registrants)

Please Print : (Name will appear on your badge as you indicate here)

Name: First _____ Last _____ Mr., Mrs., Ms. _____

Mailing Address _____ City _____ State ____ Province _____ Postal Code _____ Country _____

Daytime Phone (with area code) (_____) _____ Fax (_____) _____ E-mail _____

FEES: (Please mark the appropriate boxes)

☐ $150 Conference fee (per person)* Fee includes all meals, refreshment breaks, access to all sessions, printed program materials and gala banquet

All meals are included. However, we need an accurate count for the following:

☐ I will attend the Friday lunch ☐ I will attend the Friday banquet ☐ I require vegetarian meals

☐ I will attend the Saturday lunch ☐ I will attend the Saturday breakfast ☐ I require Kosher meals

☐ I require handicapped assistance. (Note: a few hotel rooms are equipped for people with disabilities. Please indicate your needs with the hotel. Please contact us should you require further assistance.)

PAYMENT OPTIONS:

☐ Make check payable to UMDF ☐ Credit card payment: ☐ VISA ☐ MasterCard

Card Number _____ Expiration Date: _____

Signature: (Not valid without signature) _____

For credit card payees only: To expedite your registration, please fax your form to: UMDF, 412-793-6477. Once faxed, DO NOT mail in original registration form.

Mail check and registration form to: UMDF, P.O. Box 1151, Pittsburgh, PA 15146-1151

Questions? Call 412-793-8077.

* A limited number of funds to offset part of the cost of attending the symposium are available for those experiencing financial hardship. To receive the application form for a partial scholarship, please call 412-793-8077. Our sincere thanks to Allen and Marsha Barnett for underwriting the cost of the scholarships.