

## **Coenzyme-Q10 (Co-Q10)**

Coenzyme-Q10 plays a critical role in your Diphasic Nutrition Plan. Like lipoic acid, Co-Q10 is found in both your Diphasic A.M. and your Diphasic P.M. supplements, and, for the same reasons. Co-Q10 is a powerful anti-oxidant that participates in several of the anti-oxidant systems, and, Co-Q10 is a powerful metabolic activator. So, like lipoic acid, Co-Q10 gives you protection against both pathological hyperplasia and pathological disintegration. In other words, Co-Q10 is a powerful ADAPTOGEN.

As a NUTRI-SPEC practitioner, you (and your patients) all enjoy the extraordinary benefits of Co-Q10, since it is an important part of several NUTRI-SPEC supplements. Most fundamentally, Co-Q10 is in your Activator. It is not there in a therapeutic dose, but in sufficient quantity that when taken day after day over the course of a lifetime it provides what we like to consider a continuous “metabolic spark.” Who else do you know that offers you a multiple supplement containing such precious goodies as Co-Q10? (The inclusion of Co-Q10 is just one of many reasons why we’ve said repeatedly over the years that you will not find a multiple supplement that can begin to match Activator.)

Because of its extraordinary anti-oxidant qualities, Co-Q10 is also an important part of the Oxygenic D you give your Dysaerobic patients. Then, because of its specific beneficial impact on the cardiovascular system, Co-Q10 is found as a therapeutic dose in your Formula ES.

Coenzyme-Q10 (CoQ), as found in your Formula ES, is an essential component of the mitochondrial electron transport chain, which is the fundamental unit for energy production in our cells. In addition to being essential for generating energy, CoQ is an important antioxidant. The heart, with its high energy requirements, is especially rich in CoQ.

1. CoQ deficiency is a significant part of myocardial failure.
2. CoQ improves cardiac response to exercise.
3. End stage heart failure patients who supplement with CoQ have a 40% survival rate compared to a 10% survival rate without CoQ.
4. CoQ lowers blood pressure.
5. CoQ reduces angina.
6. Co Q prevents arrhythmias.

There seems to be no end to the flood of research highlighting the cardiovascular protective effects of Co-Q10. This nutrient is turning out to be one of the most valuable clinical tools you have for patients with a diversity of health problems, but particularly for those at risk for cardiovascular disease (CVD).

A study published in Clinical Investigations, 1993; 71/8 Supplement: S140-4 entitled, "Isolated Diastolic Dysfunction of the Myocardium, and its Response to Co-Q10 Treatment," studied patients in the early stages of congestive heart failure and found that Coenzyme-Q10 resulted in:

- a decrease in high blood pressure in 80% of hypertensives
- an improvement in diastolic function in all patients based on endocardiograms
- a reduction in myocardial thickness in 53% of hypertensives and in 36% of those with combined mitral valve and fatigue syndrome

A study published in Clinical Investigations, 1993; 71(8 Supplement) S116-23 entitled, "Perspectives on Therapy of Cardiovascular Diseases with Co-Q10," showed that Co-Q10 myocardial tissue levels were significantly lower in patients with more advanced heart failure compared with those in the milder stages of heart failure. Administering Co-Q10 to these patients showed significant improvement in patients' capacity for physical activity and overall quality of life. The benefits were found to be far greater than those from treatment with traditional methods such as angiotensin converting enzyme inhibitors.

A study published in The International Journal of Tissue Reactions, 1990; 12(3):163-8 entitled, "Pronounced Increase of Survival of Patients with Cardiomyopathy when Treated with Co-Q10," showed that patients with all classes of cardiomyopathy accompanied by low ejection fractions experienced dramatic improvement in ejection fractions and pronounced increase in survival, which was attributed to Co-Q10's bioenergetic activity in regard to myocardial function.

