

## How CoQ10 Protects Your Cardiovascular System

At least 35 controlled clinical trials in Japan, Europe and the U.S. have demonstrated the effectiveness of CoQ10 therapy in congestive heart failure, angina and ischemic heart disease, and myocardial infarction.

CoQ10 levels in heart tissue decline disproportionately with age. At age 20, the heart has a higher CoQ10 level than other major organs. At age 80 this is no longer true, with heart levels cut by more than half. CoQ10 pioneer Karl Folkers (1985), in agreement with earlier Japanese studies, found lower CoQ10 levels in patients with more severe heart disease and showed that CoQ10 supplements significantly raised blood and heart tissue levels of CoQ10 in these patients.

### Arterial health

As the bloodstream distributes antioxidants to tissues and organs throughout the body, they do double duty protecting the bloodstream's other cargo from oxidation. A case in point is LDL (low-density lipoprotein), the major cholesterol-carrying blood lipid. Until about ten years ago, excessive LDL cholesterol per se was thought to cause atherosclerosis. It is now widely accepted that LDL cholesterol must first undergo oxidation to set in motion the chain of events that ends in artery-clogging plaque. Robust antioxidant defense is therefore as important as low LDL cholesterol in maintaining arterial health.

Nature has provided LDL particles in the bloodstream with antioxidant chaperones, primarily CoQ10 and vitamin E. Most CoQ10 and vitamin E circulate through the bloodstream attached to LDL particles. Studies suggest that CoQ10 may protect LDL from oxidation more efficiently than vitamin E, but average CoQ10 levels do not provide each LDL particle in the bloodstream with its own CoQ10 chaperone. As researchers suggest (Thomas S et al., 1995):

An increase in the number of CoQ10H2 [CoQ10 in its antioxidant form] molecules per LDL particle from less than one to more than one is likely to substantially increase the resistance of the lipoprotein toward oxidation. This increase in the number of CoQ10H2 molecules may be crucial: it means that every LDL particle will contain a molecule of this efficient coantioxidant.

A recent animal study demonstrates the potential of CoQ10 as a preventive therapy for atherosclerosis. Two groups of rabbits were fed a diet rich in trans fatty acids in order to provoke elevated cholesterol and triglyceride levels (hyperlipidemia). Later in the study, oxidants were added to the rabbit chow to provoke lipid peroxidation. The group of rabbits treated with CoQ10 displayed significant reductions in arterial plaque, with less than half the atherosclerosis score and plaque thickness in both the aortic and coronary arteries, compared to the control group. Measures of oxidative damage also declined.

The arteries of the rabbits in the CoQ10 group showed significant reductions in each of the stages of atherosclerotic development: fewer fatty streaks, atheromatous plaques (fatty deposits in the arterial wall), and fibrous plaques. Moreover, the plaques that were present had a more stable character. Plaques in the CoQ10 group were flatter and stronger, with less than one-seventh as much ulceration and thrombosis, as those in the control group. Since it is the instability of plaques that is particularly dangerous, this finding suggests another mechanism by which CoQ10 may help reduce the incidence of serious cardiovascular events.

### Partnership with vitamin E

Vitamin E, on the other hand, is a double-edged sword. A series of groundbreaking studies by Roland Stocker and his colleagues at The Heart Research Institute in Sydney, Australia demonstrates that vitamin E (alpha-tocopherol) systematically promotes LDL oxidation. Stocker calls this pro-oxidant action of vitamin E "tocopherol-mediated peroxidation," or TMP. Through TMP, vitamin E amplifies mild oxidative stresses so that they do much

more damage to LDL. There has been a spate of papers and much lively debate in recent years on pro-oxidant side effects of vitamin E, but as we shall see below vitamin E works better in cooperation with CoQ10 than it does in isolation.

