Mitochondrial Dysfunction, Post-Exertional Malaise and ME/CFS

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Editorial notes

1. The article below is germane to ME/CFS patients who have post-exertional malaise. This is a requirement for meeting the (**2003 Canadian Definition** of ME/CFS and the proposed definition in the **Institute of Medicine Report Guide for Clinicians** in 2015. The majority of ME/CFS patients meeting the **1988 CDC** criteria have this symptom. Far fewer of those meeting the **1994 CDC** or other definitions will have this symptom. A patient who lacks post-exertional malaise as described below does not have mitochondrial dysfunction. This type of exhaustion is unique to mitochondrial problems.
2. This article is intended to be read by lay readers as well as health care providers. Thus, we will sometimes explain medical terms. We will use the term ME/CFS for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome/Chronic Fatigue and Immune Dysfunction Syndrome in deference to our health-care provider readers.
3. Mitochondrial dysfunction is only a partial cause of the fatigue most ME/CFS patients have. It has been well documented that there is an abnormal increase in cytokines (chemicals released by the immune system) in ME/CFS patients following mild exercise. This causes another type of fatigue on top of the mitochondrial dysfunction fatigue discussed below. Cytokines in general, without the exercise trigger, can cause fatigue. There are probably additional causes of fatigue (such as orthostatic intolerance) as well.
4. The author of this article is an elected member of the New York Academy of Sciences, and Sigma Xi: The Scientific Research Honor Society, as well as other scientific societies. She is also a past member of the board of the Massachusetts CFIDS/ME & FM Association.

The role of mitochondria in cellular function

Except for red blood cells [1], every cell of the human body contains mitochondria—which are cellular bodies that manufacture the energy needed by the cell in order to function. The energy is essentially created by the conversion of ATP (adenosine triphosphate) to ADP (adenosine diphosphate). Thus, a molecule of adenosine with three phosphate molecules attached becomes adenosine with two phosphate molecules attached, and energy is released during the reaction. In a reverse chain of chemical reactions, ATP can be created from ADP or from AMP, which is adenosine with one phosphate molecule attached. All of these reactions involve multiple chemicals and enzymes. The ATP is initially derived from either carbohydrate (in the form of glucose or glycogen (a form of glucose stored in cells)) or fatty acids. [2]

Glycolysis is the metabolic pathway in mitochondria that converts glucose/glycogen into pyruvate and hydrogen. The pyruvate is transformed into acetyl-coenzyme A (acetyl –CoA). *If* there is sufficient oxygen, the acetyl-CoA then undergoes the Krebs cycle (also called the citric acid cycle). The biochemistry of the Krebs cycle is very complex. [2, 3, 4] We will not go into it here. The rate of the Krebs cycle transformations determines how much ATP is ultimately generated. [3] The Krebs cycle involves vitamin B-1 (thiamine), vitamin B-2 (riboflavin), magnesium, and malate (from malic acid), which has implications for treatment of mitochondrial disorders. [2]

As a result of the Krebs cycle and what is called the Electron Transport Chain, ADP is transformed into ATP. (This transformation of ADP into ATP using oxygen is called *oxidative phosphorylation*.) Reactive oxygen species (ROS) build up as a byproduct and these damage mitochondrial membranes (inner and outer), cellular RNA, cellular DNA, proteins made by the cell, and cellular membranes .[4, 5] Damage caused by ROS is called *oxidative stress*. ROS can cause apoptosis of the cell (cellular suicide.) [4, 5, 6, 7]

If there is *not* sufficient oxygen, then less ATP is created and lactate builds up as a byproduct. To quote from Wikipedia [8] (which is an exposition of material in *Science* [9]):

> "When the energy in ATP is utilized during cell work (ATP hydrolysis), protons are produced. The mitochondria normally incorporate these protons back into ATP, thus preventing buildup of protons and maintaining neutral pH. If oxygen supply is inadequate (*hypoxia*), the mitochondria are unable to continue ATP synthesis at a rate sufficient to supply the cell with the required ATP. In this situation, glycolysis is increased to provide additional ATP, and the excess pyruvate produced is converted into lactate and released from the cell into the bloodstream, where it accumulates over time. While increased glycolysis helps compensate for less ATP from oxidative phosphorylation, it cannot bind the protons resulting from ATP hydrolysis. Therefore, proton concentration rises and causes acidosis."