Here is a question pertinent to the essentiality of Co-Q10 supplementation for your CVD patients:

What family of drugs generates more \$\$\$\$\$ for the pharmaceutical industry than any other? Anti depressants? Anti inflammatories? Antibiotics? No, no, no --- by far it is the Statin drugs to lower cholesterol --- generating nearly 20 billion dollars in annual revenues for the drug companies. If this family of drugs were to cause serious side effects, how much would the drug companies invest in terms of financial incentives and political pressure to keep the truth buried?

The truth, aggressively suppressed, is that the Statin drugs have irreversible and often fatal consequences, including cardiomyopathy, congestive heart failure, and rhabdomyolysis. Researchers have now discovered that the reason for the deadly side effects of cholesterol lowering drugs is that they deplete the body of Coenzyme-Q10. To their credit, the Canadian government is way ahead of the US government in its resistance to drug company lobbyist pressure. In Canada, Statin drugs are required to carry a label with an explicit precautionary warning that the drug can cause Co-Q10 depletion and lead to impaired cardiac functioning in patients with congestive heart failure. Consider these studies:

Proc Natl Acad Sci USA. 1990 Nov;87(22):8931-4. Lovastatin decreases Coenzyme-Q10 levels in humans. Folkers, et al.

Mol Aspects Med. 1997;18(suppl):s137-s144. Dose-related decrease of serum Coenzyme-Q10 during treatment with HMG CoA-reductase inhibitors. Mortenson et al.

Biofactors. 2003;18(1-4):113-24. Statins lower plasma and lymphocyte ubiquinol/ubiquinone. Passi, et al.

Biofactors. 2003;18(1-4):101-11. The clinical use of HMG CoA- reductase inhibitors and the associated depletion of Coenzyme-Q10. Langsjoen, et al.

In this last study the head researcher says, “The depletion of the essential nutrient Co-Q10 by the increasingly popular cholesterol-lowering drugs, HMG CoA-reductase inhibitors (Statins), has grown from a level of concern to one of alarm. With ever higher Statin potencies and doses, and with a steadily shrinking target LDL cholesterol, the prevalence and severity of Co-Q10 deficiency are increasing noticeably. We are currently in the midst of a congestive heart failure epidemic in the United States --- as physicians, it is our duty to be absolutely certain that we are not inadvertently doing harm to our patients by creating a widespread deficiency of a nutrient critically important to heart function.”

The following study further proposed that Co-Q10 levels might be used to measure myocardial diastolic function as an early marker of ventricular dysfunction:

Biofactors. 2003;18(1-4):125-7. A Statin cardio-myopathy? A potential for Co-Q10 therapy for Statin-induced changes in diastolic LV performance: Description of a clinical protocol. Silver, et al.

The reasoning behind this study is that Statins inhibit HMG-CoA reductase, the rate limiting step that not only inhibits cholesterol but also inhibits Co-Q10 synthesis in the liver. Because Co-Q10 plays an important role during

oxidative phosphorylation in the myocardial cell, evaluating Co-Q10 action on ATP might be used as an early warning indicator of heart problems. Studies have also indicated that Co-Q10 supplementation can reverse Statin-induced heart failure and muscle damage:

Drug Metabol Drug Interact. 2003;19(3):151-60. Reversal of Statin toxicity to human lymphocytes in tissue culture. Pettit; et al.

Biofactors. 2003;18(1-4):91-100. Systematic review of the effect of Coenzyme-Q10 in physical exercise, hypertension and heart failure. Rosenfeldt, et al.

This last study may be the most comprehensive demonstrating the capacity for Co-Q10 supplementation to improve circulatory processes, and prevent the cardiac and muscular consequences of Statin drug toxicity.

Imagine --- a drug given to millions upon millions of patients with cardiovascular disease that actually causes cardiovascular disease. Imagine that this drug also causes cognitive dysfunction, memory loss, and in many cases severe muscle pain. Is it any wonder that these drugs are on your NUTRI-SPEC list of "RED FLAG" medications? Compounding the absurdity of this Statin drug fiasco is that high cholesterol --- the only condition that Statin drugs "cure" --- is not even a primary risk factor for cardiovascular disease.

