

Lyndonville News

Volume 5, Number 2: April 2008

Information and Support for the ME/CFS/FM Community

David S. Bell MD, FAAP, Editor

LynNews@DavidSBell.com

ME/CFS as a Mitochondrial Disease

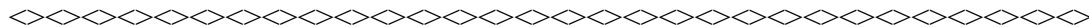
Introduction: A second issue of Lyndonville News within a month. Unheard of! But don't get your hopes up; it will probably never happen again. The main reason I put this newsletter out for free is that I never know if there will be a next issue.

Many of you have written to the e-mail address attached to the website, and I apologize for having neglected it for the past year. I read some letters and feel so overwhelmed that I cannot write back, so I have not even gone to the mailbox recently. I also get so angry when I read the nightmare stories many of you have experienced. All you did wrong was to get sick. Then the medical industrial complex made your life miserable. The medical industrial complex includes the drug companies who are not interested unless they make a big profit, the health insurance companies who will use any excuse to deny patients medications or testing, and the disability industry who survive only because they take your money and deny benefits if you get sick. All of this is done under the guise of "modern evidence-based medicine". But evidence-based medicine only works in illnesses like hypertension where you have enormous funding.

I think I have become an old codger. Cynical, disappointed..... Enough of that. In my office I have a sign for ME/CFS patients "Whining will be allowed for ten minutes only".

We are continuing to sell a few copies of Cellular hypoxia, and for those interested, please send \$25 to 1276 Waterport Road, Waterport, NY 14571. I have not made much progress in the book on how to help your primary care physician. Maybe sometime. My new passion is a book about the twenty most influential moments in ME/CFS history. It is a way to combine all the seeming disparate areas of this illness with some interesting history. I have hopes to write this over the next year, particularly if I retire. If anyone knows of a publisher who might be interested, please let me know by writing to the Waterport Road address.

Also I would like to thank a generous sponsor who kindly is sending me to the upcoming HHV6 conference. It is my hope that the next issue will be devoted to describing the science behind the ME/CFS – HHV6 link.



Clinical Notes

In the past week I have seen two patients who had an exercise lactate test which showed an elevation of blood lactate after mild exercise. They were told by their physician that they had “mitochondrial disease”. They were advised to take some vitamins, maybe some CoQ10, and have a nice day. Like nearly everything else, the term mitochondrial disease left these patients feeling bewildered and somewhat lost. While I agree that ME/CFS is a mitochondrial disease, this term needs clarification because ME/CFS is a mitochondrial disease like no other.

Until recently, when a child was diagnosed as having a mitochondrial disease, it was a disaster, even a death sentence, for it meant that there were major abnormalities in the mitochondrial or nuclear DNA that regulated energy production. Without energy (ATP) it is impossible to survive. These diseases are called MELAS, Kearns-Sayre, Leber hereditary optic neuropathy and so on. Nearly three hundred mitochondrial illnesses have been identified from genetic mutations. It is a specialized area of pediatrics, where it is possible to measure severe abnormalities in the mitochondria on muscle biopsy testing. This is what most clinicians think of when the words mitochondrial disease are mentioned, but these illnesses do not, in general, apply to ME/CFS. Many patients with ME/CFS have had muscle biopsies and most of the mitochondrial tests on these biopsies are relatively normal. We will return to why this is in a bit.

What are mitochondria? Think of mitochondria as the power factories of the cell. Nearly every cell in the body has them, usually around 500 or so in every cell. They take in oxygen and glucose and put out carbon dioxide and energy (ATP). There are two hundred different steps in this process and we will quiz you after this article. Actually all you need to know is ATP, the prime energy storage chemical (battery) of the body, and oxidative phosphorylation (ox-phos) the complex electron transport chains that do the major work. Because the mechanism of energy production is essential to nearly every cell, a defect will have symptoms in every organ system. Sound familiar?

Oxidative metabolism, the ability to utilize oxygen to produce energy, is quite efficient, and it is fascinating to look at the theories of how they came to be part of our cells. However, when the energy demand is excessive, the cells revert to a more primitive, and less efficient, form of energy production, anaerobic metabolism (metabolism without oxygen). For an interesting study on the anaerobic threshold in ME/CFS, see the literature review article that follows.

When to suspect mitochondrial disease. In a recent review article (Haas 2007) there is a list of symptoms that suggest looking for mitochondrial disease. Among these symptoms are neurologic symptoms such as ataxia, myoclonus, and encephalopathy, exercise intolerance, sensitivity to general anesthesia, and constipation. A score sheet has been developed to help in when to suspect mitochondrial disease and most ME/CFS patients would fall into the positive range. For lots of information on mitochondria please go to www.mitosoc.org, but remember that they are talking about “conventional” mitochondrial disorders, not ME/CFS.