We will discuss the consequences of this below in the section on the **characteristics and consequences of mitochondrial dysfunction fatigue**.

When there is insufficient glucose/glycogen for the mitochondria to synthesize ATP, then fatty acids are used as a fuel source. This involves the release of fatty acid from fat cells into the blood stream, "activation" and transport of the free fatty acids into the mitochondria of a cell, and the break-down of the fatty acid into acetyl-CoA, which ultimately yields ATP. This last step is called beta-oxidation. [2, 10] Unfortunately, the process of the activation and transport of long chain fatty acid into mitochondria involves breaking down ATP into byproducts and transporting the relevant byproduct (acyl-CoA—which isn't the same as acetyl-CoA) via what is called the *carnitine transport system*. [2, 10, 11, 21] Thus ATP has to be used to transport a byproduct of fatty acid into the mitochondria in order to create more ATP.

Once in the mitochondria, the acyl-CoA is transformed into acetyl-CoA as part of beta-oxidation. After acetyl-CoA is created, it enters the Krebs cycle and the process of creating ATP is like that for creating ATP from glucose using oxygen. Involved in the transport system and beta-oxidation are acetyl-carnitine, co-enzyme Q-10, biotin, and vitamin B-12, which has implications for the treatment of mitochondrial disorders. [2, 10, 11, 12]

Most types of cells can utilize fatty acid as a fuel except for the cells of the brain. [10] When the cells of the liver utilize fatty acid in their mitochondria, they generate chemicals called *ketone bodies*. The ketones then enter the blood stream. All cells of the body, including brain cells, can use ketones as an alternate source of energy. [10]

Generally speaking, cells prefer to use glucose as a fuel, under oxygenation. During fasting, fatty acids and ketone bodies are more important energy sources for most cells, with the idea that the glucose available is saved for brain cells. [10] The situation in skeletal muscle cells is more complicated. The choice of fuel source is largely determined by exercise intensity and duration. As exercise intensity increases, the use of glucose/glycogen intensifies. However, at low intensity or moderate exercise, fatty acid is the preferred fuel .[10, 11] As for the heart, fatty acids are the preferred fuel for 60-90% of its energy needs. [14]

Illnesses with mitochondrial dysfunction, including the case for ME/CFS

The first appearance of a mitochondrial disease in the medical literature was probably the description of adult onset blindness by

Theodur Lebur in 1871. [15] (This is now known as Leber's Hereditary Optic Neuroretinopathy (LHON).) [16] However, the existence of mitochondria in cells was still in the process of discovery and their role in the illness was not known. The existence of mitochondria in cells was discovered over time from 1857-1886. [17] The elucidation of their function and the role of ATP in cellular energy generation took most of the 20th century (1912-1997). [17] In 1962, Luft's disease (which involves hypermetabolism and elevated core temperature) was the first proposed mitchondrial disease. [18] It wasn't until 1989 that the mitochondrial and genetic bases of LHON and Luft's illness were confirmed. [18] The first discovery of pathogenic mitochondrial mutations in DNA was in

1988. [15] The role of inherited genetic mitochondrial defects in mitochondrial myopathies was only elucidated in the late 1980s and 1990s. [17] The role of inherited genetic mutations in fatty acid beta-oxidation enzymes started to be elucidated in the 1970s and 1980s. Many aspects are still unknown. [10]

While many inherited genetic mitochondrial disorders occur in the mitochondria of all cells in the body, some are limited to specific cell sites, such as the eye, motor neurons (as in Lou Gerhig's disease or amotrophic lateral sclerosis), skeletal muscle, or brain (as in Huntington's disease). [10, 11, 12, 13, 14, 15, 19, 20]