Please do not continue to be wishy-washy in getting your patients off these Statin drugs. I know your patients' general practitioners and cardiologists will fight to the death to defend their prescription --- but better it be their death than the death of your patients. Copy and print the section of this article dealing with Statin drugs and distribute it to your patients. Suggest to your patients that they stop Statin drugs immediately. Tell them they are welcome to share the information you have provided with their prescribing doctor. But caution them. Tell them that if their GP or their cardiologist provides objective evidence refuting the information that you have provided, then they should consider the merits of his case versus yours. If, however, the physician responds with nothing more than a tantrum, ask your patient not to be bullied, but to stand on a foundation of truth as he exercises his better judgement.

Cancer? Yes! As an antioxidant, Co-Q10 protects against the oxidative free radical damage that often triggers a cancer. Then, Co-Q10 inhibits the aberrant oxidative metabolism of existing cancers by promoting normal mitochondrial electron transport. One interesting study showed the benefits Co-Q10 in prostate cancer. Co-Q10 supplementation significantly lowered cell growth of the PC3 cancer line without affecting non-malignant cells.

Biofactors. 2003;18(1-4):265-270. Coenzyme-Q10 differentially moderates phospholipid hydroperoxide glutathione peroxidase gene expression and free radical production in prostate cancer. Quiles, et al.

Premature aging, cardiovascular disease, end-stage renal disease, Statin drug damage, muscular dystrophy, cancer --- and ...

### **MALE INFERTILITY?**

Yes!

Metabolism. 2003 Apr;52(4):402-6. Coenzyme-Q10: Another biochemical alteration linked to infertility. Mancini, et al.

These researchers have demonstrated that Co-Q10 is present in seminal fluid, and is directly correlated to sperm motility in infertile men.

Males are not the only ones to require Co-Q10 for normal reproductive function. Pre-eclampsia, a life-threatening disorder affecting about 7% of late-stage pregnancies, is associated with extreme edema, hypertension, and proteinuria. Serum levels of Co-Q10 are severely depressed in pre-eclampsia patients.

Free Radic Biol Med. 2003 Dec 1;35(11):1453-6. Pre-eclampsia is associated with a decrease in plasma Coenzyme-Q10 levels. Teran, et al.

These researchers showed that Coenzyme-Q10 levels should rise approximately 20% in pregnant women relative to non-pregnant women who have normal blood pressure. In women with pre-eclampsia, however, Co-Q10 drops nearly 20% to a level more than 35% lower than found in healthy pregnant women.

The eye is one of the more metabolically active tissues in the body. As such, it is subject to oxidative free radical damage. One manifestation of PUFA's destructive influence is macular degeneration. A recent research study reports that Co-Q10 may improve retinal function in patients with age-related macular degeneration by improving the performance of mitochondria in the retinal pigment epithelium.

Ophthalmol. 2003 Sept-Oct;217(5):351-7. Mitotrophic compounds for the treatment of age-related macular degeneration. A metabolic approach and a pilot study. Feher, et al.

Perhaps the only equal of the heart in metabolic activity is the brain. Recall from our many discussions of fish oil and vegetable oil damage that lipofuscin pigment on the skin is a direct indication that there is lipofuscin pigment deposition in the brain --- a certain sign of premature aging associated with free radical damage. Many studies have shown the protective effect of Coenzyme-Q10 (plus the other three antioxidants in your Oxy-Max) in protecting the brain. One study found a Co-Q10 deficiency in the brains of

patients with cerebellar ataxia and/or cerebellar atrophy --- suggesting an ataxic syndrome responsive to therapy with Coenzyme-Q10 supplementation. The researchers studied the distribution of Co-Q10 in different brain regions in both animals and humans, before and after administering Co-Q10 supplements. The lowest levels of Co-Q10 were found in the cerebellum, suggesting selective vulnerability in that region of the brain to Co-Q10 depletion and its protective effects.

