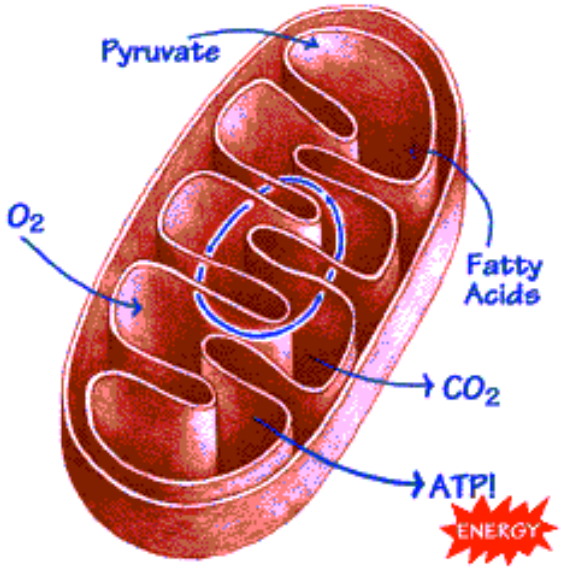
MELAS Primer 1999

Volume 4.2

This publication contains an explanation of the MELAS Syndrome in layman's terms, as well as a small paper on Mitochondrial Mechanics

(Some of the symptoms and clinical signs of the MELAS Syndrome may be applicable to other mitochondrial disorders.)



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MELAS: Mitochondrial Myopathy, Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes **-or-** Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes

My thanks go to the doctors, nurses, researchers, medical personnel and facilities, support groups and organizations, "mito" families, and individuals that all contributed some part in making it possible for me to produce this publication. My thanks go also to my parents for their support, comfort, and encouragement during my wife's illness and when she finally succumbed to the MELAS syndrome.

Special thanks to both Prof. Dr. Maria Pachalska and Prof. Dr. Bruce Duncan MacQueen of the Foundation for Persons with Brain Dysfunctions, in Kraków, Poland, for their invaluable help in translating the MELAS Primer into the Polish language.

I also have a special thank you for my son, Michael.
Thank you for loving Dad so much, helping me to adjust to Mommy going Home, and for helping me with this project and the MELAS Online Network (closed August, 1998.)

My most deeply felt thanks goes to my wife Karen Ann for so bravely enduring her illness, and for her encouragement to make her suffering into something that would help other families and individuals with mitochondrial disorders.

… and, without God's grace and mercy this publication would never have existed.

- Michael J. Jackson

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Dear Reader,

This is a paper that has been prepared to introduce you to MELAS. ***This paper is not intended to be a technical explanation of this disorder***, but rather a layman's guide to a better understanding of it. (For more technical data, please log onto the Jackson Family's Website on the Internet at: http://www.melas.org ; or, write me at the address at the bottom of the page.)

MELAS Syndrome: Mitochondrial myopathy, Encephalomyopathy, Lactic Acidosis, and Stroke-like symptoms. Here's an explanation of all of those large words:

* **Mitochondrial myopathy**: any muscle disease caused by abnormally functioning mitochondria. (Mitochondria: the "watermelon" or "cucumber" shaped objects inside each of our body's cells that process glucose [blood sugar] into the "energy" that each body cell needs to function properly. A paper on the workings of the mitochondria in our body cells has been included as the last page in this paper.)

* **Encephalomyopathy**: any disease involving both the brain and the muscles.

* **Lactic Acidosis**: a condition where an abnormal amount of lactic acid is present in the body. (Ever get a "stitch" in your side after exercising? Well, that happens when your body can't keep up with the energy demand that your exercising creates. Your body switches from producing energy **aerobically** [by using the oxygen that you breath in] to producing that energy **anaerobically** [without using that oxygen], simply because you can't breath fast enough to provide all the oxygen that your body needs during strenuous exercise. Anaerobic exercise produces an excess of **lactic acid** in your body, and that causes the "stitch" in your side. Usually, in a healthy person, this excess returns to a normal level after a short time. In an individual with MELAS, this abnormal level of lactic acid can sometimes cause seizures. The increased muscle activity during the seizures can boost the lactic acid level even higher, which in turn triggers more seizures, and a potentially dangerous cycle develops. In my wife's case, the doctors discovered that an I.V. containing sodium bicarbonate would reduce the lactic acid level in her blood stream and end the seizure episode; nothing else worked, not even high doses of Valium.)