The role of acquired mitochondrial dysfunction in common diseases has only begun to be elucidated the last fifteen years or so. It is now known that dysfunctional mitochondria play an important role in diseases of the brain such as Alzheimer's, and Parkinson's. [19, 20, 21] Type-2 diabetes mellitus is also known to be an acquired mitochondrial dysfunction disease of the mitochondria in skeletal muscle and the pancreas. [3, 6, 22, 23, 24, 25, 26, 27, 28, 29]

ME/CFS patients are not immune to the type-2 diabetes epidemic. So, we will note that in addition to any mitochondrial problems stemming from ME/CFS, patients also having metabolic syndrome or type-2 diabetes are having trouble with the mitochondrial problems from these conditions as well. Fewer and smaller-sized mitochondria are found in the skeletal muscle of metabolic syndrome or type-2 diabetic patients. [28] This is significant because normally 67% of the volume of skeletal muscle cells is occupied by mitochondria, compared to 20-30% of cardiac muscle cells. [28] There is diminished electron transport activity in mitochondria of skeletal muscle of diabetics that can't be explained just by the diminished numbers of mitochondria. [3, 28] Fatty acids tend to accumulate in the cells of skeletal muscle in type-2 diabetes and this leads to reduced mitochondrial oxidative capacity. [3, 28] There is clearly a defect in the ability of skeletal muscle to oxidize fatty acids. [27] It is also the case that evidence exists of decreased mRNA (messenger RNA) expression of several genes associated with oxidative phosphorylation in first degree relatives of type-2 diabetics. [27] For a more detailed overview of the role of mitochondrial dysfunction in type-2 diabetes, see reference #27.

Since a number of ME/CFS patients are known to be also hypothyroid, hyperthyroid or have polycystic ovary syndrome (PCOS), it should be noted that insulin resistance and mitochondrial dysfunction in skeletal muscle play roles in these conditions. [29] In the cases of both hypothyroidism and hyperthyroidism, there are decreased glycogen synthesis, down-regulated intracellular glucose catabolism, altered blood flow, and decreased muscle oxidative capacity in skeletal muscle. [29] In PCOS, it is the case that there is decreased glycogen synthesis and impaired mitochondrial oxidative metabolism in skeletal muscle. [29] Thus ME/CFS patients with one or more of these additional conditions will have increased mitochondrial dysfunction in skeletal muscle, compared to ME/CFS patients who just experience post-exertional malaise.

The evidence that ME/CFS is at least in part an acquired mitochondrial dysfunction disease of skeletal muscle is now quite strong. [30, 31. 32, 33, 34, 36, 37, 38, 39, 41, 42, 43, 44, 45] We could find only one study that looked at mitochondrial function in other types of cells in CFS/ME. [40]

Vermeulen *et al.* [30] found that in two exercise tests 24 hours apart, ME/CFS patients reached an anaerobic threshold and maximal exercise capacity at a much lower oxygen consumption than controls. This discrepancy was worse on the second test. The researchers concluded that this demonstrated an increase in lactate production and decrease in ATP production compared to controls. They did other tests that seemed to indicate that the oxidative phosphorylation occurring in both ME/CFS patients and controls was the same. So, they concluded that the dysfunction involved another pathway other than oxidative phosphorylation. (Other studies don't agree with this conclusion.)

Kennedy *et al.* [31] found increased markers of oxidative stress in ME/CFS patients and that the magnitude of the increase was correlated to the symptoms of post-exertional malaise. Paul *et al*. [32] found that both ME/CFS patients and controls showed a decrease in voluntary muscle contractions during exercise consistent with fatigue following maximum voluntary contractions. Thus the researchers concluded that even though the force of the contractions were always less in the ME/CFS group, the patients were working to their maximum capacity. ME/CFS patients were unable to recover their pre-exercise force of contraction after a 200-minute recovery period that worked for healthy sedentary controls. In addition, muscle contraction force was even less 24 hours after the exercise than immediately after the exercise for the ME/CFS group. The researchers concluded that this was consistent with mitochondrial dysfunction.