Biofactors. 2003;18(1-4):145-52. Primary Coenzyme-Q10 deficiency and the brain. Naini, et al.

Much has been made in the health food industry promotional literature about Coenzyme-Q10 as a “cure” or at least a treatment for Parkinson’s Disease. The most definitive study showing benefits of Co-Q10 supplementation for Parkinson’s Disease used a huge 1200 milligram per day dose of Co-Q10, but showed a 44% reduction in the decline of motor skills, movement, and mental function compared to the placebo group. Those receiving the supplement also demonstrated an improved ability to perform activities of daily living. This 16-month study was remarkable in that Co-Q10 slowed the progression of the disease, something the Parkinson’s drugs do not do.

Shortly thereafter, another study of Parkinson’s Disease patients used a much more reasonable 360 milligram daily dose of Co-Q10 and administered it for only 4 weeks. Even in this short period of time Parkinson’s patients receiving the supplement showed a significant improvement in performance compared with the placebo group.

Arch Neurol. 2002 Oct;59(10):1541-50. Effects of Coenzyme-Q10 in early Parkinson’s Disease; evidence of slowing the functional decline. Shultz, et al.

Neurosci Lett. 2003 May 8;341(3):201-4. Coenzyme-Q10 supplementation provides mild symptomatic benefit in patients with Parkinson’s Disease. Muller, et al.

[See the Addendum at the end of this article for an in-depth discussion of Co-Q10 and Parkinson’s Disease.]

The purpose of this Coenzyme-Q10 discussion is not that you will be motivated to go beating the bushes for new patients with Parkinson’s Disease, macular degeneration, infertility, muscular dystrophy, and pre-eclampsia. Our intent is merely to show that this phenomenal nutrient is ubiquitous in physiological function, is directly correlated with protection against oxidative damage and with promotion of normal oxidative metabolism, and, is powerful enough to slow or even reverse the most severe of pathologies. As one of the

four most physiologically active antioxidants (and the other three are also found in your Oxy-Max), its role in **PREVENTION** should be obvious.

Your patients are paying you for what they hope will be the best clinical nutrition available. If you are not giving them all Oxy-Max, then you are letting them down. Either from day one under your care as part of your Diphasic Nutrition Plan, or, after several weeks of metabolic balancing through NUTRI-SPEC analysis, every one of your patients should be taking at least 3 Oxy-Max daily. Those with moderate to severe cardiovascular disease or other known pathology should be taking as much as 10 daily to start, working down to a maintenance level of 3, twice daily. Those with even mild pathology should be started with the descending schedule of 10,9,8,7,6,5,4 daily before settling into the 3 or 4 daily maintenance dose. Standing on a foundation of Activator, plus the NUTRI-SPEC Fundamental Diet, plus the metabolic sparkplugs Oxy-Tonic, Oxy D-Plus, and Electro-Tonic, you will be giving your patients nutrition power per dollar spent far beyond their greatest expectations.

Consider these facts. In a recent clinical study, five hours after taking a 30 milligram dose of fat soluble Co-Q10, blood levels of Co-Q10 had increased by 237%. Meanwhile, five hours after a 30 milligram dose of the dry Co-Q10, the blood level increase was 112%. In other words, the fat soluble form was absorbed more than twice as well as the dry form.

Another study looked at the effect of Co-Q10 supplementation in either dry or oil soluble form over a period of 30 days. After 30 days the fat soluble Co-Q10 group had increased its basal blood levels by 265%, while the dry formulation group only showed an increase of 180%. In addition, 83% of the subjects in the fat soluble Co-Q10 group experienced an increase in energy, compared to only 58% of those in the dry formulation group. Clearly, if you want the maximum benefit from Co-Q10 you want to use the oil soluble form as much as possible.

