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The Massachusetts CFIDS/ME & FM Association Winter 2003 *UPDATE*

As a fitting close to my tenure as medical editor of The *UPDATE*, I thought it would be appropriate to give a summary of what is known about some of the more popular supplements used by the Chronic Fatigue Syndrome/Chronic Fatigue and Immune Dysfunction Syndrome/Myalgic Encephalopathy (CFS/CFIDS/ME) and fibromyalgia (FM) patients. The information is from the *Physician's Desk Reference for Nutritional Supplements* (1) and all quoted material is from that book. Of course, one always needs to avoid supplements with ingredients to which one is allergic or sensitive, and CFS/CFIDS/ME and FM patients do have a high degree of sensitivity and allergy. In addition, pregnant and lactating women are warned that not enough is known about these supplements' effects on fetuses and babies, so they should avoid all of them. I'm not going to repeat those warnings for each supplement. Always keep in mind our golden rule for any medications and supplements,
start with a low dose and gradually increase it.

Acetyl-L-Carnitine

Acetyl-L-carnitine may have neuroprotective, cytoprotective, antioxidant and anti-apoptoticactivity. (Anti-apoptotic activity means it interferes with abnormal cellular suicide, which seems to be a problem in CFIDS/ME.) There is speculation that acetyl-L-carnitine crosses the blood/brain barrier better than L-carnitine. (Dr. Bruce Ames, whose research I cited in the Fall 2002 *UPDATE* maintains that this is so.) There are some studies backing up each of the activities mentioned. Peripheral nerve function has improved in diabetes. Mitochondrial membrane potential improves with acetyl-L-carnitine, which improves the functioning of mitochondria.

Contraindication: None known.

Precaution: People with seizure disorders should only use this under medical supervision.

Adverse Reactions: Rarely, mild gastrointestinal symptoms such as nausea, vomiting, abdominal cramps and diarrhea.

Interactions: Therapy with nucleoside analogues didanosine, zalcitabine and stavudine, and with valproic acid and the pivalic acid-containing antibiotics may lead to secondary L-carnitine deficiency.

Dosage: 500-2000 mg daily in divided doses. (Dr. Ames used 500 mg. twice a day together with alpha lipoic acid.)

N-acetylcysteine (NAC)

NAC is a liver protectant with anti-oxidant and anti-apoptotic activity. It is a delivery form of L-cysteine, which is a major precursor to glutathione. It also helps liquefy mucus and has been shown to be of help in chronic obstructive pulmonary disease. There is evidence NAC has anti-apoptotic activity, especially in the pancreas and for neurons. It also helps against oxidative damage to mitochondrial synapses. There is some indication it may help with memory loss. NAC has improved myocardial contraction in an animal model of myocardial ischemia. In humans it is known to inhibit platelet aggregation and lowers "lipoprotein (a) levels to a degree not previously achieved by drugs or diet."

Contraindications: People who form kidney stones, especially cysteine kidney stones.

Precautions: NAC clearance is reduced in those with chronic liver disease. It should be used with caution in those with peptic ulcer disease since it may disrupt the gastric mucosal barrier. It can cause false-positive results in the nitroprusside test for ketone bodies used in diabetes.

Adverse reactions: Nausea, vomiting, diarrhea, headache (especially when used with nitrates) and rashes. Very rarely, kidney stones.

Interactions: Headaches may be caused when used with nitrates. Carbamazepine levels may be reduced when NAC is used with that drug. No known interactions with food, nutritional supplements or herbs.

Dosage: 600-mg. one to three times daily. Drink 6-8 glasses of water a day to avoid kidney stones. Always keep in mind our golden rule for any medications and supplements, *start*

with a low dose and gradually increase it.

Alpha-Lipoic Acid

"Most of the metabolic reactions in which alpha lipoic acid participates occur in mitochondria. These include the oxidation of pyruvic acid (as pyruvate) by the pyruvate dehydrogenase enzyme complex." Alpha-lipoic acid and its metabolite DHLA scavenge a wide range of reactive oxygen species including hydroxyl radicals, the nitric oxide radical, peroxynitrite, and hydrogen peroxide. Alpha lipoic acid is approved for treatment of diabetic neuropathy in Germany. There is some evidence it may be useful in treating other aspects of diabetes as well. There is some evidence it helps prevent the oxidation of LDL cholesterol and protects generally against oxidative stress. There is preliminary evidence that it has immune-modulating effects and may slow the aging of the brain.