In 1984, several years before CFS was defined in the U.S, Arnold *et al*. [33] found that using 31P nuclear magnetic resonance they could demonstrate an abnormal rise in intracellular acidity in the exercised forearm of a British patient with post-viral fatigue syndrome (ME). Because the rise was out of proportion to associated changes in high-energy phosphates, they concluded it demonstrated an excessive lactic acid formation due to an acquired disorder of metabolic regulation. In 1991 the Behans reported finding mitochondrial abnormalities in the biopsies of skeletal muscle of 50 ME patients. [34] (It should be noted that the patients studied by the Behans had ME after infections of skeletal muscle with enteroviruses such as Coxsackie.) Other studies have not found *structural* abnormalities in mitochondria. [35]

In two studies, the Plioplys found that there were no obvious structural changes to mitochondria in skeletal muscle biopsies of ME/CFS patients [35], but the ME/CFS patients had statistically significant lower levels of serum total carnitine, free carnitine and acylcarnitine compared to healthy controls. [36] They concluded this was due to dysfunctional mitochondria. They also found a statistically significant correlation between lower serum total and free carnitine levels and worse clinical symptomatology. [36] Earlier, Kuratsune *et al*. [37] had discovered that deficiencies of serum acylcarnitine had statistically significantly correlated with worsened fatigue symptoms in CFS/ME patients, but the researchers had not measured total and free carnitine levels.

Using ME/CFS patients identified by the 1994 CFS case definition (which is broader than the 1988 or Canadian definitions of CFS), Lane *et al*. [38] identified two subgroups of CFS patients. One group had an abnormal rise in lactate following exercise (which they called the SATET+ve group) and the other did not (SATET-ve). They did phosphorus magnetic resonance on the forearm muscles of 10 ME/CFS SATET+ve patients, 9 ME/CFS SATET-ve patients, and 13 healthy controls. There were no differences in spectra at rest for the three groups, but after exercise the ME/CFS SATET+ve patients showed a significant increase in intracellular acidity compared to the other two groups. The ME/CFS SATET+ve patients also showed a significantly lower ATP synthesis rate during recovery from exercise than the other two groups. The researchers concluded these ME/CFS patients showed impaired oxidative phosphorylation, but the others (SATET-ve) did not.

In the book *Mitochondria in Pathogenesis*, Chazotte [39] gives a detailed overview of the evidence for mitochondrial dysfunction in ME/CFS as of 2000. He observed:

> "Thus there is ample *clinical* evidence to suggest a role for mitochondrial dysfunction in many different tissues and cells in CFS, which could give rise to many of the symptoms. Whether this role is due to a specific mitochondrial defect, perhaps in genetically susceptible individuals, or is an effect of some other problem such as altered cytokine levels that in turn affect mitochondrial function, needs investigation. Due to the difficulty in obtaining human specimens in sufficient quantities per specimen for biochemically based studies of mitochondrial function, there are few (and no detailed) studies of mitochondrial function in CFS patients." [39]

Myhill *et al.* [40] undertook to rectify this lack of biochemically based studies and examined blood neutrophils (a type of white blood cell) of 71 ME/CFS patients and 53 healthy controls to obtain five numeric measurements of mitochondrial function, called the ATP profile test. The ME/CFS patients were ranked on the Bell CFS Ability Test (developed by Dr. David Bell) to give a scale measurement of ME/CFS severity from 0 to 10 (with 0 being "constantly bedridden with severe symptoms and unable to care for himself/herself"). The ME/CFS patients were in the "very severe" (25 patients), "severe" (21 patients) and "moderate" (25 patients) ranges on the Bell scale.

In some of the five measurements, there were ME/CFS patients who had above the *minimum* (but below the average) measured in the controls. The three of the most severely ill patients had one value each within the low normal range for controls, but the other four values were well below the *minima* for the controls. When the number of the five measurements that were below the *minima* of the healthy controls was taken into account by the researchers, on average the "very severe" patients had 3.7 measurements totally below the normal ranges, "severe" patients had on average 3.5, and the "moderate" patients had on average 2.2 of the five measurements below the normal ranges.