Why didn't decades of vitamin E research detect this problem sooner? One reason is that scientists apply heavy oxidative stress to LDL in the laboratory to achieve rapid results, while TMP (tocopherol-mediated peroxidation) happens under the more realistic conditions of chronic mild oxidative stress. Another reason is that, as Stocker's group discovered, the CoQ10 naturally present in the body protects against TMP. They showed that one molecule of CoQ10 can prevent two TMP chain reactions involving as many as 40-80 free radicals. In pilot studies they tested LDL from the blood of human subjects given vitamin E and/or CoQ10 supplements. CoQ10 supplements reduced TMP, while vitamin E supplements increased it. When given together, the CoQ10 supplement significantly counteracted the TMP side-effect of the vitamin E supplement.

The work of Stocker and his colleagues agrees with other lines of recent research suggesting that CoQ10 cooperates with vitamin E in a complex partnership that we are only beginning to understand. Indeed these "co-antioxidants" are always found together in cell membranes and LDL. CoQ10 regenerates vitamin E, which would otherwise be quickly exhausted fighting oxidative stress. Vitamin E breaks off the chain reaction of lipid peroxidation, while CoQ10 helps to prevent it from starting.

The many studies of vitamin E supplementation published over the years did not take into account the CoQ10 naturally present in the body, but we can now see that this was a crucial factor. In these studies of vitamin E, CoQ10 served as the "silent partner," amplifying the effect of vitamin E, regenerating vitamin E as it was exhausted, and preventing TMP.

Natural (endogenous) antioxidants form a balanced complete system that, like the partnership between vitamin E and CoQ10, we are only beginning to understand. As we gain a more subtle understanding of the way antioxidants work in the body, we can use this knowledge to support the body's antioxidant defense system more intelligently.

#### The nitrogen paradox

Stocker's research team recently turned its attention to a free radical that you will hear a great deal about in future years. Peroxynitrite is a "poison cupboard" of pathological effects. It is the dark side of what might be termed the nitrogen paradox."

A nitrogen-oxygen compound virtually unknown to medicine a generation ago called nitric oxide has since been found to regulate countless biological processes from respiration to blood flow and penile erection. The scientists who discovered nitric oxide's physiological significance received the 1998 Nobel Prize in Physiology and Medicine. When nitric oxide reacts with a free radical called superoxide, it forms peroxynitrite. Many or most of the harmful effects associated with nitric oxide are now thought to be due not to nitric oxide per se, but rather to peroxynitrite. Targets include lipids, DNA, proteins, glutathione, and the cellular respiratory chain. Peroxynitrite has been implicated in chronic inflammation, neurodegenerative disease, toxic shock and many other pathologies.

What particularly interested Stocker's group is the mounting evidence that peroxynitrite promotes the formation of arterial plaques by oxidizing LDL in the inner arterial wall. Their latest research shows that low levels of peroxynitrite cause more lipid peroxidation in LDL when vitamin E is present. In fact, the more vitamin E there is, the more lipid peroxidation occurs. This is a classic case of TMP (tocopherol-mediated peroxidation).

Stocker's group then showed that CoQ10 protects LDL from peroxynitrite damage. Following a course of CoQ10 supplementation (150 mg per day for five days), peroxynitrite caused significantly less peroxidation in LDL from human subjects. This is the first direct demonstration that CoQ10 offers protection against peroxynitrite in humans.

Parameter	Percentile
Ejection fraction (how fully the heart pumps out its blood)	92%
End diastolic volume index (how fully the heart fills with blood)	88%
Cardiac index (amount of blood pumped relative to body size)	87%
Stroke volume (amount of blood pumped out per beat)	76%
Cardiac output (amount of blood pumped out per minute)	73%

Table 1. Effect of CoQ10 supplementation on key parameters in congestive heart failure.

Notes: Percentiles reflect superiority of the average CoQ10 patient to the stated percentage of control patients. Meta-analysis results should be interpreted with caution since, as in this case, data may be pooled from studies that differ from one another in certain significant respects. Adapted from Soja AM et al. (1997). Researchers have suggested that a CoQ10 blood level of at least 2.0 - 3.5 micrograms per ml speeds clinical improvement and maximizes therapeutic benefits. The normal blood level of CoQ10 is in the range from 0.6 to 1.4 micrograms per ml. The effect of CoQ10 supplements on blood levels varies considerably between people but tends to increase with age. One study found that nine months of supplementation at 90 mg per day increased blood levels of CoQ10 by about 0.6 micrograms per ml in 35 year olds, and by 1 - 1.5 micrograms per ml in 50 - 65 year olds.