Contraindications: None known.

Precautions: It lowers insulin resistance, so it may lower serum glucose levels in diabetics.

Adverse Reactions: None known.

Interactions: None except the lowering of insulin resistance in diabetics may require adjusting of diabetic medication.

Dosage: Those with diabetic neuropathy use 300 mg a day in divided doses. Dr. Ames used 200 mg. with 500 mg acetyl-L-carnitine twice a day in his brain studies.

Bromelain

Bromelain has digestant activity (it is an enzyme found in pineapple) and has anti-inflammatory, immunomodulatory, anti-diarrheal, anti-carcinogenic and wound-healing properties. "The mechanism of the putative antiinflammatory activity is not well understood. It may be accounted for, in part, by activation of plasmin production from plasminogen and reduction of kinin, via inhibition of the conversion of kininogen to kinin." (Kinin causes pain in inflammation, amongst

other activities.) Bromelain also increases T-cell activation, and enhances antigen-independent binding to monocytes. It has been shown to help in chronic bronchitis and chronic sinusitis because it also thins mucous.

Contraindications: Avoid if allergic to pineapple.

Precautions: May cause blood-thinning activity in some people. .

Adverse Reactions: Sometimes minor G I symptoms.

Interactions: Increases serum levels of amoxicillin and tetracycline. May enhance anticoagulant activity of warfarin and aspirin. .
Dosage: 500-2000 GDUs taken 1-3 times a day.

Coenzyme Q-10

CoQ-10 has cardioprotective, cytoprotective and neuroprotective activities. It "is an essential cofactor in the mitochondrial electron transport chain, where it accepts electrons from complex I and II, an activity that is vital for the production of ATP. CoQ-10 has antioxidant activity in mitochondria and cellular membranes, protecting against peroxidation of lipid membranes. It also inhibits the oxidation of LDL-cholesterol."

Contraindications: None known.

Precautions: May improve beta-cell function of the pancreas and glycemic control in type-II diabetics. Diabetes medication may have to be adjusted.

Adverse Reactions: Mild GI symptoms sometimes with doses higher than 200 mg a day.

Interactions: May decrease the effectiveness of warfarin. Statin drugs will significantly decrease CoQ-10 serum levels since CoQ-lO and cholesterol share the same metabolic pathways. Some beta-blockers block CoQ-10 dependent enzymes.

Dosage: 5-300 mg. (My mitochondrial specialist at Beth Israel recommends 200 mg twice a day for those with mitochondrial dysfunction. He warns against more than 600 mg. a day.)

Dehydroepiandrosterone (DHEA)

DHEA is a steroid hormone produced in the adrenal glands, gonads and brain. "Extracts of the Mexican yam Dioscorea or the wild yam Dioscorea villosa are not converted to DHEA following ingestion." The *PDR* emphasizes that DHEA and its metabolite DHEA-S should not be used unless ordered by a doctor for documented abnormally low levels of DHEA. It says, "Regarded as a drug by many researchers and banned for all uses in the United Kingdom and Canada, the use of DHEA as a supplement is not indicated for the treatment or prevention of any condition without qualified medical recommendation and monitoring. The best available research suggests that DHEA, particularly at the high doses many have reported are being used, poses potentially serious health risks." Dr. Nancy Klimas has warned us of its strong potential to cause breast and ovarian cancer as well as prostate cancer during her talks to the Massachusetts CFIDS/ME & FM Association..

Magnesium

"Magnesium is an essential mineral in human nutrition with a wide range of biological functions. Magnesium is involved in over 300 metabolic reactions. It is necessary for every major biological process, including production of cellular energy and the synthesis of nucleic acids and proteins. It is also important for the electrical stability of cells, the maintenance of membrane integrity, muscle contraction, nerve conduction and the regulation of vascular tone, among other things." Not mentioned by the *PDR* is the fact that many of those 300 metabolic reactions involve the functioning of the immune system. An activated immune system uses magnesium and zinc at rapid rates. It has been shown that CFS/CFIDS/ME patients in particular have lower levels of intracellular magnesium than healthy controls.