The researchers pointed out that if they had only measured one factor instead of five, significant numbers of the patients would have been classified as "normal" (albeit usually very low normal) for the factor. They stated, "For example, if only ATP had been measured, 28% of all the patients would be classified as normal, and if only Ox Phos had been measured, 32% of the 'very severe' patients would be classified as normal." [40]

Finally, the researchers concocted a Mitochondrial Energy Score for each patient using the five factors, which they said measured the overall mitochondrial energy-producing efficiency of the neutrophils of the study participants. Only *one* of the 71 patients had a Mitochondrial Energy Score *above the minimum* for the healthy controls. That patient had a Bell CFS Ability Score of 7, but also had two of the five factors below the minima for the healthy controls. Since the CFS Severity Score had been computed first for the patients, the researchers looked at predicting CFS severity from the Mitochondrial Energy Score.

They concluded that mitochondrial dysfunction is a major risk factor for severity in ME/CFS. However, they also noted that since they measured the ATP factors only in neutrophils, conclusions could only be reached concerning adverse effects on the function of the immune system, not in skeletal muscle. The researchers observed:

> "Our observations strongly implicate mitochondrial dysfunction as the immediate cause of CFS symptoms. However, we cannot tell whether the damage to mitochondrial function is a primary effect, or a secondary effect to one or more of a number of primary conditions, for example cellular hypoxia or oxidative stress including excessive peroxynitrite." [40]

Characteristics and consequences of mitochondrial dysfunction fatigue in skeletal muscle

Those who have mitochondrial dysfunction of the skeletal muscle can experience two main types of fatigue. One is the result of increased acidosis inside the muscle cells and has as a marker increased lactate in the blood. This is a result of muscle cells trying to create ATP when there is insufficient oxygen. Endurance athletes (such as marathoners) can experience this type of fatigue. They refer to it as "hitting the wall." [8, 9] It is also referred to as "metabolic fatigue." [46]

The second type of fatigue is the result of a large build-up of Reactive Oxygen Species (ROS) and depletion of ATP in the muscle cells. As far as we can determine from a careful search of the medical literature, this second type of fatigue is unique to patients with known inherited genetic mitochondrial diseases of skeletal muscle, AIDS patients undergoing treatment with antiretroviral drugs (who have severe mitochondrial dysfunction), [47] and ME/CFS patients experiencing post-exertional "malaise." It is this second type of fatigue that has the most permanent serious consequences for patients.

The first type of fatigue, metabolic fatigue, feels like a burning, dull aching weariness in muscles. The affected muscles feel stiff and affected limbs feel heavier and heavier, as the ability of the muscles to contract declines. [49] The increased acidity in the muscle cell lowers the sensitivity of the contractile apparatus to calcium Ca^{2+}. It is unclear what exact role lactic acid has in this process, but increased lactate in the blood is a marker for this type of fatigue. [46]

As mentioned in the preceding section, a subgroup of ME/CFS patients have an abnormal rise in lactate with minor exercise and a very slow recovery from this condition. [30, 32, 35, 38, 48] It is not unusual for these patients to require 24-48 hours or more of bed rest to fully recover. Even in healthy people, delayed onset muscle soreness (DOMS) occurs with severe muscle tenderness as well as loss of strength and range of motion, usually reaching a peak 24 to 72 hours after the "extreme" exercise event that caused the excessive lactate in the blood. [49] (Healthy people don't have to retire to bed to recover, however.) Exercise physiologists still do not understand why DOMS occurs, but most research points to actual muscle cell damage and an elevated release of various metabolites into the tissue surrounding the muscle cells. [49] These lead to an inflammatory repair response that lasts a couple of days in healthy people. [49] How long it lasts in ME/CFS patients who have excessive lactate after very little exercise is unknown. For some ME/CFS patients, just standing up for 10 minutes is enough to create this problem. It should be noted that excess lactic acid is now known to be neurotoxic, so continual problems with this could lead to the death or damage of motor neurons in skeletal muscle. [50]

The more serious type of fatigue is the one resulting from excessive build-up of ROS in the muscle and depletion of ATP. This type of "fatigue" is extreme prostration that occurs 8 or more hours after exercise (or what passes for "exercise" in ME/CFS patients and would be considered normal activity by healthy people.) Patients feel a deep, whole-body weariness and feel the necessity to lie still and not move due to extreme fatigue. Trying to even turn over in bed requires a great deal of painful effort of will. In addition, patients feel very sore all over their bodies. ME/CFS patients often describe this as feeling being beaten up and run over by a Mack truck or bus. The term post-exertional "malaise" seems pathetically inadequate as a descriptor of this feeling.