## Heart failure

The primary cause of heart failure is the inability of the heart to properly fill or empty the ventricles. The right ventricle circulates blood to the lungs, while the left ventricle circulates blood to the rest of the body. The ventricles empty when the heart contracts to pump out blood (the systole), and fill when the heart relaxes (the diastole).

CoQ10 deficiency is commonly seen in patients with heart failure. The degree of deficiency corresponds to the degree of impairment in the function of the left ventricle. CoQ10 supplements may correct this deficiency noticeably in one to four weeks, and maximally in several months.

It has long been observed that CoQ10 improves the relaxation of heart muscle (in medical terms, diastolic function). Until recent years doctors thought that weak contraction of the heart muscle was the main cause of heart failure, but we now know that this becomes less true with advanced age. Aging affects the ability of the heart to relax far more than its ability to contract. When the heart muscle cannot fully and quickly relax, the heart does not fill properly with blood. By age 70, the rate of filling may be only half what it was at age 30.

Contrary to previous thought, the heart needs more energy and oxygen to relax than it does to contract. When energy production in heart muscle cells declines with age, the heart muscle takes longer to relax. This may explain CoQ10's beneficial effect upon heart muscle relaxation (see "End diastolic volume index" in Table 1).

The older a person is at the onset of heart failure, the more likely it is that the main cause is impaired heart muscle relaxation, and this is especially true in women. Diastolic dysfunction is difficult to diagnose and often goes unrecognized, leading to inappropriate treatment of heart failure in some patients. The American College of Cardiology/ American Heart Association recommends echocardiography, a noninvasive diagnostic procedure, to assess diastolic as well as systolic function in patients with suspected congestive heart failure.

The clinical experience with CoQ10 in heart failure is reflected in the results of a recent meta-analysis. This study pooled data from eight randomized controlled clinical trials of CoQ10 in congestive heart failure. The study found

that patients supplemented with CoQ10 had on average better scores than 73%-92% of unsupplemented patients on five key measures of heart performance, as detailed in Table 1.

### Angina and heart attack

Comparable benefits have been demonstrated for patients with ischemic heart disease, including angina. Several small controlled clinical trials have found significant improvements in exercise tolerance, number of angina episodes, and need for medications. The dosages employed in these studies ranged from 150 to 600 mg of CoQ10 daily.

Heart attack victims may benefit as well. A new study finds that CoQ10 rapidly reduces the risk of complications and further cardiac events in the aftermath of a heart attack. This well-designed clinical trial demonstrated that CoQ10 given within two to three days of the attack at 120 mg per day improved clinical outcomes by every measure studied. Patients given CoQ10 had significantly lower rates of angina pectoris, poor left ventricular function, and arrhythmias during the four week study period than those not on the CoQ10 regimen. Only half as many in the CoQ10 group suffered another heart attack or died from a cardiac event as in the control group.

The "Energy Starved Heart" What most forms of heart disease have in common is low energy production by the mitochondria in heart muscle cells, which leads to a condition dubbed the "energy starved heart." As Danish cardiology researchers Soja and Mortensen (1997) put it: In spite of the many and various causes of myocardial dysfunction and CHF [congestive heart failure] (ischemia, hypertension, valvular defects, cardiomyopathy, congenital heart disease), it seems that an apparently disturbed energy production, which presumably occurs because of a deficient substrate delivery and/or substrate exploitation ('energy starved heart'), results in an increased need for CoQ10. This need both exceeds the body's own capacity for synthesis and the relatively small amount of CoQ10 that is taken in the diet.

It is intriguing that the levels of several antioxidants increased significantly in patients given CoQ10, even though CoQ10 was the only antioxidant supplement they were given. Blood levels of vitamins A, E, and C, and beta-carotene rose significantly in the CoQ10 group compared to the control group. The CoQ10 group likewise showed lower levels of lipid peroxidation and peroxidation byproducts such as MDA. CoQ10 thus exerted broad protective and preventive effects in these patients.