Now consider this. Since most clinical studies with Co-Q10 use the dry powder form in determining the effective clinical dosage, you must realize that if you are getting fat soluble Co-Q10 from your Diphasic P.M. you are actually giving your patients effectively a far higher dose than you may think. In the standard dose of Diphasic A.M. and P.M. you are giving your patients 50 milligrams of Co-Q10. But, since 30 of those are in fat soluble form, which makes them more than twice as effective as the dry form, you are giving an effective dosage of 80 milligrams per day. This is in the range of the therapeutically effective dose determined by all the studies showing the benefit of Co-Q10 on:

1. preventing myocardial failure
2. improving cardiac response to exercise
3. lowering high blood pressure

4. reducing angina
5. preventing arrhythmias
6. quenching free radicals
7. increasing biochemical energy production

Most Co-Q10 products that your patients buy, whether at the health food store or from health care professionals, still have a daily dosage in the range of 10-30 milligrams, and thus, while somewhat beneficial to over-all health, do not begin to offer the mega metabolic impact you are achieving with the Co-Q10 in your Diphasic A.M. and Diphasic P.M. supplements, especially when timed to coincide with the natural diphasic diurnal metabolic cycle.

Earlier in this article, we discussed the oxidizing effects of cholesterol-lowering Statin drugs. Based on the research presented, we now know that statins deplete Co-Q10 levels and thus exacerbate cardiovascular disease. Perhaps this oxidative damage is why vision loss is one of the leading side effects of taking Statin drugs. The depletion of Co-Q10 leaves the retina more vulnerable to oxidative stress & free radical damage. The eye, and especially the retina, is extremely susceptible to oxidative stress. Oxidative stress can lead to a host of degenerative retina conditions. Co-Q10 is another major supplement recommended for all patients with degenerative vision loss.

Coenzyme-Q10 will decrease prothrombin time.

Coenzyme-Q10 decreases the malondialdehyde and hydroxyproline levels and increases glutathione peroxidase in ochratoxin (mold) toxicity of the liver, but has no beneficial effect on the kidneys.

In both Ulcerative Colitis and Crohn's Disease, mucosal biopsies revealed antioxidant deficiencies as follows: urate = CD decreased 62%, UC decreased 47%; glutathione = CD decreased 59%, UC decreased 65%; Co-Q10 = CD decreased 76%, UC decreased 91%; ascorbic acid = CD decreased 35%, UC decreased 73%. The mean alpha tocopherol content was unchanged. These observations support decreased reduced and total ascorbic acid in inflamed IBD mucosa, and demonstrate the loss of antioxidant defenses that severely compromise the inflamed mucosa, rendering it more susceptible to oxidative tissue damage.

Supplementation with 20 mg per day of PQQ resulted in improvements on tests of higher cognitive function in a group of 71 subjects between ages 40 and 70, who outperformed the placebo group by more than two-fold in their standardized memory tests. --- This study also suggests a synergistic relationship between PQQ and Co-Q10, which further amplified performance on standardized memory tests when subjects also took 300 mg per day of Co-Q10.



**STOP!**

Be careful! ----- Just when you begin to think that Coenzyme-Q10 is a nutrient you can give your patients in mega doses to help “cure” just about every condition imaginable, we have to stop and ask ourselves --- is there a potential downside to Coenzyme-Q10 supplementation? The answer is a very definite and alarming “Yes!”...

Vitamin C is an important antioxidant in the brain. Astrocytes are capable of recycling ascorbate by taking up and then reducing its oxidation product dehydroascorbic acid (DHAA) using reducing equivalents derived from NAD(P)H. Coenzyme-Q10 and Coenzyme-Q analogs have been proposed as therapeutic agents for neurodegenerative diseases --- but --- it turns out that Coenzyme-Q10 and its analogs actually cause oxidative stress by depletion of NAD(P)H.

