Summary – Mitochondrial Function Disorders
Dr. Richard Boles

Introduction  As a clinician and researcher Dr. Boles is dedicated to discovering treatments which will offer a greater quality of life and a decrease in symptoms for children and adults suffering from mitochondrial functional disorders such as autism, cyclic vomiting syndrome and depression. The application of science and research to the care of his patients is apparent in his role as Director of the Metabolic and Mitochondrial Disorders Clinic at Children's Hospital, Los Angeles, and as Director of the genetics laboratory at Sabin Research Institute. Dr. Boles has an active clinical practice while he also studies the common genetic changes in maternally inherited DNA and their effect on the development of functional disorders. He is an associate Professor of Pediatrics at the Keck School of Medicine at USC and provides leadership to other organizations like CureMito. His insights today will address questions like these:

- What does the term "functional disorders" mean?
- Why is there often a history of chronic pain or illness in families with mitochondrial disease?
- How are mitochondrial disorders and symptoms inherited and how do genetics relate to chronic symptoms of pain, fatigue, vomiting and depression?
- How do autism, ADHD, and SIDS relate to mitochondrial dysfunction?
- Are there any differences in treatment approaches for these conditions in families who have a mitochondrial diagnosis already?

Discussion  The slides which accompany this summary can be found on the MitoAction website and will be referred to by number. Functional diseases or functional disorders do not exist in all patients with mitochondrial disease, but they do occur in many and this discussion will focus on these disorders and those who have them. Slide # 2 notes that Dr. Boles and his group are seeking a patent for a new test that could identify the polymorphic changes that seem to be at the route of functional disorders. This is noted here in the interest of disclosure and conflict of interest. Right now, a company in California called MEDomics (www.medomics.org) can sequence the entire DNA for maternally transferred Mitochondrial Disease; however, there is no test for the polymorphic changes which will be discussed here today.

Slide # 3 depicts a patient of Dr. Boles, "Zachary", who has autism as well as cyclical vomiting syndrome. Slide # 4 notes that he has also had multiple hospitalizations and a breakdown of his skeletal muscles with complex regional pain syndrome. Zachary, now 16 years old, has had extreme exercise intolerance and could not walk more than 15 minutes without excruciating pain. Slide 5 shows complex regional pain syndrome - also known as "mito rash" which here appears red but can sometimes be purple or even white. There is sometimes swelling, but its severity is noted by the extreme pain caused when the skin is merely touched. Often this rash appears as reddened ears.

Slide # 6 demonstrates the "pedigree" of Zachary's disorder - by this we mean the mitochondrial DNA in his family tree. Those members who share Zachary's DNA appear to have many functional symptoms. Functional disorders are those that would not be picked up on an MRI but rather show themselves through function. Slide #7 shows Zachary AFTER mito treatment (amitriptyline and other treatments which will be discussed later in this summary) when he is able to walk much longer distances and for longer duration without pain, his cyclic vomiting is gone and though he still has autism, the symptoms are much improved.

Slide #8 shows functional disorders like fatigue and pain; these are really "symptoms" and are the reason why people go to see their doctors and about 1/3 of the time these symptoms are
unexplainable medically. Slide #9 cites how Western medicine divides these symptoms into diseases depending on which medical specialist the patient decides to see. These disorders all stem from the same thing, but may affect different parts of the body; they are also common to about 10% of the population. Slide #10 notes that it has been known for over 1000 years that if you have one of these functional disorders, you probably have several of them; lots of data demonstrates this "co-morbidity."

Slide # 11 notes that these disorders also have a genetic component. If you have migraines, it is likely that other members of your family will also have migraines. Co-morbidities also tend to run in families as does the response to treatments. Amitriptyline plus Coenzyme Q10 can be useful in chronic pain syndromes and for migraines. Slide #12 demonstrates the shared genetic connections in these functional disorders.

Slide #13 depicts the old story of the blind man describing an elephant. Depending on what part the man is feeling, he describes a very different animal...when in fact the parts all together make up just one elephant. This is exactly how one needs to deal with these many symptoms of the functional disorders being described today; they are often the same thing, just emerging as different symptoms.

Slide # 14 is Dr. Boles' daughter; he just likes to show her picture and emphasize that this is not "magic", but is emerging science.

When we look at the pedigree of these disorders, we are looking at family histories. In some cases some one person in the family may have primary mitochondrial disease and passes it on, but in many cases it may be a cluster of family members who end up with functional disorders. It may even be that they have normal mitochondria (Slide # 15) or different patterns of familial functional disorders (Slides #16-20). These all demonstrate how functional disorders can exist in different families.

Slides #21 - 23 use a mathematical formula to look at how the disorders can exist more on one side of the family tree than on the other (i.e., maternal side or paternal side). The formula can divide those with mito from those without mito and can also show "probable maternal inheritance patterns." Slide #23 applies math to cyclical vomiting syndrome and shows where it came from as well as family members with other disorders.