There is another form of mitochondrial disease, or secondary mitochondrial disease. In secondary mitochondrial disease the primary problem is not with the mitochondria, but some other problem messes up mitochondrial function. There are many illnesses where the primary defect ends up causing problems with the generation of energy in mitochondria. For example,

thyroid hormone is needed for successful oxidative phosphorylation. With hypothyroidism (low thyroid) energy production is impaired and fatigue, weakness, temperature regulatory problems, and difficulty concentrating result. This is one of the reasons that when you start to describe fatigue to your primary care physician, he or she begins to write out a script to test for thyroid hormone.

So what is the problem? Why has ME/CFS not been diagnosed, studied and classified as other mitochondrial diseases? There are several reasons:

- a) Mitochondrial disease is thought of by clinicians as a fatal disease of infancy, not one that occurs later in life.
- b) Mitochondrial disease is usually thought of as a fixed, structural disease, and ME/CFS is a relapsing, remitting illness with some persons even becoming entirely well.
- c) Mitochondrial diseases are hard to diagnose, requiring muscle biopsies and detailed ox-phos testing
- d) Ox-phos testing is often normal in ME/CFS, and this has been the critical piece that has diverted attention from mitochondria.
- e) Physicians are used to thinking of organ-specific diseases (liver, kidney, etc) and mitochondria are in all cells.
- f) Few physicians have taken ME/CFS seriously until recently, and research in this area has been scant.

Of the above reasons, only reason “d” is important to us here. In 1990 I did a muscle biopsy study on ten ME/CFS patients with Dr. June Aprille. All ten persons had relatively normal ox-phos studies. Although we did not publish this finding, it is consistent with the few published studies that have been done. How can you have mitochondrial disease when the mechanism tests normal? I think that the answer to this paradox is just around the corner.

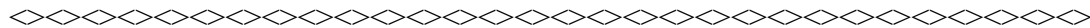
Hypothesis: If you have a patient with emphysema who is sitting in an armchair, he or she is not out of breath. You can measure the damage in tests, but to make symptoms, you have to “stress” the system – make the patient run up and down stairs. If a person with G-6-PD deficiency is sitting quietly, the blood looks normal. But feed this person fava beans and abnormalities quickly become obvious.

Persons with ME/CFS keep themselves at a balance point. They rest for two hours, then do a half hour of activity, then rest, then do more and so on. The worse the illness, the less overall activity is possible. If a ME/CFS patient does absolutely nothing for a few days, they usually feel pretty good. But go to the shopping mall for eight hours and the crash occurs. Here is the problem: in the patients studied for mitochondrial disease, they have been resting up (staying above the balance point) and a muscle biopsy done at that moment will probably not show much. But have a ME/CFS patient exercise, and then study mitochondrial function. My hunch is that the ox-phos

reactions will be seriously impaired, but this has not been systematically and methodically done. For me, this hypothesis is generated by the VanNess, Snell, and Stevens study described in the next section.

There are lots of studies that implicate mitochondrial problems; Dr. Kuratsune and carnitine. Dr. Versnon and genomics; Dr. DeMeileir, Dr. Pall, Dr. Cheney and many others. But this problem cannot be studied in tiny fragments. It is time for a good study to look at the different steps of the body's ability to generate energy. Lets hope we get to see it within our lifetimes.

1. Haas R, Parikh S, Falk M, Saneto R, Wolf N, Darin N, et al. Mitochondrial Disease: A practical approach for primary care physicians. Pediatrics 2007;120(6):1326-1333



Literature Review

Review of the “Two-day Exercise Test”

In the most recent Journal of Chronic Fatigue Syndrome (Vol 14, Number 2, 2007) there are two articles which may be the first to offer an objective proof of disability in ME/CFS. More importantly, if shown to be correct, they may give us an avenue to test and measure the biochemical abnormality which causes the symptom pattern. In this short review I would like to review these two papers and present a case of pediatric CFS which demonstrates the same abnormalities.

In the first of these papers, Margaret Ciccolella, a lawyer, teams up with Staci Stevens, Chris Snell, and Mark Van Ness of the University of the Pacific to review the legal issues surrounding exercise testing and disability (1). As everyone familiar with CFS well knows, insurance companies require proof of disability, which a standard exercise test may or may not demonstrate. However, even if disability is present, insurance companies have been quick to say that the patient was not trying hard enough, or that the patient is de-conditioned. The second paper of this series by VanNess, Snell and Stevens explain the two-day exercise test and presents results for six patients with ME/CFS (2).

As clinicians have observed, the symptom of “post-exertional malaise” is one of the most distinguishing features of CFS. This symptom is listed as one of the eight in the criteria of the Centers for Disease Control (3), and is central to the diagnosis in the recent Canadian Case Definition (4) and the proposed pediatric case definition (5). It is beginning to look like the symptom of post-exertional malaise is at the root of disability, and may be central to the pathophysiology of this complex illness spectrum.