NAD(P)H levels in astrocytes are impaired by Co-Q10, and the ability of these cells to replace the extracellular DHAA with ascorbate via ascorbate recycling is blocked. So, while Coenzyme-Q lowers intracellular levels of reactive oxygen species, it unfortunately also produces marked decreases in the concentrations of NADH and NAD(P)H. Studies show that astrocyte NAD(P)H depletion and inhibition of ascorbate recycling is particularly pronounced in those individuals with impaired glucose metabolism. In summary, since ascorbate produced by astrocytes is neuroprotective, excess Coenzyme-Q supplementation may adversely affect brain function.

## Addendum: An in-depth look at Co-Q10 and Parkinson's Disease

- Iron plays an important role in Parkinson's Disease (PD) pathology. It has been demonstrated that Co-Q10 has a neuroprotective role in iron-induced apoptosis in cultured human dopaminergic neurons. Iron-induced mitochondrial damage and apoptosis are characterized by ROS production, increased metallothionein and glutathione synthesis, caspase-3 activation, NF-kappa B induction. Higher concentrations of iron sulfate in mitochondria-induced Co-Q10 depletion, plasma membrane perforations, mitochondrial damage, and nuclear DNA condensation and fragmentation. Iron sulfate induced deleterious changes were attenuated by pretreatment with Co-Q10 and by deferoxamine, a potent iron chelator. MPTP induces striatal release of free iron and increases the expression of NF-kappa B, whereas ferritin and melanin synthesis are significantly reduced in the substantia nigra of PD model mice compared with controls. Co-Q10 treatment inhibits MPTP-induced NF-kappa B induction in all genotypes. These data suggest that glutathione and metallothionein synthesis may be induced as an attempt to combat iron-induced oxidative stress, whereas exogenous administration of Co-Q10 or metallothionein induction might provide Co-Q10-mediated neuroprotection in PD.
- Nitric oxide synthase activation and peroxynitrite ions are involved in the pathogenesis of PD, and metallothionein-mediated Co-Q10 synthesis may provide neuroprotection.
- Experimental and clinical data point to a defect of the mitochondrial respiratory chain as a major pathogenetic factor in PD. Although the restoration of mitochondrial respiration and reduction of oxidative stress by Co-Q10 could induce neuroprotective effects against the dop cell death in PD, these effects of Co-Q10 could also improve the dopaminergic dysfunction. Thus, Co-Q10 might theoretically exert both neuroprotective and symptomatic effects in PD.

Nanoparticulate Co-Q10 at a dosage of 300 mg/day is safe and well-tolerated and leads to plasma levels similar to 1,200 mg/day of standard formulations. However, 100 mg 3 times daily of nanoparticulate Co-Q10 did not display symptomatic benefits in mid-stage PD.

In another study, PD subjects were evaluated with the UPDRS scale, and at 16 months those supplementing with 1,200 mg/day of Co-Q10 had an increase in UPDRS of 6.69 compared to 11.99 for the placebo group.

- Elevated serum cholesterol in women is associated with a significantly decreased risk of PD. These findings may indicate a role for lipids in the pathogenesis of PD, or, they could reflect the strong correlation (especially in women) between levels of serum cholesterol and the antioxidant Co-Q10.