### Cholesterol-lowering drugs

The public is hardly aware that an increasingly popular class of cardiovascular drugs interferes with the body's synthesis of CoQ10. These drugs are the "statins" (drugs with names ending in "statin"), widely prescribed to reduce cholesterol levels. The problem is that the action of the statins is nonspecific. They inhibit CoQ10 synthesis along with cholesterol synthesis, significantly reducing CoQ10 blood levels. A recent study documented increased oxidation of LDL cholesterol after six weeks of lovastatin therapy, believed to result from lower CoQ10 levels.

Newly published studies from Japan suggest that there may be an important distinction in this respect between lipophilic (fat soluble) and hydrophilic (water soluble) statins. These studies found that lipophilic statins increased "myocardial stunning" in dogs following a brief period of ischemia (coronary artery occlusion). This increase was associated with decreases in ATP levels, indicating depressed cellular energy production. However water soluble pravastatin did not have these effects. Further exploration of this distinction is clearly needed.

When patients are given CoQ10 along with statins, CoQ10 levels rise rather than fall. This supportive measure does not interfere with the cholesterol-lowering effect of the statins, yet very few physicians recommend it. The

[http://www.lef.org/magazine/mag2001/oct2001\\_report\\_coq10\\_01.html](http://www.lef.org/magazine/mag2001/oct2001_report_coq10_01.html)

LE Magazine Special Edition, Winter 2004/2005

Page 4 of 7

Bernard

Tel: +6016 9833139

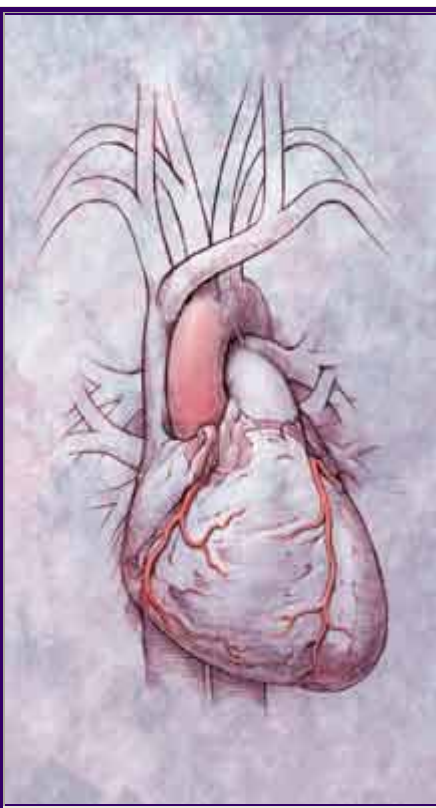
<http://www.oxyfreshap.com/distweb/index.asp?id=4501>

<http://www.streetram.com/coq10.htm>

scientists who coined the term "Q Effect" offer this caveat on the growing use of statins at higher dosages and potencies (Langsjoen PH et al., nd):

As the "target" or "ideal" cholesterol level is steadily lowered, the CoQ10-lowering effect will be more pronounced and the potential for long term adverse health effects enhanced. Before the results of this vast human experiment become obvious over the next decade, it is incumbent upon the medical profession to more closely evaluate the clinical significance of this drug-induced CoQ10 depletion. The combined use of CoQ10 and statins not only prevents the depletion of CoQ10, but may also enhance the benefits of the cholesterol lowering by lessening the oxidation of LDL cholesterol.

Since the sixties, scientists in Japan, Europe, America, Australia and India have studied the effects of CoQ10 in cardiovascular disease. More recently, research has shown the potential of CoQ10 in other age-related conditions as well as in aging itself. The therapeutic power of CoQ10 stems from its unique dual action inside the cell, which we explore in the following [article](#).