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* **Stroke-like episodes**: strokes that are caused by the damage done to brain cells by the MELAS; not by the "normal" causes of strokes.

MELAS Syndrome is a rare disorder, and an individual "gets" it at conception (the individual is born with it). MELAS is a genetic disorder that, in **some** cases, is passed from mother to child through the **DNA of the mitochondria**; this is important, because while we get half of our genes from each parent, we get **all** of the genetic material (the DNA) in the mitochondria **from our mothers**. (So it's possible in these particular cases for a mother to pass MELAS on to her children; but only her daughters, and not her sons, could possibly pass it on to their children.) In **most other cases**, the way that MELAS is inherited is not clear, and the primary biochemical/genetic defect is not known. If a fertilized egg cell contains the biochemical/genetic defect that produces MELAS, as that egg cell divides into an embryo, some of the developing organs will end up with more of the defect than other organs. The greater the amount of the defect in the affected cells, the more severe the damage done to the affected organs. Here's a list of the clinical and laboratory features of MELAS:

* **Weakness**

* **Seizures**

* **Dementia** (deteriorated mentality)

* **Short stature** (under average height)

* **Episodic vomiting** (periods of vomiting with no obvious cause)

* **Cortical blindness** (blindness caused by damage to the cortex [outer layer] of the brain)

* **Hemiparesis** (muscle weakness or partial paralysis of one side of the body)

* **Hemianopia** (defective vision or blindness in half of the visual field

* **Sensorineural hearing loss** (loss of hearing due to nerve damage)

* **Lactic acidosis**

* **Positive family history** (the syndrome can be traced back to other family members)

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* **Ragged-red fibers** (abnormal accumulations of normal and/or abnormal mitochondria, seen as purplish blotches when a chemically stained muscle tissue sample from a biopsy is viewed under a microscope; hence, the "ragged-red" appearance)

* **Spongy degeneration** (deterioration of brain tissue; impairing its ability to function properly, and resulting in the eventual loss of the affected cells)

The brain and muscle cells deteriorate because the mitochondria, the "energy factories" of the cells, do not process enough glucose (blood sugar) into **ATP**, the chemical compound that carries the energy that the cells need to function and survive. Without enough ATP, the cells deteriorate and die. This causes the symptoms that we see in the individual. The greater the demand for energy, the greater the damage done. That's why the brain, heart, and especially the eye muscles can show the greatest damage sooner than some of the less demanding organs.

MELAS can become "active" at any age, but most commonly shows up between the ages of three (3) and eleven (11). The severity of the individual's condition is determined by the number of affected cells, where they're located (in which organs), and how energy demanding those particular organs are. There is a medical history of an individual with MELAS included in the “Downloads” section of the MELAS Online Network (see website address at the bottom of this page). This particular individual was born in 1956, but the MELAS did not begin to become apparent until 1980, and was not diagnosed until 1987. This particular individual had the entire syndrome.

Treatments are being developed and tested for the increasing number of individuals with MELAS that have been or are being diagnosed (when my wife was diagnosed in 1987, there were less than thirty cases reported worldwide. Now there are cases being studied in at least 20 nations around the world). Here in the United States, work is being done on MELAS and other related disorders at a number of medical and research centers. Here are a few of them:

Emory University School of Medicine
Website: http://www.emory.edu -- Phone: 1-404-727-5624
North Decatur & Oxford Roads
Atlanta, GA 30322
USA

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Department of Pediatrics, Oregon Health Sciences University
Website: http://www.ohsu.edu/som-Pediatrics -- Phone: 1-503-494-8194
3181 S.W. Sam Jackson Park Road, Mailcode PED
Portland, Oregon 97201-3098

Children's Hospital of Philadelphia
Website: http://www.chop.edu -- Phone: 1-800-879-2467
34th Street and Civic Center Blvd.
Philadelphia, PA 19104-4399
USA

The Milton S. Hershey Medical Center
Website: http://www.hmc.psu.edu/peds/division/neuro.htm
Phone: 1-717-531-8790
500 University Drive
Hershey, PA 17033
USA

H. Houston Merritt C.R.C. for M.D. and Related Disorders
Phone: 1-212-854-1754
2960 Broadway
New York, NY 10027-6902
USA

The Mitochondrial and Metabolic Disease Center Biochemical Genetics and Metabolism UCSD Medical Center
Website: http://biochemgen.ucsd.edu/mmdc -- Phone: 1-800-3LEIGHS
214 Dickinson Drive, CTF-C103
San Diego, CA 92103-8467
USA