- Features of PD include oxidative stress, nigral mitochondrial complex-1 deficiency, and visual dysfunction, all of which are also associated with Co-Q10 deficiency. Daily oral supplementation with 360 mg of Co-Q10 lasting 4 weeks on scored PD symptoms and visual function provided significant mild symptomatic relief on PD symptoms, and a significantly better improvement in visual function.
- Oral Co-Q10 significantly decreased elevated lactate levels in patients with Huntington's Disease. Co-Q10 is a powerful antioxidant that buffers the potential adverse consequences of free radicals produced during oxidative phosphorylation in the inner mitochondrial membrane. Oxidative stress, resulting in glutathione loss and oxidative DNA and protein damage has been implicated in many neurodegenerative disorders including Alzheimer's Disease, PD, and HD.
- A 16-month randomized placebo-control pilot trial in 80 subjects with mild PD found significant benefits for oral Co-Q10 at 1,200 mg/day to slow functional deterioration. Dosages up to 2,400 mg/day are shown to be safe.
- Agents that have shown to be beneficial in animal models of PD include Co-Q10, creatine, Gingko biloba, nicotinamide, and acetyl-L-carnitine.
- PD, ALS, HD, Friedreich's ataxia, and mitochondrial cytopathies and other neuromuscular diseases share to some extent the final common pathway leading to cell death through either necrosis or apoptosis. Compounds such as creatine monohydrate, and Co-Q10 offer substantial neuroprotection against ischemia, trauma, oxidative damage, and neurotoxins. Miscellaneous agents, including alpha lipoic acid, beta-hydroxy beta-methylbutyrate, riboflavin, and nicotinamide, have also been shown to improve various metabolic parameters in brain and/or muscle.
- Lonnrot, et al. The effect of ascorbate and ubiquinone supplementation on plasma and CSF total antioxidant capacity. Free Radic Biol Med, 1996.

Free radicals are thought to be involved in the onset of neuronal disturbances such as AD, PD, and neuronal ceroid lipofuscinosis. It is also assumed that they play a role in the cerebral injury caused by ischemia or trauma. Plasma and CSF Total (peroxyl) Radical-trapping Antioxidant Parameter (TRAP), and the known antioxidant components of TRAP, for instance ascorbic acid, uric acid, protein sulfhydryl groups, tocopherol, and ubiquinol, were analyzed, and the remaining unidentified fragment was calculated in 5 healthy volunteers before and after 4 weeks of ascorbate and ubiquinone supplementation. TRAP in CSF was significantly lower than in plasma. The major contributor to plasma antioxidant capacity was uric

acid, whereas in CSF it was ascorbic acid. In CSF, ascorbic acid concentrations were 4 times higher than in plasma.

Oral supplementation of ascorbic acid (500 mg per day first 2 weeks, 1,000 mg per day following 2 weeks), and Co-Q10 (100 mg per day first 2 weeks, 300 mg per day following 2 weeks) induced a significant increase in plasma ascorbic acid and Co-Q10. Surprisingly, in spite of the high lipophilicity of Co-Q10, its concentration did not change in CSF. The supplementation of ascorbic acid increased its concentration in CSF by 28%. However, the increase in ascorbic acid did not result in an increase in CSF TRAP. This indicates that ascorbic acid had lost 1/3 of its radical trapping capacity as compared to that in plasma. The fact that ascorbic acid is the highest contributor to CSF TRAP, and its effect on TRAP is concentration dependent, could indicate that the peroxy radical-trapping capacity of CSF is buffered by ascorbic acid.

- A 3-month trial with 200 mg Co-Q10 supplementation daily in PD patients showed no significant improvement.
- Oral supplementation with creatine or cyclocreatine, which are substrates for creatine kinase, may increase phosphocreatine or cyclophosphocreatine and buffer against ATP depletion and thereby exert neuroprotective effects in MPTP-induced PD. These results further implicate metabolic dysfunction in MPTP neurotoxicity and suggest that creatine supplementation may have applicability for PD.
- Environmental toxins are associated with PD, causing inflammation with activation of phagocytic microglia, release of cytokines, invasion by T cells, and complement activation playing roles in damaging dopaminergic neurons. Excess production of ROS, mitochondrial dysfunction leading to apoptosis, accumulation and oligomerization of the protein alpha-synuclein, and defective protein disposal by the ubiquitin proteasome system are involved in the complex web of events mitigating nigral cell demise. Co-Q10 and creatine, as well as omega 3 fatty acids and vitamin D may be disease modifying. The association with serum cholesterol levels and the effects of statin drugs are uncertain but must be considered.
- Co-Q10 and creatine are promising agents for neuroprotection in neurodegenerative diseases via their effects on improving mitochondrial function and bioenergetics and their properties as antioxidants. In mouse studies, the combination of the 2 agents produced additive neuroprotective effects against dopamine depletion in the striatum, and loss of tyrosine hydroxylase neurons in the substantia nigra following chronic subcutaneous administration of MPTP. The combination treatment resulted in significant reduction in lipid peroxidation and pathologic alpha-synuclein accumulation. The combination treatment showed significant effects on