The typical magnesium test only measures serum levels of magnesium. Serum levels of magnesium can be normal but intracellular levels can be low at the same time. Magnesium deficiency is an important cause of low potassium. There is evidence that magnesium has anti-osteoporotic activity. It definitely has anti-arrhythmic activity. Magnesium may have anti-hypertensive, glucose-regulatory and bronchodilatory activity and possible anti-migraine activity. "Magnesium has been used with some success in a few studies to promote bronchodilation and improve lung function in some asthmatic patients." Magnesium can help relieve some types of pain. There is evidence it may reduce the occurrence of kidney stones.

Contraindications: Contraindicated in kidney failure and in those with certain types of heart problems.

Precautions: Those with myasthenia gravis should avoid the use of magnesium supplements.

Adverse reactions: Usually none in doses of 350 mg a day or less. However, since magnesium is an electrolyte which influences heartbeat and potassium levels (which also affect heartbeat), it is wise to only supplement with magnesium or potassium with regular checks by a doctor of serum blood levels of both minerals.

Interactions: Concomitant intake of bisphosphonate, a quinolone or a tetracycline and magnesium may decrease the absorption of the other drug. Concomitant intake of more than 2 grams of calcium with magnesium will decrease the absorption of magnesium. Concomitant intake of inositol hexaphosphate and magnesium may depress absorption of magnesium. Concomitant intake of magnesium and iron or manganese may decrease the absorption of the other mineral. Concomitant intake of phosphate and magnesium may decrease the absorption of both.

Dosage: 100 to 300 mg a day.

Malic Acid

Malic acid is from apples and other fruit. "Malic acid, in combination with magnesium, has putative anti-fibromyalgic activity. The mechanism of malic acid's anti-fibromyalgic activity is unknown." I personally have had very noticeable improvement in my CFS/CFIDS/ME symptoms pertaining to muscle function with a malic acid/magnesium combination. I believe the reason is in the further information given in the *PDR*. "Malic enzyme catalyzes the oxidative decarboxylation of L-malate to pyruvate with concomitant reduction of the cofactor NAD+ or NADP+. These reactions require divalent cations magnesium or manganese...Pyruvate formed from malate can itself be metabolized in a number of ways, including metabolism via a number of steps to glucose. Malate can also be metabolized to oxaloacetate via the citric acid cycle. The mitochondrial malic enzyme, particularly in brain cells, may playa key role in the pyruvate recycling pathway, which utilizes dicarboxylic acids and substrates, such as glutamine, to provide pyruvate to maintain the citric acid cycle activity when glucose and lactate are low." In other words, malic acid is involved in the Krebs cycle and mitochondrial creation of energy.

Contraindications: None known.

Precautions: None.

Interactions: None known.

Dosage: 1200-2400 mg daily with 300 to 600 mg daily magnesium.

NADH

"NADH is a natural substance found in most life forms and is necessary for energy production. NADH is located both in the mitochondria and cytosol of cells...and is synthesized by the body and thus is not an essential nutrient. It does require the essential nutrient nicotinamide [a form of niacin] for its synthesis" The *PDR* goes on to say "There is scant pharmacokinetic data on supplemental NADH. It is unclear how much of an administered dose is absorbed and what the metabolic course is of any absorbed NADH. If any NADH were to be transported into cells, it is highly unlikely that any would enter the mitochondria." It is thus my opinion that a person with CFIDS/FM with reason to believe that there is mitochondrial malfunction would probably be better served by taking a nicotinamide supplement rather than NADH. Your pocketbook would definitely be better served and you probably would increase the NADH in your mitochondria.

Contraindications: None known.

Precautions: None mentioned by the PDR. I personally know people allergic to eggs should beware of most commercially available forms of NADH.

Adverse reactions: Some GI side effects.

Interactions: None known.

Dosage: 5 mg daily or 5 mg twice a day.