	<p style="text-align: center;"><b>CoQ10 and Cardiovascular Disease</b></p> <p>"Supplemental CoQ10 alters the natural history of cardiovascular illnesses and has the potential for prevention of cardiovascular disease through the inhibition of LDL cholesterol oxidation and by the maintenance of optimal cellular and mitochondrial function throughout the ravages of time and internal and external stresses." -Peter H. Langsjoen M.D. &amp; Alena M. Langsjoen (Langsjoen PH et al., nd)</p> <p>The effects CoQ10 produces in cardiovascular disease:</p> <ul style="list-style-type: none"><li>o Improves bioenergetics in heart muscle</li><li>o Improves hemodynamics</li><li>o Normalizes diastolic function</li><li>o Improves exercise tolerance in angina</li><li>o Improves functional classification in congestive heart failure</li><li>o Reduces need for medications</li><li>o Improves clinical outcomes</li><li>o Reduces cardiac mortality</li><li>o Reverses CoQ10-lowering side effect of cholesterol-lowering drugs ("statins")</li><li>o Produces modest blood pressure reductions in hypertension</li><li>o Reduces oxidation of LDL cholesterol</li><li>o Regenerates vitamin E</li><li>o Prevents pro-oxidant side effects of vitamin E</li></ul>
---	--

A tip for using Co-Enzyme Q10. Always check the bio-availability of the CoQ10 you are purchasing. The bio-availability percentage will give you an idea of the body's ability to absorb the CoQ10 in the supplement.

Most CoQ10 powder capsules have a bio-availability somewhere in the range of 15% to 20%. **Oral Spray** designed to be applied under the tongue boasts a much greater bio-availability percentage, somewhere in the 60% to 80% range.

Liquid form has much higher bio-availability rate than above.  
Oxyfresh CoQ10 in **liquid form** with vitamin A, C, D, E and Aloe Vera is available.