blocking 3-NP-induced impairment of glutathione homeostasis and reducing lipid peroxidation and DNA oxidative damage in the striatum. Lastly, the combination of Co-Q10 and creatine produced additive neuroprotective effects on improving motor performance and extending survival.

- There is a substantial body of literature demonstrating that creatine has neuroprotective effects both in vitro and in vivo. Creatine can protect against excitotoxicity as well as against beta-amyloid toxicity in vitro. In vivo, creatine can protect against excitotoxic lesions produced by N-methyl-D-aspartate. Creatine is also neuroprotective against lesions produced by the toxins maleonate and 3-nitropropionic acid (3-NP), which are reversible and irreversible inhibitors of succinate dehydrogenase, respectively. Creatine produced dose-dependent neuroprotective effects against MPTP toxicity, reducing the loss of dopamine within the striatum and the loss of dopaminergic neurons in the substantia nigra. Creatine produced an extension of survival, improved motor performance, and a reduction in loss of motor neurons in a mouse model of ALS. Creatine produced an extension of survival as well as improved motor function and a reduction of striatal atrophy in a mouse model of HD, even when administration was delayed until after the onset of disease symptoms. The neuroprotective effects of a combination of Co-Q10 with creatine has been demonstrated against MPTP and 3-NP toxicity. The combination of Co-Q10 and creatine together produced additive neuroprotective effects in a chronic MPTP model of PD.
- Vitamin A potently destabilizes preformed alpha-synuclein fibrils in vitro: implications for lewy body diseases. ----- Vitamin A, beta carotene, and Co-Q10 dose-dependently inhibit the formation of alpha-synuclein fibrils. Moreover, they also dose-dependently destabilize preformed alpha-synuclein fibrils. With such potent anti-fibrillogenic as well as fibril destabilizing activities, these compounds could be useful in the treatment and prevention of lewy body diseases such as PD. Vitamin A also prevents and destabilizes beta-amyloid fibrils in AD.
- In PD, a defect of complex 1 of the mitochondrial respiratory chain is confirmed. Disease specificity of this defect has been demonstrated for the substantia nigra in PD. These findings and the observation that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropiperidine (MPTP), which causes a PD-like syndrome in humans, acts via inhibition of complex 1 have triggered research in the mitochondrial involvement in PD. Oxidative phosphorylation consists of 5 protein-lipid enzyme complexes located in the mitochondrial inner membrane. These complexes, designated complex 1 through 5, contain flavins (FMN, FAD), quinoid compounds (Co-Q10), and transition metal compounds (iron-sulfur clusters, hemes, protein-bound copper). Complex 1 is NADH: ubiquinone oxidoreductase, EC 1.6.5.3. A defect in mitochondrial oxidative phosphorylation, in terms of a reduction in the activity of NADH CoQ reductase (complex 1) has been reported in the

striatum of patients with PD. The reduction in the activity of complex 1 is found in the substantia nigra, but not in other areas of the brain. Therefore, the specificity of mitochondrial impairment may play a role in the degeneration of dopaminergic neurons. This view is supported by MPTP toxic effects destroying dopaminergic neurons, specifically in the substantia nigra. Although serum levels of Co-Q10 are normal in patients with PD, Co-Q10 is able to attenuate the MPTP-induced loss of striatal dop neurons.