A person with ME/CFS may be at home for several days doing little except basic activities of daily living. When this patient decides to go shopping, he or she will drive to the mall and shop for one or two hours. During this time, observers would say that the person looks entirely well, not appearing disabled. However, following this activity the patient will experience an exacerbation of pain and other symptoms of ME/CFS. This exacerbation may last one, two or

three days, and, in my opinion, the more severe the illness, the longer and more severe the exacerbation. This phenomenon is known as post-exertional malaise. The symptoms of the illness (malaise) are exacerbated by mental, physical or emotional activities (post-exertional). In an employment environment, the patient may be able to do a job well for one or even several days. However disability lies in the inability to sustain this normal level of activity. The two-day exercise test is the first to begin to explain this phenomenon.

The exercise test is no different from what has been used for years. The patient exercises on a stationary bicycle (bicycle ergometry) and breathes through plastic tubing to measure the concentration of oxygen and carbon dioxide as well as the total amount of air. The six female patients and six sedentary matched control subjects of the study were all able to achieve maximal exertion. The ME/CFS patients had a slightly lower $\dot{V}O_{2max}$ (maximal oxygen utilization) than controls (28.4 ml/kg/min vs. 26.2 ml/kg/min) and lower $\dot{V}O_2$ at anaerobic threshold (15.01 ml/kg/min vs. 17.55 mg/kg/min) on the first day of exercise testing. These values are not dramatic nor are they statistically significant. It is on the second day that interesting results are seen.

The same test was repeated the following day for all twelve subjects. As is often the case, sedentary controls improved slightly in their ability to utilize oxygen, going from 28.4 to 28.9 ml/kg/min for $\dot{V}O_{2max}$ and from 17.55 to 18.00 ml/kg/min for oxygen utilization at anaerobic threshold. The CFS patients however worsened in both categories: $\dot{V}O_{2max}$ fell 22% from 26.23 to 20.47 ml/kg/min, and oxygen utilization at anaerobic threshold fell 27%, from 15.01 to 11.01 ml/kg/min. To put this into perspective, these values are in the severe disability range on the AMA guidelines, and the decline in function from day one to day two cannot be explained by inactivity.

Sedentary or de-conditioned persons do not change their oxygen utilization because of an exercise test. Even patients with heart disease, cystic fibrosis or other diseases do not vary more than 7% from one day to the next. However, the patients with ME/CFS in this study had a significant drop; something occurred because of the test on the first day interfered with their ability to utilize oxygen on the next day. And this is exactly what patients with ME/CFS have been describing with the symptom of post-exertional malaise. As the authors state, "The fall in oxygen consumption among the CFS patients on the second test appears to suggest metabolic dysfunction rather than a sedentary lifestyle as the cause of diminished exercise capacity in CFS."

Conclusions: The results of the two-day exercise testing are objective and not dependent upon subjective symptoms. Moreover hypochondriasis, intentional falsification, and/or poor effort can be detected by the physiologic parameters. Therefore the two-day exercise test, if confirmed in a larger trial, could become a clinical trial end point. More importantly, evaluations could be designed which would demonstrate the specific metabolic abnormality generated by the exercise of day one and demonstrated on the second day exercise test. It would be my hope that these findings be explored without delay.

1. Ciccolella M, Stevens S, Snell C, VanNess J: Legal and Scientific Considerations of the Exercise Stress Test. *JCFS* 2008, 14(2):61-75.

2. VanNess JM, Snell CR, Stevens S: Diminished Cardiopulmonary Capacity During Post-Exertional Malaise. JCFS 2008, 14(2):77-85.
3. Fukuda K, Straus S, Hickie I, Sharpe M, Dobbins J, Komaroff A, Group ICS: The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994, 121:953-959.
4. Carruthers B, Jain A, DeMeirlier K, Peterson D, Klimas N, Lerner A, Bested A, Flor-Henry P, Joshi P, Powles ACP et al: Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition. diagnostic and treatment protocols. J Chronic Fatigue Syndrome 2003, 11(1):1-12.
5. Jason L, Bell D, Rowe K, Van Hoof E, Jordan K, Lapp C, A G, Miike T, Torres-Harding S, De Meirleir K. A Pediatric Case definition for myalgic encephalomyelitis and chronic fatigue syndrome. J CFS 2006, 13:1-44

.....

To Subscribe: If you wish to either subscribe or unsubscribe to the *Lyndonville News*, go to www.DavidSBell.com/DSBJoin.htm and follow the instructions. The e-mail subscription is free, while the hard copy sent by mail costs \$25 per year. For those wishing the hard copy, please send a check made out to David S. Bell MD, to 1276 Waterport Road, Waterport, NY 14571.

Disclaimer Any medical advice that is presented in the *Lyndonville News* is generic and for general informational purposes only. ME/CFS/FM is an extremely complex illness and specific advice may not be appropriate for an individual with this illness. Therefore, should you be interested or wish to pursue any of the ideas presented here, please discuss them with your personal physician.

.....