## REFERENCE

- Allen KL et al. Changes of respiratory chain activity in mitochondrial and synaptosomal fractions isolated from the gerbil brain after graded ischaemia. 1995. *J Neurochem* 64: 2222-2229.
- Ankarcrona M et al. Glutamate-induced neuronal death: a succession of necrosis or apoptosis depending on mitochondrial function. 1995. *Neuron* 15: 961-973.
- Barbiroli B et al. Coenzyme Q10 improves mitochondrial respiration in patients with mitochondrial cytopathies. An in vivo study on brain and skeletal muscle by phosphorous magnetic resonance spectroscopy. 1997. *Cell Molec Biol* 43: 741-749.
- Beal MF. Aging, energy, and oxidative stress in neurodegenerative diseases. 1995. *Ann Neurol* 38: 357-366.
- Beal MF et al. Coenzyme Q10 and nicotinamide block striatal lesions produced by the mitochondrial toxin malonate. 1994. *Ann Neurol* 36: 882-888.
- Beal MF et al. Coenzyme Q10 attenuates the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice. 1998. *Brain Res* 783: 109-114.
- Bendahan D et al. P NMR spectroscopy and ergometer exercise test as evidence for muscle oxidative performance improvement with coenzyme Q in mitochondrial myopathies. 1992. *Neurology* 42: 1203-1208.
- Bolanos JP et al. Nitric oxide-mediated mitochondrial damage in the brain: mechanisms and implications for neurodegenerative diseases. 1997. *J Neurochem* 68: 2227-2240.
- Bonilla E et al. Mitochondrial involvement in Alzheimer's disease. 1999. *Biochim Biophys Acta* 1410: 171-182.
- Bozner P et al. The amyloid b protein induces oxidative damage of mitochondrial DNA. 1997. *J Neuropathol Exp Neurol* 56: 1356-1362.
- Bresolin N et al. Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial. 1990. *J Neurol Sci* 100: 70-78.
- Brookes PS et al. Peroxynitrite and brain mitochondria: evidence for increased proton leak. 1998. *J Neurochem* 70: 2195-2202.
- Brown AM et al. Correlation of the clinical severity of Alzheimer's disease with an aberration in mitochondrial DNA (mtDNA). 2001. *J Mol Neurosci* 16: 41-8.
- Cassarino DS et al. An evaluation of the role of mitochondria in neurodegenerative diseases: mitochondrial mutations and oxidative pathology, protective nuclear responses, and cell death in neurodegeneration. 1999. *Brain Res Rev* 29: 1-25.
- Ebadi M et al. Ubiquinone (coenzyme q10) and mitochondria in oxidative stress of parkinson's disease. 2001. *Biol Signals Recept* 10: 224-53.
- Favit A et al. Ubiquinone protects cultured neurons against spontaneous and excitotoxin-induced degeneration. 1992. *J Cereb Blood Flow Metab* 12: 638-645.
- Fiskum G et al. Mitochondria in neurodegeneration: acute ischemia and chronic neurodegenerative diseases. 1999. *J Cereb Blood Flow Metab* 19: 351-369.
- Floyd RA. Neuroinflammatory processes are important in neurodegenerative diseases: an hypothesis to explain the increased formation of reactive oxygen species and nitrogen species as major factors involved in neurodegenerative disease development. 1999. *Free Radic Biol Med* 26: 1346-1355.
- Folkers K et al. Two successful double-blind trials with coenzyme Q10 (vitamin Q10) on muscular dystrophies and neurogenic atrophies. 1995. *Biochim Biophys Acta* 1271: 281-286.
- Gabuzda D et al. Inhibition of energy metabolism alters the processing of amyloid precursor protein and induces a potentially amyloidogenic derivative. 1994. *J Biol Chem* 269: 13623-13628.
- Grieb P et al. Oral coenzyme Q10 administration prevents the development of ischemic brain lesions in a rabbit model of symptomatic vasospasm. 1997. *Acta Neuropathol* 94: 363-368.
- Harman D. A hypothesis on the pathogenesis of Alzheimer's disease. 1996. *Ann NY Acad Sci* 786: 152-168.
- Koroshetz WJ et al. Energy metabolism defects in Huntington's disease and effects of Coenzyme Q10. 1997. *Ann Neurol* 41: 160-165.
- Kuroda S et al. Reperfusion damage following focal ischemia: pathophysiology and therapeutic windows. 1997. *Clin Neurosci* 4: 199-212.
- Leist M et al. Apoptosis, excitotoxicity, and neuropathology. 1998. *Exp Cell Res* 239: 183-201.
- Lodi R et al. Antioxidant treatment improves in vivo cardiac and skeletal muscle bioenergetics in patients with Friedreich's ataxia. 2001. *Ann Neurol* 49: 590-6.
- Lonnrot K et al. Control of arterial tone after long-term coenzyme Q10 supplementation in senescent rats. 1998. *Brit J Pharmacol* 124: 1500-1506.
- Love S. Oxidative stress in brain ischemia. 1999. *Brain Pathol* 9: 119-131.
- Mariani C et al. Muscle biopsy in Alzheimer's disease: morphological and biochemical findings. 1991. *Clin Neuropathol* 10: 171-176.
- Mark RJ et al. A role for 4-hydroxynonenal, an aldehydic product of lipid peroxidation, in disruption of ion homeostasis and neuronal death induced by amyloid b-peptide. 1997. *J Neurochem* 68: 255-264.
- Mark RJ et al. Amyloid b-peptide impairs glucose transport in hippocampal and cortical neurons: involvement of membrane lipid peroxidation. 1997. *J Neurosci* 17: 1046-1054.
- Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. 1997. *Free Radic Biol Med* 23: 134-147.
- Markesbery WR. Oxidative alterations in Alzheimer's disease. 1999. *Brain Pathol* 9: 133-146.
- Matsumoto S et al. Blockade of the mitochondrial permeability transition pore diminishes infarct size in the rat after transient middle cerebral artery occlusion. 1999. *J Cereb Blood Flow Metab* 19: 736-741.
- Matthews RT et al. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. 1998.