Phosphatidylserine

Phosphatidylserine is located in the internal layers of biologic membranes. There is some indication that phosphatidylserine may have some cognition enhancing activity. Its action has not been established. In Alzheimer's disease the substance is believed to work by helping maintain an adequate supply of acetylcholine. Lecithin would probably work just as well for this. It is known that levels of L-serine are often low for unknown reasons in people with neurological problems. Such individuals might be helped by the L-serine component phosphatidylserine.

Contraindications: None, except those allergic to eggs or soy should avoid the product when it is derived from those sources. Also those wishing to avoid mad cow disease should not take the supplement if it is derived from bovine brain.

Precautions: Those with antiphosphpholipid-antibody syndrome should only take it under medical supervision.

Adverse reactions: GI symptoms.

Interactions: None known.

Dosage: 100 mg. three times a day.

Quercetin

Quercetin is a flavonoid found in onions, red wine, green tea and St. John's wort. It is a phenolic antioxidant and has been shown to inhibit lipid peroxidation. There is some evidence quercetin also has anti-inflammatory, antiviral, immunomodulatory, gastroprotective and anti-allergy activity as well as activity preventing the secondary complications of diabetes. Quercetin is one of several flavonoids that have effects on mast cells and basophils, which are

histamine-releasing cells involved in allergy. It "can help prevent the release of histamine and other mediators of allergic reactions, possibly by stabilizing cell membranes so they are less reactive to allergens. Quercetin also exhibits antiinflammatory properties, inhibiting formation of inflammatory prostaglandins and leukotrienes." There is some evidence that coupled with vitamin C it is an antiviral for picornaviruses (such as Coxsackie, ECHO and rhinoviruses.).

Contraindications: None known.

Precautions: None known.

Adverse reactions: Oral quercetin is well-tolerated.

Interactions: It can be a competitive inhibitor to quinolone antibiotics. It should not be taken with cisplatin.

Dosage: 200-1200 mg a day. It is best absorbed when taken with Bromelain or papain.

Vitamins B-1, B-2 and Biotin

People who have a great deal of trouble with post-exertional malaise may be interested in the following treatment. My neurologist at Massachusetts General Hospital suggested this to me a few years ago. He prescribed 100 mg of vitamin B-2 (riboflavin) once a day, 100 mg. of B-1 twice a day, and 5 mg of biotin twice a day (This is a very large amount of biotin and is difficult to find.) The result has been amazing. While I still feel wiped out the day after doing something, I'm not nearly as prostrated as I used to be. In addition, my recovery time from prostration has sped up enormously.

The *PDR* does not discuss B-1. However, when I researched its biochemistry, I found it is strongly implicated in many functions of the mitochondria. The *PDR* says vitamin B-2 "plays a key .role in the production of energy." It is an antioxidant and involved in the production of reduced glutathione. It has also been found "to be an effective migraine prophylaxis in some. The *PDR* describes biotin as "involved in the biosynthesis of fatty acids, gluconeogenesis, energy production, the metabolism of branched chain amino acids (L-leucine, L-isoleucine, L-valine)

and the de novo synthesis of purine nucleotides. Recent research indicates that biotin plays a role in gene expression, both at the transcriptional and translational levels, and that it may also play a role in DNA replication. There is some evidence it has glucose-tolerance modulating activity and reduces insulin resistance."

Coritraindications: None known for B-2 or biotin.

Precautions: None for biotin. Riboflavin may interfere with the Abbott TDX drugs-of-abuse assay. Riboflavin absorption is increased in hypothyroidism and decreased in hyperthyroidism.

Interactions: No interactions for biotin. Some drugs and vitamins lower the amount of biotin made naturally by flora of the intestine but don't interfere with supplemental biotin. There is a long list of drugs and supplements which interfere with the absorption of riboflavin or its action, including: cholestyramine, chlorpromazine, colestipol, doxorubicin, metoclopramide, nucleoside reverse-transcriptase inhibitors, probenecid, propantheline bromide, quinacrine, tricyclic antidepressants, boron, and psyllium.

Overdose: No value known for either vitamin.

1. *Physicians Desk Reference for Nutritional Supplements*, Hendler and Rorvik editors. Thomson PDR, Montvale, NJ, 2001.