Slide # 24 is a complex slide which compares two groups. In one group there are those with mitochondrial disease on the mother's side and the mother's sisters who may also meet the criteria for having functional disorders. And there is a control group. The results seem to be that it is more likely to have functional disorders in the group which has the mito disease on the maternal side.

Slide # 25 notes the very objective symptoms of Cyclic Vomiting Syndrome (CVS): severe nausea (and/or vomiting) caused by dysautonomia which comes in cycles with the time in between free of nausea. The nausea may be accompanied by vomiting and may be as infrequent as only twice a year or may be as frequent as every week. Extreme fatigue and weakness accompany the nausea.

Slides #26 & 27 show sequencing of Mitochondrial DNA as of two years ago (we have made great advances since then), and the polymorphisms (or DNA differences) that are common in the general population and cause subtle changes.

Slide #28 is used by Dr. Boles when he gives research talks and demonstrates through mathematical formulas the likelihood (or odds) of having changes and symptoms occur depending on where the change occurs on the DNA chain. For example, those with a particular change have 7% chance of having migraines, those with a different change have a greater chance, but those with
both these changes have a 78% chance of migraines. Slide #29 shows similar data but with chronic fatigue syndrome. Slide #30 demonstrates that having 2 mitochondrial polymorphisms is very predictive of functional disorders. There is no easy way right now to detect these polymorphisms.

Slides #31 and 32 show the pedigree of families with SIDS. Using this information and looking at the polymorphisms as predictors, families can be given advice about what to do if an infant becomes ill. Steps can be taken (like increasing sugared fluids, etc) to hopefully prevent SIDS since these children are at higher risk than the general population.

Slide #33 is Zachary again. Slide #34 is data from Boston's Children's Hospital about severe autism (as a pervasive disorder) and demonstrates that the presence of specific DNA markers makes autism more likely in certain children/families.

Slide #35 puts all this data together and shows how all these polymorphic changes are associated with particular disorders.

Slide #36 & 37 The best test available today to check for mitochondrial disease in children is Quantitative Urine Organic Acids and is best obtained when they are under stress - that would be when they are in bed and ill (i.e. with the flu). Elevation of this substance would be an indicator, though not perfect, and would go along with a good history and physical exam in order to make a correct diagnosis.

Slides #38 & 39 discuss treatment modalities which combine mitochondrial directed treatment with symptom directed treatment. Avoiding fasting is of utmost importance in all these disorders and the specific treatment will be based on symptoms with the idea of decreasing energy demand and increasing energy supply. Dr. Boles recommends exercise and the 3+3 diet; that is three meals a day plus three snacks a day (one being at bedtime). When ill, use IV fluids - dextrose with electrolytes added. CoQ10, carnitine, and Riboflavin are also recommended along with amitriptyline. Dr. Boles uses these treatments for his patients who range in age from infancy up to 30 years old. He does stress the need to check blood levels in order to monitor medication doses. Though amitriptyline has numerous side effects, CoQ10 seems to be fairly safe with few if any side effects noted, and its use has become a standard of care. Amitriptyline is not the drug to use for patients who have electron chain mutations nor for those with neurological disorders. It works by uncoupling the oxidative phosphotase and more or less "unblocking" the electron chain so it can move along; it does not work on patients who have dysfunctional electron chains, only for those with a "bogged down" electron chain.

Slide #40 shows a female patient with cyclic vomiting syndrome and her inheritance pattern. Slides #41 - 43 discuss the current treatment protocols for CVS. These include diet, exercise, CoQ10, carnitine, amitriptyline (if over age 5 and if needed) and then cyproheptadine and topiramate (these last two only if other treatments have not worked). Dr.Boles starts with low doses of medicines and increases until the vomiting stops. He also checks on the blood levels of the medications as well as noting if there are any side effects. According to his recent study (to be published soon) there was a 90% clinical success rate using these protocols. In most cases the migraines went away as did the pain, chronic fatigue improved and "gut function" was better if not perfect.

Slides #44-45 conclude that there are many causes of these functional disorders; mitochondrial mutations or changes may not be the only cause, but often there is a mitochondrial component. These disorders are familial and there are treatment protocols that can help. Though these disorders are complex and the symptoms may be severe, they can be treated - people should not give up.

In Slide #46 Dr.Boles thanks the rest of his family and his friends for their help.
Dr. Boles's association with CureMito.org gives him further contact with those who have functional disorders. The CureMito site on line gives more detailed histories of the families mentioned in Dr. Boles's slides as presented here today. Its purpose is to provide more advocacy for mitochondrial disease patients especially those with functional disorders. These are more common but less emphasis is placed on them than on the more severe forms of mito. Often patients with these symptoms are told, "nothing is wrong with you," or "it's all in your head." CureMito also hopes that by focusing on functional disorders more funding for research can be raised so that we can learn more about these disorders and how to best treat them.

Submitted by Joanne M. Turco, RN,MS & Cristy Balcells RN MSN (December 2010)