[Http://www.lef.org/magazine/mag2001/oct2001\\_report\\_coq10\\_01.html](http://www.lef.org/magazine/mag2001/oct2001_report_coq10_01.html)

LE Magazine Special Edition, Winter 2004/2005

Page 6 of 7

Bernard

Tel: +6016 9833139

<http://www.oxyfreshap.com/distweb/index.asp?id=4501>

<http://www.streetram.com/coq10.htm>

- Mecocci P et al. Oxidative damage to mitochondrial DNA shows marked age-dependent increases in human brain. 1993. *Ann Neurol* 34: 609-616.
- Mizuno Y et al. Mitochondrial dysfunction in Parkinson's disease. 1998. *Ann Neurol* 44, Suppl 1: S99-S109.
- Mordente A et al. Free radical production by activated haem proteins: protective effect of coenzyme Q. 1994. *Molec Aspects Med.* 15, Suppl: S109-S115.
- Munch G et al. Alzheimer's disease - synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. 1998. *J Neural Transm* 105: 439-461.
- Murphy AN et al. Mitochondria in neurodegeneration: bioenergetic function in cell life and death. 1999. *J Cereb Blood Flow Metab* 19: 231-245.
- Musumeci O et al. Familial cerebellar ataxia with muscle coenzyme Q10 deficiency. 2001. *Neurology* 56: 849-55.
- Nicotera P et al. Neuronal cell death: a demise with different shapes. 1999. *Trends Pharmacol Sci* 20: 46-51.
- Novelli A et al. Glutamate becomes neurotoxic via the N-methyl-D-aspartate receptor when intracellular energy levels are reduced. 1988. *Brain Res* 451: 205-212.
- Ogawa N et al. Survival effect of coenzyme Q10 and naloxone on experimental stroke gerbils. 1986. *Pharmacol Biochem Behav* 24: 315-317.
- Ristow M et al. Frataxin activates mitochondrial energy conversion and oxidative phosphorylation. 2000. *Proc Natl Acad Sci U S A.* 97: 12239-43.
- Sharman EH et al. Effects of age and dietary antioxidants on cerebral electron transport chain activity. 2001. *Neurobiol Aging* 22: 629-34.
- Shults CW et al. Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. 1997. *Ann Neurol* 42: 261-264.
- Shults CW et al. Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients. 1998. *Neurology* 50: 793-5.
- Proc Natl Acad Sci USA 95: 8892-8897.
- Mazzio E et al. Effect of antioxidants on L-glutamate and N-methyl-4-phenylpyridinium ion induced-neurotoxicity in PC12 cells. 2001. *Neurotoxicology* 22: 283-8.
- Volpe M et al. Abnormalities of endothelial function in the pathogenesis of stroke: the importance of endothelin. 2000. *J Cardiovasc Pharmacol* 35, Suppl 2: S45-48.
- Webster MT et al. The effects of perturbed energy metabolism on the processing of amyloid precursor protein in PC12 cells. 1998. *J Neural Transm* 105: 839-853.
- Weyer G et al. A controlled study of 2 doses of idebenone in the treatment of Alzheimer's disease. 1997. *Neuropsychobiology* 36: 73-82.
- Ying W. Deleterious network: a testable pathogenetic concept of Alzheimer's disease. 1997. *Gerontology* 43: 242-253.
- Zeng Z et al. Mitochondrial DNA deletions are associated with ischemia and aging in Balb/c mouse brain. 1999. *J Cell Biochem* 73: 545-553.
- Sobreira C et al. Mitochondrial encephalomyopathy with coenzyme Q10 deficiency. 1997. *Neurology* 48: 1238-1243.
- Tatton WG et al. Mitochondria in neurodegenerative apoptosis: an opportunity for therapy? 1998. *Ann Neurol* 44, Suppl 1: S134-S141.
- Tatton WG et al. Apoptosis in neurodegenerative diseases: the role of mitochondria. 1999. *Biochim Biophys Acta* 1410: 195-213.
- Turner C et al. Mitochondrial dysfunction in neurodegenerative disorders and ageing. 2001. *Adv Exp Med Biol* 487: 229-51.
- Veitch K et al. Global ischemia induces a biphasic response of the mitochondrial respiratory chain. 1992. *Biochem J* 281: 709-715.
- Schulz JB et al. Neuroprotective strategies for treatment of lesions produced by mitochondrial toxins: implications for neurodegenerative diseases. 1996. *Neuroscience* 71: 1043-1048.
- Smith MA et al. Widespread peroxynitrite-mediated damage in Alzheimer's disease. 1997. *J Neurosci* 17: 2653-2657.