Mitochondrial specialist Dr. Donald Johns [51] has warned that when a patient feels this way, it is very important to listen to his/her body. The extreme fatigue feeling is from depletion of ATP and the beaten-up/run-over feeling is from excessive ROS that not only *did* permanent damage to muscle cells, but also *is still doing* damage. Thus, it is essential to stay in bed and move as little as possible until the condition improves—even if that takes days. The best thing to do is for the patient to try to avoid getting into this condition in the first place by pacing and staying inside his/her "energy envelope." This is not so easy to do at times, however.

ROS produced in the mitochondria damage mitochondrial DNA, for instance. [3] This leads to alterations to the polypeptides encoded by the DNA. A decrease in electron transfer then ensues, but electron transfer is needed for generation of ATP. Thus, more ROS are produced in a vicious circle of oxidative distress and energetic decline. [52] Mitochondrial DNA damage also results in daughter cells that are mutated and in cellular apoptosis. [4, 5, 6, 7, 28]

Muscle inflammation and oxidative stress are now known to play an important role in muscle atrophy. [53] In addition, many ME/CFS patients have a low-grade fever, which means they have high levels of interleukin-1 (IL-1). [54, 55] IL-1 is known to cause muscle catabolism (muscle destruction). [54, 55] So ME/CFS patients with high levels of ROS and low-grade fevers can expect noticeable destruction of skeletal muscle with difficulty in replacing it.

ROS generated from mitochondria also damages proteins and lipid in membrane components for mitochondria membranes and cellular membranes. This results in more mitochondrial dysfunction and cellular apoptosis. [4, 5, 6, 7, 28]

All in all, ME/CFS patients need to try to avoid post-exertional malaise as much as possible in order to avoid permanent damage and permanent adverse changes to skeletal muscle.

Treatment

Living in the "energy envelope"

Mitochondrial specialists advise conserving energy to minimize the two types of fatigue. [51] ME/CFS specialists advise acknowledging the finiteness of energy for each patient for each day. Some call this the "energy envelope." [59, 60, 61] Unfortunately, the energy and ability to function will vary for the patient from day to day. Especially if more is done one day, less will have to be done on following "recovery" days. Thus, the patient needs to make constant cost/benefit judgments about doing activities that use energy. There will be times that a patient decides that the psychological and emotional benefit of an activity outweighs the physical cost. That is acceptable, as long as the patient attempts to limit the physical damage that follows the activity and recognizes the recovery time that will be necessary. [63] We consider this acceptable since it is now known that most patients either do not recover, or don't recover for years, if not decades. [62, 64 , 65] It is psychologically important for a patient to have some daily activity that creates a vestige of joy and psychological well-being, and not put everything "on hold" awaiting a recovery that might not come. [63]

Supplements to treat mitochondrial dysfunction

Other than metformin, angiotensin II receptor inhibitors, and angiotensin converting enzyme inhibitors that help with the mitochondrial dysfunction of type-2 diabetes, there are no known pharmaceuticals for mitochondrial dysfunction. [27] Thus treatment consists of pacing (as described above) and over-the-counter supplements. Physicians will have to adjust dosages for the individual patient, especially keeping in mind that ME/CFS patients tend to be very sensitive to pharmaceuticals and supplements. It should be noted that very few side effects, if any, are known for the supplements below and very few interact with pharmaceuticals. More information about side effects, maximum safe dosages and interactions with pharmaceuticals can be found in the *PDR for Nutritional Supplements* [56] and on our website in "**Review of Nutritional Supplements Used for ME/CFS/FM**.