Foundation for Persons with Brain Dysfunctions
ul. Imbramowska 1/34
31-212 Kraków
POLAND
Email: fundacja@alpha.net.pl -- Phone/Fax (+48 12) 415-17-62

(Other organizations wishing to be added to this list are welcome to contact Mike Jackson at:

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You are probably going to discover that the majority of doctors know very little about MELAS; so I hope that this short paper, and the information available on the Jackson Family's Website can provide some knowledge and help to all of you that are affected by this syndrome. I know how terrible and frightening it can be to have a doctor tell you that you or your loved one has MELAS... my wife of 15 years had the full syndrome. Karen Ann went to be with the Lord on December 4, 1992.

I would be glad to answer your email at the address below. If you would like to correspond by using your Postal Service, please send your letters to the address for WarpSite Web Publishing on the copyright page at the beginning of this publication.

You might also like to know that the **Muscular Dystrophy Association** (MDA) helps to fund a number of the researchers mentioned above. So the next time you watch the Telethon, you'll be encouraged to know that some of the money that they are raising will go to help fund research to help us and thousands of others to find better treatments, and possibly even a few cures, for the neuromuscular diseases.

Very Sincerely Yours,

Mike Jackson

(NOTE TO PHYSICIANS: This is obviously not intended to be a technical paper, but one to help us laymen to help each other. ANY suggestions or comments are most welcome, and should be addressed to my email account or to the WarpSite Web Publishing address found on the copyright page at the beginning of this publication.)

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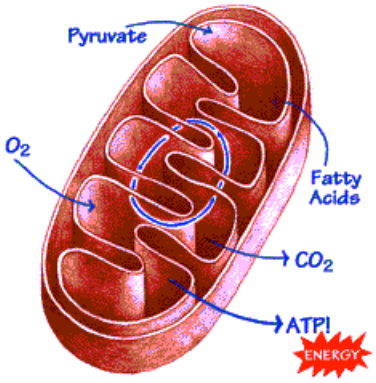
"MITOCHONDRIAL MECHANICS"

(One of these days, I'll figure out how to simplify this technical double-talk!)

In a process called **glucolysis**, the breakdown of **glucose** begins outside the **mitochondria.** In a series of steps, glucose is broken down into **pyruvic acid.** This reaction also transfers hydrogen (**"H"**) to **"NAD"** (a chemical compound) molecules producing **"$NADH_2$"** molecules and produces two **"ATP"** (another chemical compound) molecules for every glucose molecule. **"ATP"** is the principle energy "currency" within the cell. These "ATP" molecules carry energy off to fuel other cell functions. The "$NADH_2$" and the pyruvic acid are needed inside the mitochondria.

The next step is called the **Krebs Cycle** or the **Citric Acid Cycle**. It takes place in the fluid within the inner membrane. The Krebs cycle is fueled by pyruvic acid. This Krebs cycle produces the **"CO_2"** that we breathe out, and most important, the cycle generates more "ATP" and more "H" ions, which are, transported away by **electron carrier molecules.**



The final step in the breakdown of glucose takes place on the surface of the **cristae**. It uses the energy of electron carrier molecules to form an **electron transport system**. Think of an electron transport system as a set of stairs with five (5) steps, with a molecule on each step. The molecules from the Krebs cycle carry the highest free energy. Electrons "roll" down the steps from molecule to molecule losing their free energy as they go. This "lost" energy builds up, and is used in the final step. This final step combines "H" ions, electrons, and the **oxygen** that we breathe to form **water** (H_2O). Normally, this reaction releases a large amount of energy as heat, but in this electron transport system the energy is trapped instead, and ultimately converted to "ATP".

Just how the "ATP" is formed is still a subject of controversy. The most popular theory focuses on the inner membrane of the cristae. The electron transport energy is thought to "pump" "H" ions across the membrane. The result is a concentration of "H" ions on one side of the membrane, and **hydroxyl** ions on the other. The relationship of these two different concentrations represents potential free energy. This potential difference is then exploited chemically to produce "ATP".

"Mitochondrion" graphic courtesy of:
Laura Steigelman
Manager, Graphic Design
Allegheny Health, Education and Research Foundation
(Thank you!)

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