When we give dosages, we are usually quoting those given by mitochondrial specialists (which tend to be higher than those suggested by ME/CFS specialists). It is still not known what levels in the blood are needed to cross the cellular membrane and enter the mitochondria. [57, 58] Besides pacing, treatment is broken up into the categories of improving the function of mitochondria, antioxidants to help prevent damage from ROS, and recovery from excess acidosis and post exertional malaise.

Mitochondrial Function

- Magnesium (up to 600 mg a day [2, 71, 76, 80, 81] (Blood levels must be monitored periodically for patient safety))

- Co-enzyme Q-10 (100-200 mg three times a day) [27, 50, 51, 58, 66, 67, 68, 69, 72, 79, 80, 81]
- Acetyl-l-carnitine (500-1000 mg three times a day) [50, 51, 79, 81] (The acetyl-l form of acetyl-carnitine crosses the blood/brain barrier and helps brain mitochondria as well)
- Creatine [50, 77, 78]
- Folic acid [50, 79]
- Malic acid (600-1200 mg twice a day) [2, 80, 81]

Antioxidants for ROS

- Vitamin C (1000 mg twice a day) [28, 50, 51, 58, 73, 79]
- Vitamin E (400-600 IU) [50, 51, 58, 73, 79]
- Alpha-lipoic acid [28, 58, 66, 73, 79]
- Vitamin B-6 [74, 79]

Recovery from prostration fatigue

- Vitamin B-1 (thiamine) (100 mg twice a day) [70, 50, 55, 79, 80]
- Vitamin B-2 (riboflavin) (100 mg) [70, 50, 55, 79, 80]
- Biotin (5 mg twice a day) [70, 55, 71, 75, 76, 79, 80]

Postponing build-up of lactic acidosis

- Time-release guaifenesin (600-800 mg) [82]

There is anecdotal evidence that guaifenesin slows the build-up of acidosis in skeletal muscles of ME/CFS patients who had enteroviruses or other skeletal-muscle attacking viruses as the trigger for their illness. Thus they have special extra damage to their skeletal muscles. Precisely why guaifenesin works is unknown, but it definitely does work for some patients. Guaifenesin is a uricosuric—a drug that increases the excretion of uric acid from the blood into urine. [83] It seems to help the excretion of excess phosphate from the cells of the body, which might have a bearing on mitochondrial dysfunction, since excess intracellular phosphate builds up with the hydrogen ion H+. [82, 83] Thus it might just act as a chemical buffer in the blood, slowing the build-up of acidity. The ME/CFS patient population that might be helped by this drug is a probably a small subset of the ME/CFS patient community.

Exercise and ME/CFS

Since ME/CFS patients get substantial bed rest and have excess cytokines which cause skeletal muscle destruction, as well as having the two types of fatigue mentioned above that create more muscle damage, it is important that ME/CFS patients get some exercise. However, typical physical therapy does not work, since the patients' ability to safely exercise is limited. Any physical therapy that is undertaken has to be supervised by a physical therapist familiar with ME/CFS and the consequences of mitochondrial dysfunction with exercise. There are many studies showing that Graded Exercise Therapy (GET) can be very damaging to ME/CFS patients. [84] There is also anecdotal evidence that ME/CFS patients do not build up the muscle strength after exercise that a healthy person would.

Dr. Charles Lapp, an ME/CFS specialist at the Hunter-Hopkins Center, recommends, "Exercise no more than two to five minutes at a time and follow it up with five minutes of rest." [85] It is essential that this sort of pacing while exercising is done so that more damage is not done and the two types of fatigue don't develop.

Disclaimer for Patients

The various vitamins and supplements mentioned in this article have precautions, adverse reactions and side effects. Patients should check with their doctors before undertaking any part of the regimen suggested in the article. Patients also would be advised to read the article linked above, "**Review of Nutritional Supplements Used for ME/CFS/FM** (/more-resources-for-me-cfs/14-review-of-nutritional-supplements-used-for-cfidsfm)" to note the general and specific cautions for a number of the supplements and vitamins

reviewed in this article. As not enough is known about some of these supplements' effects on fetuses and babies, pregnant and lactating women should especially review the linked article as well as checking with their physicians before taking any of the cited vitamins or supplements.

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